SCREENING OF MODULAR AND READILY AVAILABLE LIGAND LIBRARIES FOR C-X (X=H, C, N AND O) BOND FORMING REACTIONS. THE USE OF DFT STUDIES FOR CATALYSTS OPTIMIZATION

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Screening of modular and readily available ligand libraries for C-X (X=H, C, N and O) bond forming reactions. The use of DFT studies for catalysts optimization

PhD-Thesis
Supervised by Prof. Montserrat Diéguez
and Dr. Oscar Pàmies
Departament de Química Física i Inorgànica

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PROF. MONTSERRAT DIÉGUEZ FERNÁNDEZ i DR. OSCAR PÀMIES OLLÉ, Catedràtica i Professor Agregat del Departament de Química Física i Inorgànica de la Facultat de Química de la Universitat Rovira i Virgili

FEM CONSTAR:

Que aquest treball, titulat "**Screening of modular and readily available ligand libraries for C-X (X=H, C, N and O) bond forming reactions**. **The use of DFT studies for catalysts optimization**", que presenta JÈSSICA MARGALEF PALLARÈS per a l'obtenció del títol de Doctor, ha estat realitzat sota la nostra direcció al Departament de Química Física i Inorgànica de la Universitat Rovira i Virgili i que acompleix els requeriments per poder optar a la Menció Europea.

Tarragona, Juny de 2016

Prof. Montserrat Diéguez Fernández

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Table of contents

Chapter 1

Introduction

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1. Introduction

There are many applications in which only one enantiomer has the desired properties while the other enantiomer is either inactive or can give undesirable secondary effects. Consequently, the preparation of enantiomerically pure compounds is growing in several important fields such as pharmaceuticals, agrochemicals, fine chemicals and natural product chemistry.[1] The discovery of synthetic routes for preparing enantiomerically pure compounds is therefore one of the most persistent challenges in chemistry. Asymmetric catalysis is one of the most attractive approaches, because it can provide very high reactivity and selectivity, and is environmentally friendly. Usually with this strategy, a transition-metal complex containing a chiral ligand catalyzes the transformation of a prochiral substrate to one enantiomer as major product. The importance of asymmetric catalysis is reflected by the many publications in this field and the Nobel Prize award in 2001 to W. S. Knowles, K.B. Sharpless and R. Noyori and in 2010 to E. Negishi, R. F. Heck and A. Suzuki.[1]

To reach the highest levels of reactivity and selectivity in catalytic enantioselective reactions, several parameters must be optimized. Of these, the selection and design of the chiral ligand is perhaps the most crucial step.[1] One of the simplest ways of obtaining chiral ligands is to transform or derivatize natural chiral compounds. In this respect the use of highly modular ligand scaffolds is desirable, because it facilitates the synthesis and screening of series of chiral ligands (ligand libraries) in the search for high activities and selectivities for each particular asymmetric catalytic reaction.[1]

The most widely used chiral ligands in asymmetric catalysis are phosphorus donors.[1c,2] Among them, phosphines and phosphinites have played a dominant role.[2] Despite the advantage of phosphite-based ligands, such as being less sensitive to air and other oxidizing agents than phosphines and phosphinites and being easier to synthesize from readily available alcohols, their use as efficient chiral ligands has only been demonstrated more recently.[2d,3] In general, transition-metal complexes with chiral sulfur ligands have been less investigated than complexes with other donor atoms,[4] although in recent decades the number of studies on sulphur-containing catalytic systems has increased notably.[4] Compared to phosphorus, sulfur has a less donor and acceptor character. In addition to these electronic considerations, the sulfur atom in thioether ligands has only two substituents, which can create a less hindered environment than trivalent phosphorus. The formation of mixtures of diastereomeric thioether complexes (because the S atom becomes a stereogenic center when coordinated to the metal) and the difficulty to control their interconversion in solution have also been regarded as a problem for asymmetric induction in catalytic reactions. Nevertheless, in recent years, S-containing ligands have proven to be as useful as other classical asymmetric ligands, especially when combined with other donor atoms.[4] Thioethers have been combined with several donor atoms in heterodonor ligands. S,X-Donor ligands have several advantages over homodonors. They can provide different electronic environments because of the different *trans* influence of the sulfur and X atom. Recently, our group has shown their potential with the successful

application of phosphorus-thioether ligands in the Ir-catalyzed hydrogenation of minimally functionalized olefins and Pd-allylic substitution reactions.[5]

In this context, this thesis focuses on the development of new chiral ligand libraries derived from cheap and available sources and their application in different metal-catalyzed asymmetric processes. In this respect, a series of phosphorus-thioether ligands have been developed for the enantioselective Rh- and Ir-catalyzed hydrogenation of functionalized and unfunctionalized olefins, asymmetric Pd-catalyzed allylic substitution reactions and Ni-catalyzed asymmetric addition of trialkylaluminum reagents to aldehydes. We have also synthesized phosphite-pyridine and phosphorus-triazole ligands and applied them in the enantioselective Ir-catalyzed hydrogenation of minimally functionalized olefins and asymmetric Pd-catalyzed allylic substitution reactions. Finally, we have also successfully developed and evaluated new amino acid-carbohydrate based ligand libraries and their corresponding thioamide counterparts in the Ru- and Rh-catalyzed asymmetric transfer hydrogenation of several ketones. In the following sections we describe the background of each area of the catalytic reactions studied in this thesis.

1.1. Asymmetric hydrogenation reactions

Because of its high efficiency, atom economy and operational simplicity, the metal-catalyzed asymmetric hydrogenation using molecular hydrogen to reduce prochiral olefins, ketones and imines is one of the most suitable and direct synthetic tools for preparing chiral compounds (Figure 1.1).[1,6] Both academic and industrial research groups have studied and developed this reaction for decades. Many intermediates and building blocks which are key to organic synthesis are obtained through this reaction.[1,6]

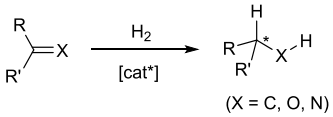
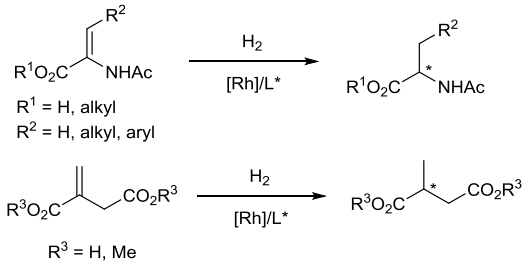


Figure 1.1. Asymmetric hydrogenation of prochiral substances.

1.1.1. Asymmetric Rh-catalyzed hydrogenation of functionalized olefins

The hydrogenation of functionalized carbon-carbon double bounds is widely used to prepare high value compounds that can be used as building blocks in asymmetric synthesis (Scheme 1.1). The hydrogenation of dehydroamino acid derivatives and esters provides access to unnatural amino acids and amines that are useful intermediates for the pharmaceutical and agrochemical industries.[1,6] Their hydrogenation is also a typical reaction for testing the efficiency of new chiral ligands. Rh- and Ru- complexes containing chiral ligands with phosphorus and nitrogen donor centers have proven to be the best catalysts for the asymmetric hydrogenation of this type of substrates. Excellent activities and enantioselectivities have been therefore achieved for the asymmetric hydrogenation of dehydroamino acids and other functionalized substrates.[1,6]



Scheme 1.1. Hydrogenation of dehydroamino acids and itacotanes.

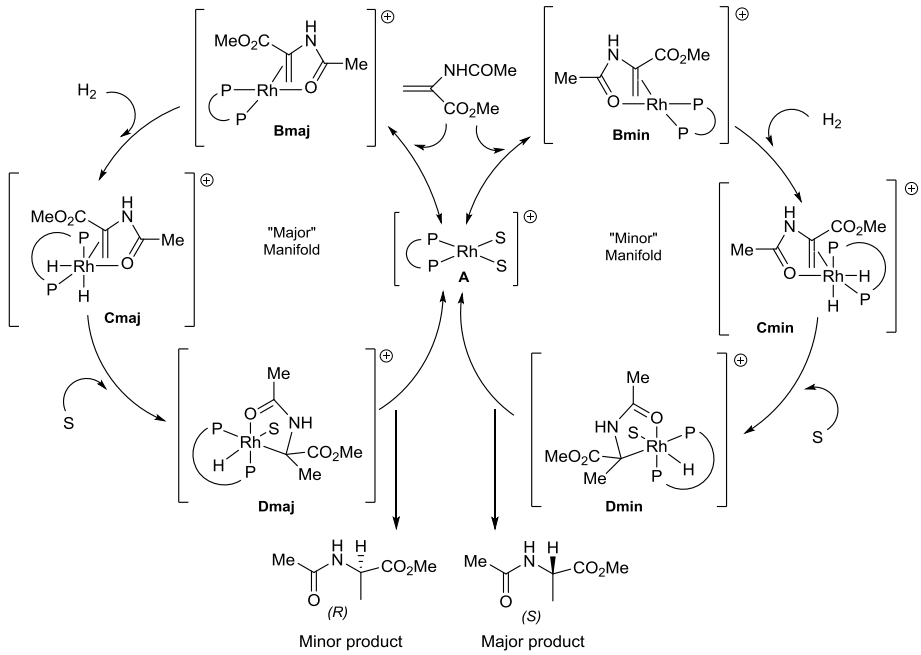
The asymmetric hydrogenation of ketones is a useful way to synthesize chiral secondary alcohols. Ru and, to a lesser extent, Rh, are the most widely used metal sources.[1]

The enantioselective hydrogenation of carbon-nitrogen double bonds is a simple and convenient way to synthesize chiral amines. However, their hydrogenation has some serious drawbacks: coordination can take place through the nitrogen atom and the double bond, and both the substrate and the catalyst intermediates are unstable under catalytic conditions. Homogeneous catalyst can complex both the imine substrate and the amine product. In consequence, catalytic activity is often low. Unlike the asymmetric hydrogenation of functionalized substrates, iridium complexes are the best catalyst for imines.[1] The use of enamides offers an alternative to imines for the synthesis of chiral amines without the problems associated with imine reduction. Rh-complexes have shown to be extremely efficient catalyst in the reduction of enamides.

1.1.1.1. Mechanism

Scheme 1.2 shows the mechanism for the asymmetric hydrogenation of dehydroamino acids and their esters with cationic precursors with diphosphines.[7] In the last decade, this mechanism has proved to be valid for other phosphorus-based ligands (i.e. diphosphinites, diphosphites, etc.).[8] The catalytic cycle consists in two coupled diastereomeric manifolds. The species starting the catalytic cycle is a square planar Rh(I) complex containing the chelating diphosphine and two molecules of solvent **A**. This species reacts with the substrate e.g. methyl α-acetamidoacrylate.

The substrate displaces the solvent molecules to produce the square planar diastereomeric adducts $\mathbf{B}^{maj}$ and $\mathbf{B}^{min}$, where the substrate acts as a bidentate ligand bonded via the olefinic double bond and the oxygen atom of the acetyl group. The next step is the irreversible oxidative addition of hydrogen, which converts the square planar diastereoisomers **B** into the octahedral *cis*-dihydrorhodium complexes **C**. Then, the coordinated olefin is inserted into one of the Rh-H bonds to produce the two diastereomeric alkyl complexes **D**. By reductive elimination, they generate the enantiomeric forms of the hydrogenated product and regenerate the catalytically active square planar species **A**.[7]



Scheme 1.2. Mechanistic scheme for the Rh-catalyzed asymmetric hydrogenation of methyl α-acetamidoacrylate.

It is accepted that the oxidative addition of hydrogen is the rate- and enantioselective determining step. The reactivity of the minor diastereomer $\mathbf{B}^{min}$ is much higher than that of the major diastereomer $\mathbf{B}^{maj}$, so the minor isomer is the product determining. Brown's and Landis' research groups have conducted studies to explain this phenomenon. They show that the oxidative addition of both major and minor adducts requires the substrate to be rotated in the opposite direction of the rhodium phoshphine axis. In the minor adduct, which is less stable, there is a more hindered configuration that will rotate more easily. The minor species is therefore much more reactive towards dihydrogen than the major species.[6,7,9]

1.1.1.2. Ligands

The development of homogeneous asymmetric hydrogenation was initiated by Knowles[10] and Horner[11] in the late 1960s after the discovery of Wilkinson's hydrogenation catalyst $[RhCl(PPh_3)_3]$.[12] By replacing the triphenylphosphine of Wilkinson's catalyst with resolved chiral monophosphines, Knowles and Horner reported the earliest exemples of enantioselective hydrogenation, although with poor enantioselectivity. Later, two advances were made in asymmetric hydrogenation by Kagan and Knowles. Kagan reported the first diphosphine ligands successfully used in asymmetric hydrogenation (**DIOP**) (Figure 1.2).[13] Knowles made his significant discovery of the C_2-symmetric chelating diphosphine ligand, **DIPAMP** (Figure 1.2).[14] Because of its high catalytic efficiency, DIPAMP was used in the industrial production of L-Dopa, a drug used to treat Parkinson's disease.[15] For this work Knowles was awarded the Nobel Prize in 2001.[16]

Following the significant contributions by Kagan and Knowles came the development of hundreds of successful chiral diphosphorus ligands for asymmetric hydrogenation. These include Bonisch's **CHIRAPHOS** and **PROPHOS**, Kumada's ferrocene ligands **BPPFA** and **BPPFOH**, Achiwa's **BPPM**, Rhode Poulenc's **CBD** and Giongo's bis(aminophosphine) ligand **PNNP** (Figure 1.2).[17] However, development in the early 1980s focused mainly on the chiral Rh-catalyst, and the substrate scope was limited to α-dehydroamino acids. Noyori's research on the **BINAP**-Ru catalyst opened up opportunities for the efficient hydrogenation of various substrates (Figure 1.2). Several prochiral olefins and ketones were hydrogenated with excellent enantioselectivity.[18] For this work Noyori was awarded the Nobel Prize in 2001. In the 1990s, the introduction of some efficient chiral diphosphorus ligands, such as **DUPHOS** and **BPE** developed by Burk and coworkers (Figure 1.2) for the hydrogenation of various functionalized olefins, significantly expanded the scope of asymmetric hydrogenation.[19]

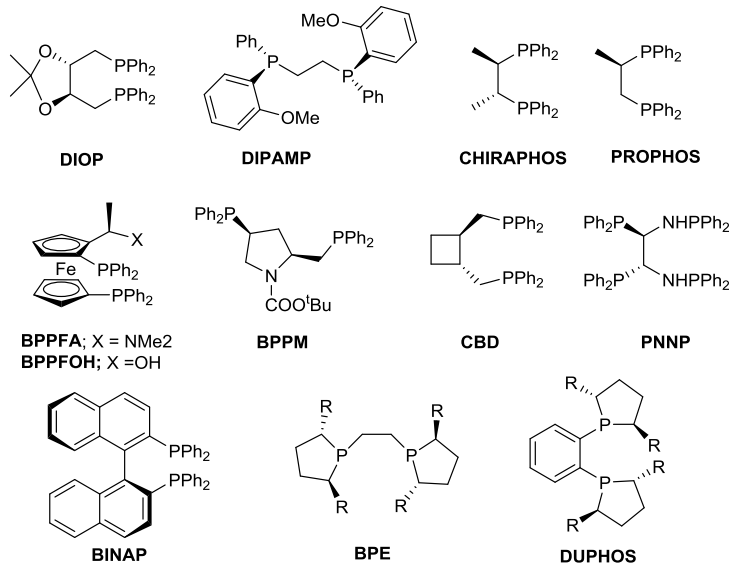


Figure 1.2. Successful diphosphine ligands in asymmetric hydrogenation.

Nowadays, many chiral ligands, mainly phosphorus donor ligands with either C_2- or C_1-symmetry, have been successfully applied. Catalysts containing diphosphine and diphosphinite have played a dominant role among the P-ligands.[1,6,17] However, some catalysts containing a group of less electron-rich phosphorus compounds, phosphite and phosphoramidite ligands, have also demonstrated their potential utility in asymmetric hydrogenation.[2c,3,6,17,20] Other donor atoms, such as sulfur and heterodonor ligands, have also received attention. Several systems with dithioether have led to low-to-moderate enantioselectivities (from 6% to 68%).[4] Mixed P,P'-ligands[3,21] (such as phosphine-phosphite and phosphoramidite-phosphite) have been developed and have proved to be very effective for this process. Although it has been generally accepted that bidentates are the most appropriate ligands for metal-catalyzed enantioselective hydrogenation, in recent years it has been shown that some monophosphorus ligands are very efficient for Rh-

catalyzed asymmetric hydrogenation.[22] Mixed chiral P,S-ligands have also demonstrated their potential utility. Among P,S-ligands, especially phosphinite-thioether ligands have shown the best results in Rh-catalyzed hydrogenation of prochiral olefins.[4] In the next section, we collect the most relevant catalytic data published for Rh-catalyzed asymmetric hydrogenation with phosphorus-thioether ligands.

1.1.1.2.1. Phosphorus-thioether ligands

Phosphinite-thioether ligands

In 1998 was reported the first use of Rh complexes containing P-S donor ligands in the hydrogenation of prochiral olefins. These chiral bis(phosphinite)-thioether ligands **1a**-**d** (Figure 1.3) were tested in the asymmetric hydrogenation of methyl α-acetamidocinnamate, providing only moderate enantioselectivities (up to 55% ee).[23]

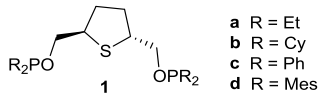


Figure 1.3. Bis(phosphinite-thioether ligands **1a**-**d**.

Lately, a new class of thioether-phosphinite ligands, developed by Evans et. al., proved to be very efficient for the rhodium-catalyzed asymmetric hydrogenation of a variety of α-dehydroamino acid derivatives (Figure 1.4)[24]. In order to control the configuration at sulfur once coordinated to the metal center, the authors optimized the structure of the ligand backbone. They proved that the introduction of bulky substituents adjacent to the sulfur donor forced the sulfur substituent into an *anti* orientation to minimize the steric hindrance. This sulfur-induced asymmetry together with the electronic differentiation of the two donor atoms were used to control the orientation of the olefin, making this system strongly enantioselective. Ligands **3c** and **4** afforded the highest enantioselectivities in the hydrogenation of a variety of alkyl- and aryl-substituted α-acetamidoacrylates (ee's up to 97% and 98% respectively). It should be noted that the inversion of the stereocenter α adjacent to the sulfur donor in ligands **3c** and **4**, provided the opposite product enantiomer ((*S*) and (*R*) respectively) (Figure 1.4). These catalysts were also interestingly described as tolerant to a wide range of *N*-protecting groups. Ligand **3c** was also effective in the hydrogenation of the more challenging tetrasubstituted enamide providing an enantioselectivity of 93% ee.

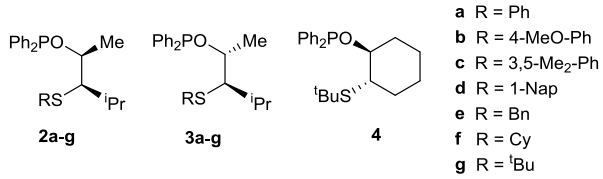


Figure 1.4. Phosphinite-thioether ligands **2**-**4** developed by Evans and coworkers.

Furanoside phosphinite-thioether ligands **5a**-**c** (Figure 1.5) were successfully applied in the Rh- and Ir-catalyzed asymmetric hydrogenation of α-acylaminoacrilates and itaconic acid derivatives (ee's up to 96%).[25] Enantiomeric excesses depended strongly on the steric

properties of the substituent in the thioether moiety, the metal source and the substrate structure. A bulky group in the thioether moiety in conjunction with the use of Rh has a positive effect on enantioselectivity.

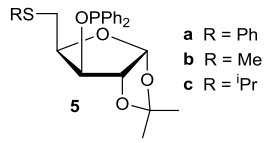


Figure 1.5. Furanoside phosphinite-thioether ligands **5a**-**c**.

Figure 1.6 shows another family of phosphinite-thioether ligands derived from carbohydrates. Cationoic Rh(I) complexes derived from ligands **6**-**8** were used efficiently as catalysts in the enantioselective hydrogenation of enamides. Ligand **7b** provided the best result, giving the desired (*S*)-*N*-acetyl phenyl alanine methyl ester in quantitative yield and in 94% ee. The conformational similarity of α-D-arabinopyranose with β-L-galactopyranose allowed the synthesis of both enantiomers of α-amino acid derivatives such as D- and L-DOPA in excellent ee's (97% and 98% respectively), using derivatives of the formal sugar as catalyst precursors (ligands **7b** and **8**).[26]

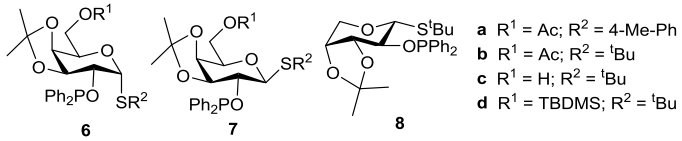
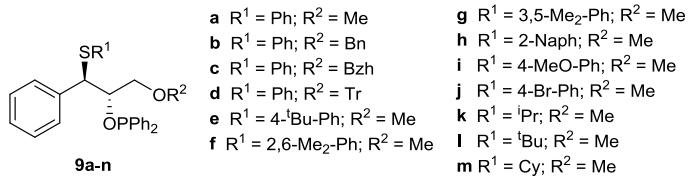


Figure 1.6. Phosphinite thioglycoside ligands **6**-**8**.

More recently, a highly modular family of phosphinite-thioether ligands derived from readily accessible enantiopure epoxides, was systematically studied in the Rh-catlyzed hydrogenation of dehydroamino esters (Figure 1.7).[27] Ligand **11** contains the best combination of all ligand parameters, providing the highest enantioselectivity and activity in the Rh-catalyzed hydrogenation of methyl (*Z*)-α-acetamidocinnamate (ee% = 84% (*S*); $TOF_{1/2}$ = 284 h^{-1}).



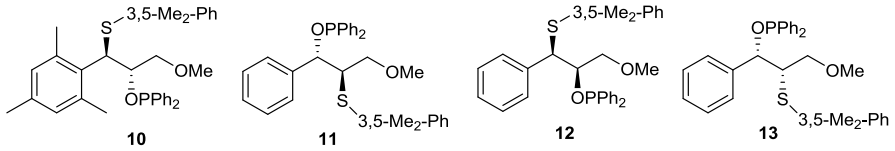


Figure 1.7. Highly modular phosphinite-thioether ligands **9**-**13**.

Phosphine-thioether ligands

The same group that reported the first phosphinite-thioether ligands applied in asymmetric hydrogenation (Figure 1.3), described the synthesis of a readily accessible phosphine-thioether ligand family **14**-**16** (Figure 1.8).[28] All ligands showed high activities (up to 100% conv.) but enantiomeric excesses never exceeded 50% (ligand **14b**).

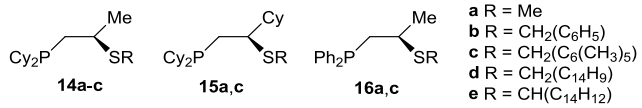


Figure 1.8. Episulfide based phosphine-thioether ligands **14**-**16**.

As far as we know, only another family of phosphine-thioether ligands has been used in the asymmetric hydrogenation of prochiral olefins (Figure 1.9). The enantioselectivities obtained with ligands **17**-**19** were low-to-moderate, ranging from 5 to 47% ee.[29]

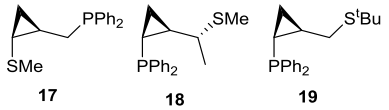


Figure 1.9. Phosphine-thioether ligands **17**-**19** based on a cylopropane backbone.

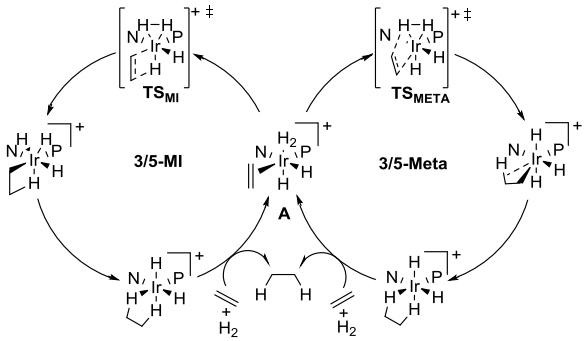
1.1.2. Asymmetric Ir-catalyzed hydrogenation of unfunctionalized olefins

Whereas the reduction of olefins containing an adjacent polar group (i.e. dehydroamino acids) by Rh- and Ru- catalysts precursors modified with phosphorus ligands has a long history,[1,6] the asymmetric hydrogenation of minimally functionalized olefins is less developed because of the difficulty of having no adjacent polar group to direct the reaction. Iridium complexes with chiral P,N-ligands have become established as efficient catalysts for the hydrogenation of unfunctionalized olefins, and their scope is complementary to those of Rh- and Ru-diphosphine complexes.[30]

1.1.2.1. Mechanism

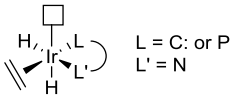
Although the mechanism of olefin hydrogenation by Rh catalysts is well understood,[7,8a] the mechanism that uses chiral iridium catalysts is not, despite being investigated both experimentally and computationally. In the first case, there is enough evidence to support a Rh^{I}/Rh^{III} mechanism in which substrate chelation to metal plays a pivotal role in stereodiscrimination (Scheme 1.2), but in the second four different mechanisms have been proposed (two of them involving Ir^{I}/Ir^{III} intermediates[31] and the other two Ir^{III}/Ir^{V} species[32]). In 2010, Andersson and coworkers used DFT calculations and a full, experimentally tested combination of ligands (mainly phosphine/phosphinite-N) and substrates to study all of the possible diastereomeric routes of the four different mechanisms.[33] Their studies agree with the two already proposed catalytic cycles involving Ir^{III}/Ir^{V} intermediates;[32] however, they fail to distinguish the two Ir^{III}/Ir^{V} mechanisms. One of the mechanisms involves an Ir^{III}/Ir^{V} migratory-insertion/reductive-elimination pathway (labeled 3/5-MI in Scheme 1.3)[32c] whereas the second mechanism uses an Ir^{III}/Ir^{V} σ-methatesis/reductive-elimination

pathway (labeled 3/5-Meta in Scheme 1.3)[32a,b]. From these cycles, it has been demonstrated that the π-olefin complex **A** and the transition states for the migratory-insertion in 3/5-MI (**TS_{MI}**) and the σ-methatesis in 3/5-Meta (**TS_{META}**) are responsible for the enantiocontrol in iridium hydrogenation.[33] It has been demonstrated that the enantioselectivity can be reliably obtained from the calculated relative energies of migratory insertion transition states.[33] Recently, Hopmann and coworkers performed a computational study using a phosphine-oxazoline (**PHOX**)-based iridium catalyst.[34] At the same time our group, in conjunction with Norrby's and Andersson's groups has also performed DFT calculations using Ir-phosphite-oxazoline ligands.[35] Both studies indicate that in the hydrogenation of uncfunctionalized olefins, the 3/5-MI pathway is more energetically favorable than 3/5-Meta pathway.



Scheme 1.3. 3/5-MI and 3/5-Meta catalytic cycles for the Ir-hydrogenation of uncfunctionalized oelfines.

Very recently, Pfaltz et. al. reported an NMR study that supports the Ir^{III}/Ir^{V} mechanism via an $[Ir^{III}(H)_2(alkene)(H_2)(L)]^+$ intermediate (this complex would correspond to **A** in Scheme 1.3).[36] In their study, they were able to synthesize and characterize Ir intermediates with the structure depicted in Figure 1.10 (complex **B**). In these complexes, the NMR shifts of the two hydrides indicated that one of them is coordinated *trans* to an empty site (Figure 1.10).[37] After investigating the reactivity of these complexes, it was concluded that additional H_2 was required to convert the catalyst-bound alkene into the hydrogenated product. These observations support an Ir^{III}/Ir^{V} cycle via an $[Ir^{III}(H)_2(alkene)(H_2)(L)]^+$ intermediate, as originally proposed based on DFT calculations.[32-35] However, no signals of a dihydride complex with an additional coordinated H_2 could be detected, thus indicating that complex **B** intermediate is the resting state. Furthermore, another dihydride Ir-complex was present in a very low concentration and from NOESY experiments it was attributed to an isomer of complex **B**, resulting from an enantioface exchange of the coordinated olefin. They concluded that these two isomers would be in a fast equilibrium via alkene dissociation/association. As the configuration of the hydrogenated product didn't correspond to the one that should lead to the major isomer, they suggested that similarly to the Halpern mechanism for asymmetric hydrogenation with Rh catalysts[7], the minor intermediate, which is less stable, is converted to the major product enantiomer.



B

Figure 1.10. Structure of the iridium intermediates **B** studied in NMR experiments performed by Pfaltz and coworkers.

In order to understand the catalytic performance under hydrogenation conditions of new catalysts bearing other coordinating atoms rather than N-donor atoms, our group has performed HP-NMR experiments together with DFT calculations using P,S-ligands.[5d] The most relevant Ir-dyhidride intermediates were identified. The structure of the intermediates found was in line with that previously observed by Pfaltz and coworkers. The evidence of a Halpern-type mechanism was also concluded.

1.1.2.2. Ligands

A breakthrough in the hydrogenation of unfunctionalized olefins came in 1997 when Pfalz and coworkers used phosphine-oxazoline ligands **PHOX**[38] (Figure 1.11) to design [Ir(**PHOX**)(cod)]PF_6 (cod = 1,5-cyclooctadiene), a chiral anolgue of Crabtree's catalyst ([Ir(py)(PCy_3)(cod)]PF_6)[39] that enantioselectively hydrogenated prochiral imines.[40] Although this catalyst also hydrogenated prochiral olefins highly enantioselectively, it was unstable to the reaction conditions. Pfaltz and coworkers overcame this problem by changing the catalyst anion to [3,5-$(F_3C)_2$-$C_6H_3)_4B]^-$ ([$Bar_F]^-$). The result was [Ir(**PHOX**)(cod)]BAr_F (Figure 1.11), an active enantioselective and stable catalyst library for olefin hydrogenation.[41] **PHOX** ligands together with other similar phosphine-oxazoline ligands have been successfully used for the asymmetric hydrogenation of a limited range of alkenes (mainly trisubstituted (*E*)-olefins, Figure 1.11).[41,42] Lately, Bolm's group successfully applied Ir-**PHOX** catalytic systems in the hydrogenation of α,β-unsaturated ketones (ee's up to 99%, Figure 1.11).[43] Hydrogenation of of α,β-unsaturated ketones leads to the formation of ketones with α-chiral carbon centers; which are an important group of compounds in organic synthesis.[44]

Since then, the composition of P,N-ligands has been extended by initially replacing the phosphine moiety with a phosphinite or a carbene group, and the oxazoline moiety with other N-donor groups (such as pyiridine, thiazole and oxazole).[30] The structure of the chiral ligand's backbone has also been modified. More recently, the use of iridium catalysts containing P-S[5] and P-O[45] heterodonor ligands has been also developed. All these modifications have led to the discovery of new ligands that have considerably broadened the scope of Ir-catalyzed hydrogenation.[30] The latest innovation in the design of ligands for this process was the replacement of the phosphine/phosphinite moiety by a biaryl phosphite group.[30e,35,46] The presence of biaryl-phosphite moieties in these P,N-ligands provides greater substrate versatility than previous Ir-phosphine/phosphinite,N catalyst systems. Nowadays, several unfunctionalized olefins, vinyl phosphonates, vinyl fluorides, CF_3-substituted olefins, vinyl silanes, enol phosphinate esters, enol ethers, enamides, and even heteroaromatic rings, can be hydrogenated.[30]

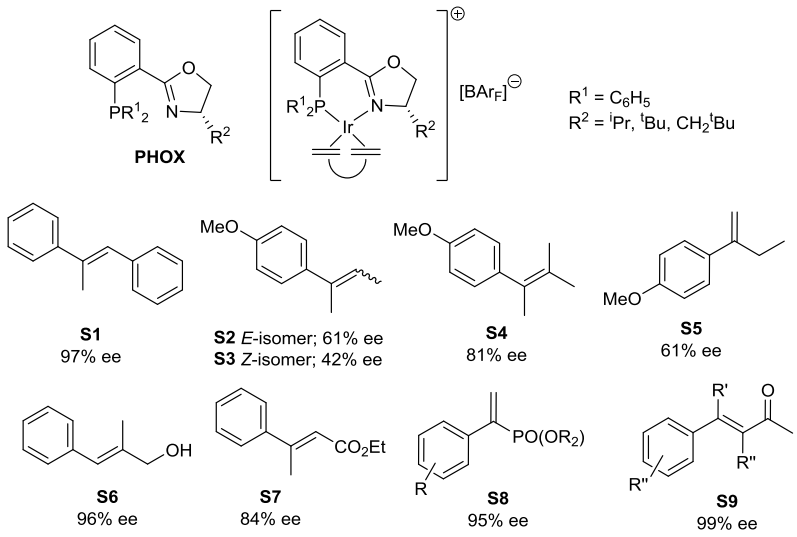


Figure 1.11. Selected Ir-hydrogenation results using **PHOX** and similar phosphine-oxazoline ligands.

In the next section we summarize the most relevant catalytic systems for Ir-catalyzed hydrogenation of minimally functionalized olefins. As mentioned, most of the successful ligands are P,N-ligands bearing an oxazoline functionality. However, other ligands bearing more robust groups rather than oxazoline, such as pyridine or thioether moieties, have proved to be also efficient ligands for this catalytic process.

1.1.2.2.1. Phosphorus-nitrogen ligands

Inspired by the work of Pfaltz and coworkers using **PHOX** ligands, several other phosphorus-oxazoline compounds have been developed for this process. Apart from ligands bearing an oxazoline moiety, ligands containing other nitrogen donor groups have been also developed. Figure 1.12 shows a selection of the most successful phosphorus-nitrogen ligands reported to date for this catalytic process.

The replacement of the flat *ortho*-phenylene tether by a benzylic group led to the development of ligands **20** (Figure 1.12). These ligands were successfully applied in the Ir-catalyzed hydrogenation of (*E*)- and (*Z*)-stilbene derivatives (ee's up to 97% and 90%, respectively), α,β-unsaturated esters (up to 98% ee), allyl alcohols (up to 90% ee), α,β-unsaturated ketones (up to 99%), and imine (up to 88% ee).[47]

Phosphinite-oxazolines **21** (Figure 1.12) constitute one of the most effective ligand class for Ir-catalyzed asymmetric hydrogenation of minimally functionalized olefins.[48] (*E*)- and (*Z*)-2-aryl-2-butenes were hydrogenated in very high enantioselectivities for the first time (ee's up to 99% and 92%, respectively), including α,β-unsaturated esters.[48b] These ligands have also been successfully used in the reduction of more challenging terminal olefins (ee's up to 94%).[49] Recently, it has been shown that base-activated ligands **21** are able to smoothly hydrogenate α,β-unsaturated nitriles in excellent enantioselectivities (ee's up to 98%), at low catalyst loadings.[50] Ligands **22** (Figure 1.12) are based on the successful ligands **21** but the chirality is shifted from the alkyl chain to the oxazoline substituent. The scope of

these ligands is narrower in comparison with the phosphinite-oxazoline ligands **21**, but they are complementary.[51] For instance, ligands **22** provided higher enantioselectivities for allylic alcohols (ee's up to 99%) and for alkenes bearing heteroatomic subtituents, than privileged ligands **21**.

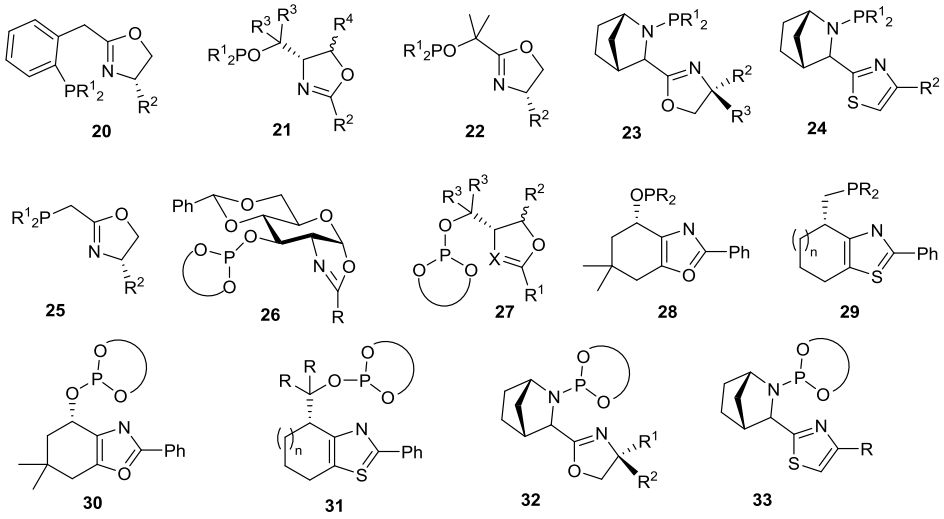


Figure 1.12. Successful phosphorus-nitrogen ligand families developed for their Ir-catalyzed hydrogenation of minimally functionalized olefins.

N-Phosphine ligands **23** (Figure 1.12), containing a chiral bicyclic rigid backbone, are also excellent ligands for the Ir-catalyzed hydrogenation of minimally functionalized olefins.[52] High enantioselectivities have been obtained in the reduction of (*E*)-isomers (up to 99% ee).[52a,g] These catalysts afforded also high enantioselectivities in the hydrogenation of enol phosphinates,[52c,e] vinyl silanes,[52b] fluorinated olefins, [52d] vinyl boronates[52f] and α,β-unsaturated esters.[52h] The *N*-phosphine-thiazole ligands **24** were also prepared and evaluated. High enantioselectivities were obtained in the reduction of (*E*)-trisubstituted olefins (ee's up to 97%)[53] and more recently, in the hydrogenation of unsaturated sulfones (ee's up to 99%).[54]

The simple and readily available phosphine-oxazoline ligands **25** (Figure 1.12) provided excellent enantioselectivities for a broad range of unfunctionalized tetrasubstituted olefins (ee's up to 97%).[55] It was an important discovery since the low reactivity of this substrate class and because it opens up the possibility to introduce two adjacent stereogenic centers in a single step. Very recently, Ir/**25** catalytic systems have been efficiently used in the challenging hydrogenation of 3,3-disubstituted allylic alcohols and related homoallylic alcohols.[56]

Ligands **26** (Figure 1.12) represent the first successful application of phosphite-oxazoline ligands for this process. Excellent enantioselectivities were obtained in the hydrogenation of a wide range of (*E*)- and (*Z*)-trisubstituted olefins (ee's up to 99% and 98%, respectively), including 4-methyl-1,2-dihydronaphtalenes (ee's up to 98%) and triarylsubstituted alkenes (ee's up to ee's up to >99%). The effectiveness of this ligand

family extends to the use of 1,1-disubstituted olefins and also to the use of olefins containing a neightboring polar group.[46a,35]

The replacement of the phosphinite moiety in ligands **21** by a biaryl-phosphite moiety (ligands **27**, (X = O); Figure 1.12) was highly advantageous in terms of catalytic activity and substrate versatility. Therefore, these ligands provided higher enantioselectivities and activities for a wider range of alkenes, including (*E*)- and (*Z*)-trisubstituted olefins (ee's up to >99% and up to 96%, respectively), 1,1-disubstituted alkenes, and alkenes containing a neighboring polar group.[46b,c] More recently, the oxazoline moiety has been replaced by a thiazoline group (ligands **27**, (X = S); Figure 1.12).[46f] This modification allowed to expand the scope that can be hydrogenated with this ligand class.

Phosphinite-oxazoles **28** and phosphinite-thiazoles **29** have also been evaluated (Figure 1.12). Both families of ligands have proven valuable in the hydrogenation of minimally functionaliazed olefins, providing excellent enantioselectivities in the hydrogenation of (*E*)- and (*Z*)-aryl/alkyl trisubstituted olefins (ee's up to >99% for (*E*)-substrates and up to 94% for (*Z*)-substrates).[57] Thiazole ligands **29** have also proved to be optimal for the hydrogenation of cyclic alkenes (ee's up to >99%),[58] dienes (ee's up to >99% for the *trans* product)[59] and 1,1-diaryl trisubstituted olefins (ee's up to >99%).[60]

Later, ligands **30** and **31** have been prepared by replacing the phosphinite group by a biaryl phosphite moiety in ligands **28** and **29** (Figure 1.12). These ligands have also provided excellent enantioselectivities in the reduction of a wide range of (*E*)- and (*Z*)-trisubstituted and 1,1-disubstituted terminal alkenes (ee's up to >99%).[46d] The introduction of a biaryl phosphite moiety in the ligand backbone increased the substrate scope (i. e. ee's increased up to 99% in the reduction of 4-methyl-1,2-dihydronaphtalene).

Similarly, the *N*-phosphane group in ligands **23** and **24** was substituted by a biaryl phosphoroamidite group (ligands **32**; Figure 1.12).[46g] This modification extended the range of olefins that could be successfully hydrogenated, and furnished enantioselectivities that were comparable, in most of the cases, to the best reported so far. Thus, a wide range of (*E*)- and (*Z*)-trisubstituted and 1,1-disubstituted alkenes, vinyl silanes, enol phosphinates, tri- and di-substituted alkenylboronic esters and α,β-unsaturated enones were hydrogenated with enantioselectivities up to >99% and high conversions.

1.1.2.2.1.1. Phosphorus-pyridine ligands

Several P-N ligands bearing a pyridine moiety as a N-donor have been developed. This modification has led to more robust ligands rather than oxazoline containing ligands. Some of the reported phosphorus-pyridine ligands have provided competitive results with those obtained with P-N ligands containing other N-heterocyclic functions.

Phosphine-pyridine ligands

Knochel and coworkers were the first to synthesize chiral P-N ligands containing a pyridyl group. Phosphine-pyridine ligands **28** and **29** (Figure 1.13) were synthesized from readily available D-(+)-camphor and were applied in the hydrogenation of trisubstituted olefins. Moderate-to-high enantioselectivities were obtained in the reduction of (*E*)-stilbenes (ee's up to 96%, ligand **28d**).[61]

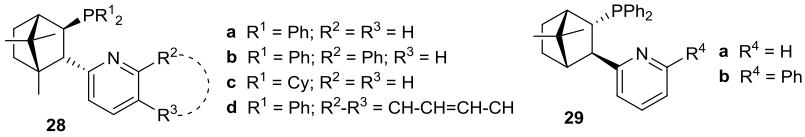


Figure 1.13. Phosphine-pyridine ligands **28**-**29** derived from D-(+)-camphor.

Phosphine-pyridine ligands **30**-**31** (Figure 1.14) were prepared with the aim to mimic the coordination sphere of Crabtree's catalyst with a chiral bidentate ligand, while generating a similar steric environment around the Ir atom as the successful **PHOX** ligands. Despite this, the catalytic performance of [Ir(cod)**30**-**31**][BAR_F] was inferior to that of the **PHOX** ligands (ee's up to 88%).[62]

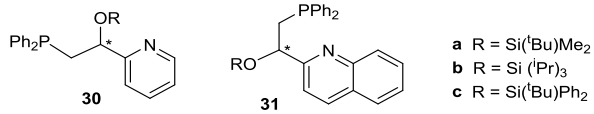


Figure 1.14. Phosphine-pyridine ligands **30**-**31**.

Ligand **32** (Figure 1.15), derived from α-pinene, was prepared to increase the rigidity of ligand **30** by introducing an enantiomerically pure bicyclic moiety. Although enantioselectivities were high (ee's up to 97%), poor activities were obtained. However, the *cis* ligand **32** gave higher conversions than its corresponding *trans* ligand **33**.[63] A modification of ligand **32** in which the phosphine group is attached directly to the pinene moiety to form a five-member chelate ring yielded ligand **34** (Figure 1.15). Ligand **34** proved to be more effective in the reduction of enol phosphonates (ee's up to 90%) rather than aryl/alkyl trisubstituted olefins.[64] Chelucci and co-workers increased the range of phosphine-pyridine ligands derived from α-pinene with the synthesis of compounds **35** and **36** (Figure 1.15). However, these ligands provided lower enantioselectivities than ligand **32** (ee's up to 94% in the reduction of **S1**).[65]

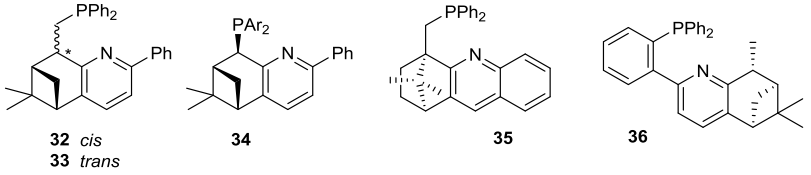
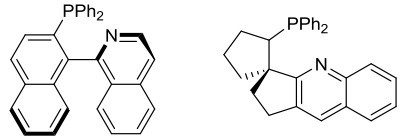


Figure 1.15. Phosphine-pyridine ligands **32**-**36** derived from α-pinene.

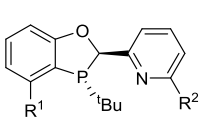
In 2007, the phosphine-quinoline ligand **37** (Figure 1.16), with axial chirality, was applied in the Ir-catalyzed hydrogenation of minimally functionalized olefins with promising results (ee's up to 95% for both (*E*)- and (*Z*)-isomers).[66] The concept of axial chirality was also used in the spiro phosphine-quinoline ligand **38** (Figure 1.16).[67] This ligand showed low enantioselectivities in the Ir-hydrogenation of the model substrate **S1**.



37 **38**

Figure 1.16. Axial chirality containing phosphine-ligands **37**-**38**.

Recently, tunable P-chiral pyridil-dihydrobenzooxaphosphole ligands **39** were synthesized and applied in the asymmetric Ir-hydrogenation of uncfuntionalized tri- and tetrasubstituted alkenes.[68] Ligand **39c** provided the most optimal results of up to 76% ee and 90% of conversion in the reduction of tetrasubstituted 2,3-dimethylindene. Ligand **39c** was further evaluated in the hydrogenation of other challenging tri- and tetrasubstituted olefins, furnishing enantioselectivities ranging from 76% to 90%.

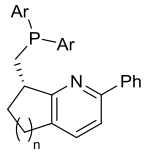


39

a R^1 = OMe; R^2 = H
b R^1 = Ph; R^2 = H
c R^1 = 2,6-$(MeO)_2$-Ph; R^2 = H
d R^1 = 9-Anth; R^2 = H
e R^1 = OMe; R^2 = OMe
f R^1 = OMe; R^2 = Ph

Figure 1.17. P-chiral pyridil-dihydrobenzooxaphosphole ligands **39**.

Bicyclic phosphine-pyridine ligands **40** were recently prepared by Andersson and coworkers. These ligands were evaluated in the asymmetric Ir-catalyzed hydrogenation of various olefins, providing low-to-high enantioselectivities (14-99% ee). In general, Ir complexes based on five-membered-ring containing ligands **40a**-**b**, showed better catalytic performance than **40c**-**d**.[69]



40

a n = 1; Ar = Ph
b n = 1; Ar = *o*-Tol
c n = 2; Ar = Ph
d n =2; Ar = *o*-Tol

Figure 1.18. Bicyclic phosphine-pyridine ligands **40**.

Phosphinite-pyridine

Phosphinite-pyridine ligands **41** (Figure 1.19) are related to **28** (Figure 1.13), but the camphor moiety is replaced by a cycohexanol group. This modification led to lower enantioselectivities in the reduction of (*E*)-stilbenes, indicating the importance of the bulky camphor component for high enantioselectivity. A maximum of 93% ee was obtained with ligand *cis*-**41d**.[70]

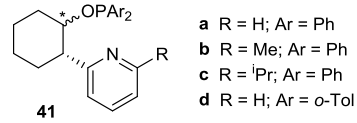


Figure 1.19. Phosphinite-pyridine ligands **41**.

The phosphinite version of ligands **30** (Figure 1.14) were also tested in the asymmetric Ir-catalyzed hydrogenation of minimally functionalized olefins (ligands **42a**-**j**; Figure 1.20).[62] The presence of a phosphinite moiety had a positive effect in terms of catalytic performance. Therefore, the enantiomeric excess in the hydrogenation of **S1** increased from 88% to 97%. The best enantioselectivities were obtained with ligand **42i** which contains *tert*-buthyl substituents at both the phosphinite (R^1) and the alkyl backbone (R^2) moieties. A drawback of ligands **42a**-**j** is that they are accessible from the appropriate chiral pyridyl alcohols, which were obtained from the racemates by preparative HPLC using a chiral column. To address this point, a series of phosphinite-pyridine ligands derived from cheap and available menthol and mandelic acid (ligands **42k**-**l**; Figure 1.20) were prepared.[71] However, these ligands were less enantioselective (i.e. ee's up to 80% in the reduction of **S1**).

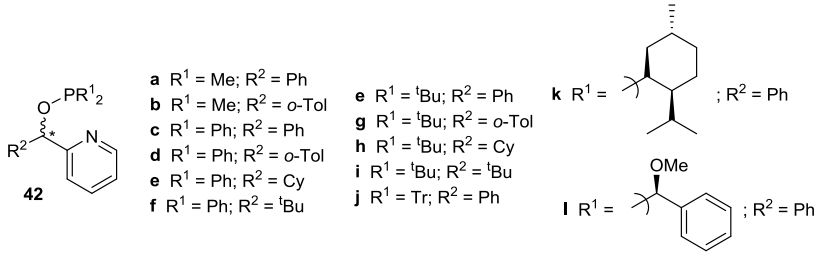
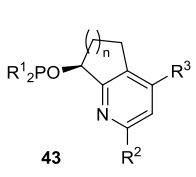


Figure 1.20. Phosphinite-pyridine ligands **42**.

A second generation of phosphinite-pyridine ligands with the general structure **43** (Figure 1.21) has also been developed with the aim of increasing the rigidity in the alkyl bridge moiety. This ligand family gave excellent enantioselectivities for a wide range of olefins (ee's up to >99%) including purely alkyl trisubstituted ones.[72] In general, the enantioselectivity was higher with a bulky substituent at the phosphinite moiety (R^1 = ^{t}Bu or *o*-Tol) and a phenyl substituent at R^2 = Ph (ligands **43a** and **43b**; Figure 1.21). Ligand **43b** was also useful in the hydrogenation of several N-protected indoles.[73] The utility of this catalytic system was demonstrated in the hydrogenation of ϒ-tocotrienyl acetate to obtain ϒ-tocopherol, a principal component of vitamine E, resulting in enantioselectivity >98% for the (*RRR*)-enantiomer with ligand **43a**.[74] To obtain excellent enantiocontrol in the reduction of cyclic dihydronaphtalenes and α-substitued α-β-unsaturated esters, the introduction of a large aryl substituent (i. e. 9-anth or Mes) at R^2 is necessary.[72c] Hence, ligands **43d**-**f** (Figure 1.21) were able to reduce these difficult substrates furnishing enantioselectivities up to 99%. Ligand **43d** was also able to reduce (*E*,*E*)-farnesol in an enantioselectivity greater than 99% ee and in high diastereoselectivity. Very recently, ligands **43b**,**c** proved to be efficient catalysts for the asymmetric hydrogenation of furans and benzofurans.[75] The asymmetric

hydrogenation of a 3-methylbenzofuran derivative was used as a key step in the formal total synthesis of the cytotoxic naphtoquinone natural product (-)-thespesone (92% ee). Finally, the new Ir catalyst based on ligand **42g** (Figure 1.21) have been used in the hydrogenation of a wide range of 2-alkyl and 2-arylmaleic acid diesters to yield the corresponding succinates in high enantiomeric purity (ee's ranging from 84% to >99% ee).[76] Interestingly, mixtures of *cis*/*trans* substrates can be hydrogenated in an enantioconvergent fashion with high enantioselectivities (ee values between 87-93%). The products obtained by ligand **42g** are valuable chiral building blocks with a structural motif found in many bioactive compounds, such as metalloproteinase inhibitors.

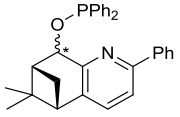


43

a n = 1; R^1 = *o*-Tol; R^2 = Ph; R^3 = H
b n = 1; R^1 = ^{t}Bu; R^2 = Ph; R^3 = H
c n = 2; R^1 = ^{t}Bu; R^2 = Me; R^3 = H
d n = 1; R^1 = *o*-Tol; R^2 = 9-Anth; R^3 = Me
e n = 1; R^1 = ^{t}Bu; R^2 = Mes; R^3 = Me
f n = 1; R^1 = *o*-Tol; R^2 = 9-Anth; R^3 = H
g n = 1; R^1 = ^{t}Bu; R^2 = 2,6-F_2-Ph; R^3 = Me

Figure 1.21. Representative phosphinite-pyridine ligands **43**.

The phosphinite version of byciclic ligands **32**-**34** (Figure 1.15) was also developed (ligands **44**-**45**; Figure 1.22). Unfortunatelly, ligands **44** were less active than their corresponding phosphine counterparts. The authors attributed the low activity observed to a decomposition of the catalyst over the course of the reaction, possibly due to high steric strain around the metal.[63]



44 *cis*
45 *trans*

Figure 1.22. Byciclic phosphinite-pyridine ligands **44**-**45**.

Phosphite-pyridine ligands

The phosphinite moiety in ligands **42** (Figure 1.20) was replaced by a phosphite group (ligands **47**-**54**; Figure 1.23).[46e] By carefully selecting the ligand components, a wide range of (*E*)- and (*Z*)-trisubstituted alkenes were successfully hydrogenated (ee's up to 99%), including more demanding triaryl-substituted olefins and dihydronaphthalenes. These ligands were also useful in the reduction of the very challenging class of terminal disubstituted olefins (ee's up to 99%) and are also very tolerant to the presence of a neighboring polar group. A range of allylic alcohols, acetates, α,β-unsaturated esters and ketones, allylic silanes, vinylboronates and trifluoromethyl olefins were thus hydrogenated with high enantioselectivities. The new Ir-phosphite-pyridine catalyst library also performed well in propylene carbonate, an alternative environmentally friendly solvent, which allowed the catalyst to be reused while maintaining the excellent enantioselectivities.

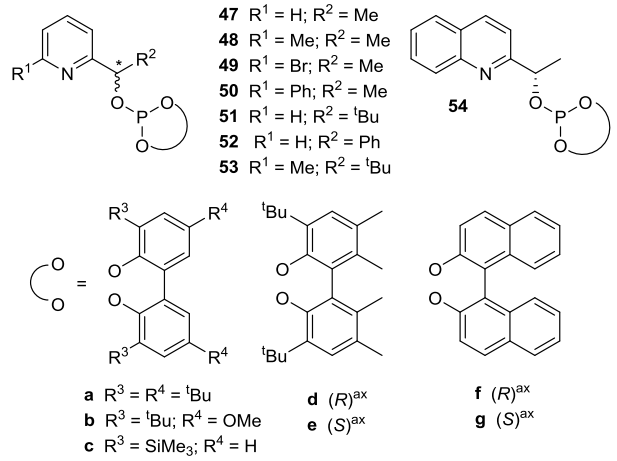


Figure 1.23. Phosphite-pyridine ligands **47**-**54**.

1.1.2.2.1.2. Phosphorus-triazole ligands

Click chemistry has recently drawn considerable attention as a powerful and efficient way to synthesize desired compounds under mild conditions, high yields and regioselectivities, and requiring simple reaction and work-up procedures. Particularly Cu(I)-catalyzed azide-alkyne cycloaddition (CuAAC) is interesting since it can yield 1,4-disubstituted 1,2,3-triazoles, which can be part of easily modulable P,N-type ligands. However, 1,2,3-triazoles have only generated interest as ligands in some metal-catalyzed organic reactions.[77] Concretely, in the field of asymmetric Ir-catalyzed hydrogenation of minimally functionalized olefins, only one application of chiral triazole containing P,N-ligands has been reported to date.[78] Ligands **55** (Figure 1.24) have been applied in the reduction of di- tri- and tetrasubstitued olefins achieving enantioselectivities up to 90%. It's remarkably that an enantioselectivity up to 87% was achieved in the reduction of the tetra-substituted alkene **S4**, which is among the highest selectivities reported for this substrate class.

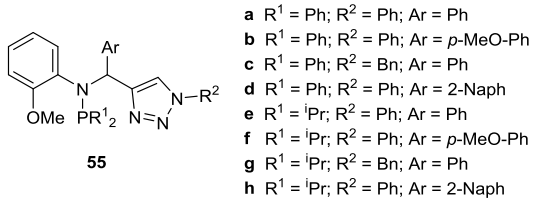


Figure 1.24. Chiral triazole containing P,N-ligands **55**.

1.1.2.2.2. Phosphorus-thioether ligands

As mentioned above, Ir complexes containing P,N-ligands emerged as powerful tools in the asymmetric hydrogenation of minimally functionalized olefins.[30] However, the possibility of changing the nature of the N-donor in these heterodonor ligands has been poorly contemplated. The presence of a thioether moiety in the ligand may be beneficial

for the enantioselecivity because its coordination to the iridium creates a stereocenter with a substituent that is very close to the iridium atom and therefore, strongly shields one of the faces of the coordination sphere. Furthermore, compared with the oxazoline moiety present in most of the successful hydrogenation catalysts, the thioether moiety is much more robust. In this respect, our group reported for the first time new classes of non N-donor heterodonor ligands thioether-phosphite/phosphinite/phosphine (ligands **56**-**70**; Figure 1.25) for the asymmetric Ir-catalyzed hydrogenation of minimally functionalized olefins.[5a-b,79]

Catalytic results by using sugar-derived ligands **56**-**70** indicated that enantioselectivities were highly affected by the position of thioether group at either C-5 or C-3 of the furanoside backbone, the configuration of C-3, the thioether substituent, the substituents/configuration in the biaryl phosphite moiety (**a**-**h**), and the replacement of the phosphite moiety by a phosphinite group. Enantioselectivities were excellent (ee's up to >99%) in a wide range of (*E*)-and (*Z*)-trisubstituted alkenes with ligands **66a** and **66e**, which contain the optimal combination of ligand parameters. It should be pointed out that these catalysts are also very tolerant to the presence of a neighboring polar group. Thus, a range of allylic alcohols, acetates, α,β-unsaturated esters and vinylboronates were hydrogenated in high enantioselectivities, and again ligands **66a** and **66e** provided the best results (ee's from 90% to 99%). These ligands were also applied in the asymmetric hydrogenation of the more challenging terminal disubstituted aryl/alkyl olefins, providing enantioselectivities up to 98% in the case of aryl/heteroaryl/tert-butyl substrates. Interestingly, for these substrates, both enantiomers of the hydrogenation product could be obtained in high enantioselectivities, simply by changing the configuration of the biaryl phosphite moiety.

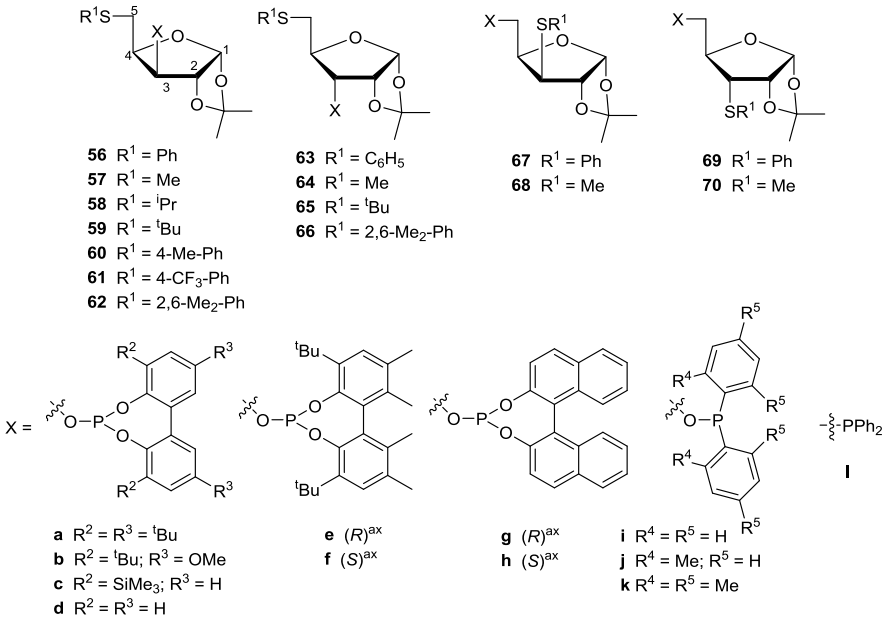
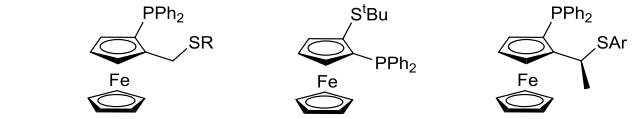


Figure 1.25. Thioether-phosphite/phosphinite/phosphine ligands **56**-**70a**-**l**.

Very recently our group, together with Manoury's research group, has reported the application of a novel ferrocenyl-based phosphine-thioether ligand family (Figure 1.26) in the Ir-catalyzed hydrogenation of minimally functionalized olefins.[80] The ferrocenyl moiety gives to ligands **71**-**82** planar chirality and in addition, ligands **81** and **82** present a second stereogenic center next to the sulfur atom. By fine tuning the ligand parameters, good to excellent enantioselectivities were achieved in the asymmetric Ir-catalyzed hydrogenation of many substrates. For example, enantioselectivities up to 98% ee were achieved in the reduction of several α,β-unsaturated esters and ee's between 92 and 99% in the reduction of di- and trisubstituted enol phosphinates. In addition promising high enantioselectivities were achieved for challenging substrates such as cyclic enones (ee's up to 85%), enamides (90% ee) and δ-lactones (84% ee).



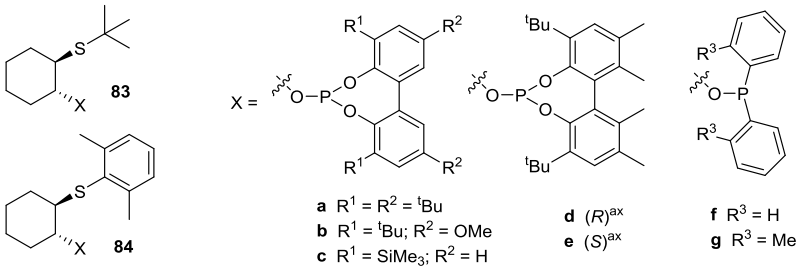
71 R = Et
72 R = ^{i}Pr
73 R = Cy
74 R = ^{t}Bu
75 R = Ad
76 R = Ph
77 R = Bn
78 R = 1-Naph
79 R = 2,6-Me$_2$-Ph

80

81 Ar = Ph
82 Ar = 2,6-Me$_2$-Ph

Figure 1.26. Ferrocenyl-based phosphine-thioether ligands **71**-**82**.

Very recently, our group has reported the application of a phosphite/phosphinite-thioether ligand library **83**-**84a**-**g** (Figure 1.27) for the Ir-hydrogenation of several minimally functionalized alkenes.[5d] These ligands are synthesized in only two steps from commercially accessible cyclohexene oxide. By tuning the thioether and phosphite/phosphinite moieties, a wide range of olefins has been reduced in enantioselectivities up to 99%, including relevant examples with poorly coordinative groups such as α,β-unsaturated esters (ee's up to 98%) and α,β-unsaturated enones (ee's up to 92%). It should be pointed out that terminal aryl-substituted boronic esters have been reduced for the first time, achieving enantioselectivities ranging from 96% to 98% ee. Furthermore, the origin of the enantioselectivity obtained with ligands **83** and **84** was explained by performing a combined experimental and theoretical study. It was concluded that the minor intermediate, which is less stable, reacts faster to afford the hydrogenated product than the major intermediate, similarly to the classical Halpern mechanism.



a $R^1 = R^2 = {}^t$Bu
b $R^1 = {}^t$Bu; R^2 = OMe
c R^1 = SiMe$_3$; R^2 = H

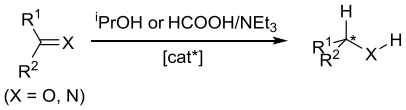
d $(R)^{ax}$
e $(S)^{ax}$

f R^3 = H
g R^3 = Me

Figure 1.27. Phosphite/phosphinite-thioether ligands **83**-**84a**-**g**.

1.2. Asymmetric transfer hydrogenation (ATH) of ketones

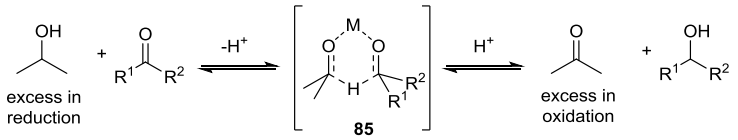
Asymmetric transfer hydrogenation (ATH) can be defined as "the reduction of prochiral compounds with a hydrogen donor other than hydrogen gas in the presence of a chiral catalyst" (Scheme 1.4).[81] The asymmetric transfer hydrogenation[82] of prochiral ketones and imines is one of the most attractive methods for synthesizing optically active secondary alcohols and amines, which are important intermediates for the preparation of fine chemicals and pharmaceuticals. Ever since the discovery of the Meerwin-Ponndorf-Verley reaction,[83] in which a ketone is reduced by an alcohol in the presence of an aluminum alkoxide, the use of metallic compounds to promote hydrogen transfer between alcohols and carbonyl compounds has been widely studied in organic synthesis.[84] After this discovery, transition metal-catalyzed versions of these reactions have been developed.[82] Of all the catalysts reported so far, those that are based on the transition metal catalysts with Ru, Rh and Ir complexes have been the most successful.[82] Recently, however, iron[85]- and osmium[86]-based catalysts have also shown useful activity and selectivity. Metal-catalyzed ATH reactions are most often performed in 2-propanol or the azeotropic mixture of formic acid and triethyl amine (HCOOH:NEt_3 in the molar ratio 2.5:1), which act as both solvent and reductant.[82]



Scheme 1.4. Asymmetric transfer hydrogenation of prochiral compounds.

1.2.1. Mechanism

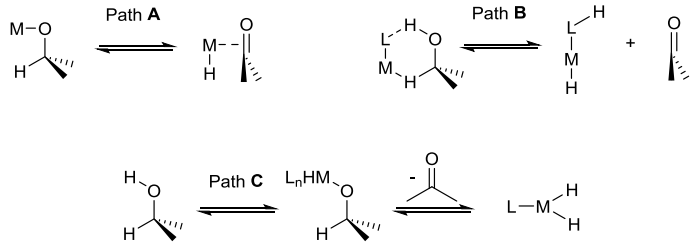
From a mechanistic point of view, two general pathways have been proposed for transfer hydrogenation: direct hydrogen transfer and the hydride route.[87] Direct hydrogen transfer, proposed for the Meerwin-Ponndorf-Verley (MPV) reduction is a concerted process involving a six membered transition state (**85**) in which both the hydrogen donor and the hydrogen acceptor are coordinated to the metal center (Scheme 1.5). This mechanism is claimed to occur with main group metals.[87a,b]



Scheme 1.5. Direct hydrogen transfer.

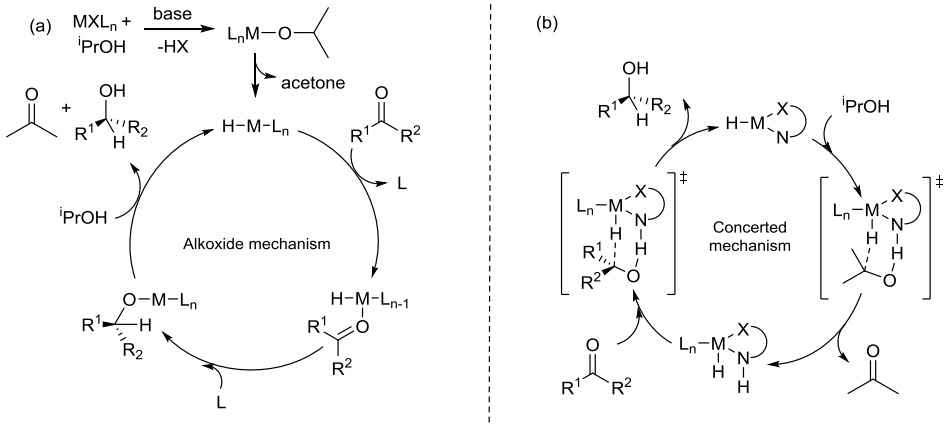
The hydride route, which is generally accepted to occur for transition metal catalysts, involves metal hydrides as key elements. The hydride route is further divided into the monohydride route (Path **A** and **B**; Scheme 1.6) and dihydride route (Path **C**; Scheme 1.6), depending on the nature of the complex. Most of the representative catalysts developed for ATH (i.e. Ru catalysts modified with amino alcohols, pseudo-dipeptides and monotosylated diamines, etc.) follow the metal monohydride mechanism.[87] Hydrogen transfer reactions catalyzed by metal monohydride may proceed via two slightly different

pathways: the alkoxide mechanism (Path **A**, Scheme 1.6) and the concerted mechanism (Path **B**; Scheme 1.6).



Scheme 1.6. Hydridic pathways **A**, **B** and **C**.

In both pathways (**A** and **B**) the metal hydride migrates from the metal to the carbonyl carbon giving rise to the α-C-H bond. In the first mechanism (Scheme 1.7 (a)), the formation of a metal monohydride involves the formation of a transition metal alkoxide followed by β-elimination. Then, insertion of a ketone into the metal hydride bond results in the formation of the corresponding alkoxide. Finally, ligand exchange between alkoxide species and the hydrogen donor (isopropanol in Scheme 1.7 (a)) followed by β-elimination complete the catalytic cycle. In this mechanism the hydride transfer occurs in the inner sphere of the metal. In the second mechanism (Scheme 1.7 (b)), the formation of the metal monohydride involves a concerted pathway with simultaneous transfer α-C-H of the hydrogen donor to the metal and transfer of O-H to the ligand. This involves a single 6-membered transition state. The same transition state is the responsible of the transfer of H^+ from ligand to carbonyl oxygen and M-H to carbonyl carbon of the ketone. It should be noted that the latter mechanism would not involve the intermediacy of a transition metal alkoxide, thus the hydride transfer proceeds through the outer-sphere of the metal.[87] The concerted pathway has been supported by several groups studying Ru-complexes modified with amino alcohols and monotosylated diamines.[88] Recently, a special case of the concerted pathway has been suggested for Ru-pseudo-dipeptide catalysts, which involves the simultaneous transfer of a hydride and an alkali cation instead of a proton.[89]



Scheme 1.7. Hydrogen transfer reactions catalyzed by metal monohydride species (X = O or NTs).

1.2.2. Ligands

Different types of chiral ligands have been reported for transition metal-catalyzed asymmetric transfer hydrogenation.[82] Some of the earliest reported catalytic systems for ATH involved phosphine ligands combined with Ru, Rh or Ir.[90] However, these catalytic systems led to low conversions and enantioselectivities. The first important breakthrough came with the work of Noyori and coworkers in the mid 1990's. They discovered that the monotosylated diamine ligand **86** (**TsDPEN**, Figure 1.28) in combination with Ru-arene complexes lead to excellent catalysts for the asymmetric reduction of a wide range of aryl-ketones (ee's up to 99%).[82e,91] Noyori introduced the term metal-ligand bifunctional catalyst for **TsDPEN**-type catalysts. A key feature of these catalysts is that one of the sites of the ligand acts as a basic center. This basic center is suggested to interact with the alcohol or amine through a hydrogen bond and thereby it facilitates the hydride transfer.[82e,88,91a]

Although in the presence of the Noyori's catalyst (**86**) a large variety of simple aryl alkyl ketones can be smoothly reduced in excellent enanatioselectivities, there are still some limitations. For instance, ketones having a bulky alkyl substituent or *ortho*-substituted acetophenones react slowly, and because of the reversibility of the process when using ^{i}PrOH as H-donor, the enantiomeric purity of the process is deteriored.[82e,91a] In addition, the class of substrates that can be selectively reduced by catalysts containing Ru-arene complexes is limited to aryl ketones. The high selectivity associated with these reactions is ascribed to a stabilizing dipolar interaction between the arene-CH of the catalyst (e.g p-cymene) and the π-system of the substrate.[92] Therefore, the development of new catalysts is still needed. In this respect, the range of successful ligands has been expanded (Figure 1.28) by including other monotosylated diamines (i.e. **87**),[91,93,94] 1,2-aminoalcohols (i.e **88**-**90**),[95] chiral amino-pyridines (i.e **91**),[96] diphosphinites (**92**)[97] and tetradentated P,N,N,P ligands (**93**)[98].

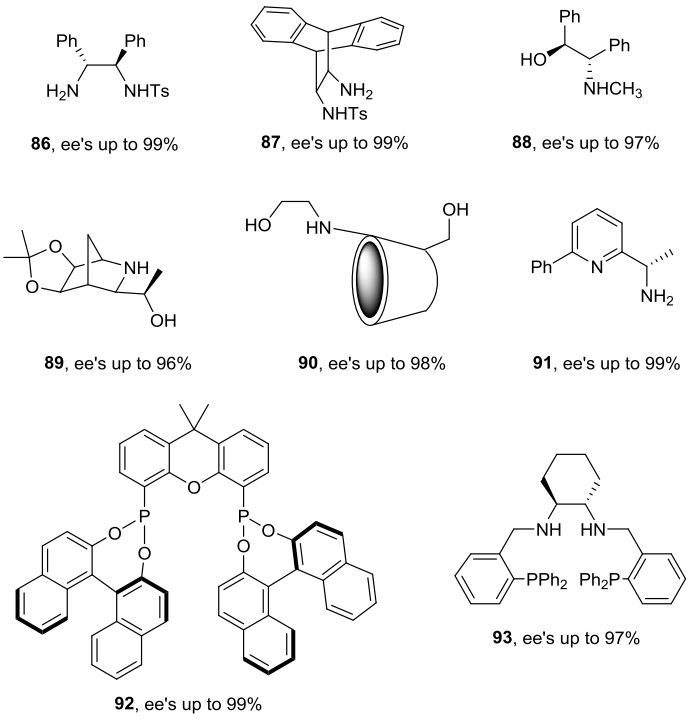


Figure 1.28. Representative chiral ligands developed for ATH reactions.

1.2.2.1. Hydroxyamide/thioamide based ligands

Adolfsson and coworkers have developed a new class of readily accessible pseudo-dipeptides (ligands **94**; Figure 1.29) that are excellent ligands for Ru- and Rh-catalyzed asymmetric transfer hydrogenation of aryl ketones.[89,99] Ligands **94** are synthesized by combining cheap and available *N*-Boc-protected α-amino acids with amino alcohols obtained from the natural and unnatural amino acids. The best performing catalyst for ATH of ketones was found to be the amino acid hydroxyl amide **95** (Figure 1.29) in combination of $[Ru(p\text{-cymene})Cl_2]_2$.[99d,f] It was observed that the amino acid part of the ligand dictates the stereochemical outcome of the reduction reaction, thus allowing the formation of either of the product enantiomers in high enantioselectivities (up to 99% ee).[99d,f] It was also found that the important structural features of pseudo-dipeptide ligands to be successful are: a) to have a base-stable carbamate at the N terminus (e. g. Boc-protection); b) the amide involved in the peptide bond has to be secondary; and c) bearing an unprotected hydroxyl functionality at the C terminus.[89b]

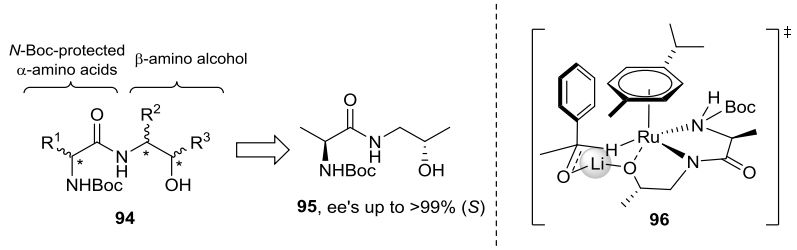
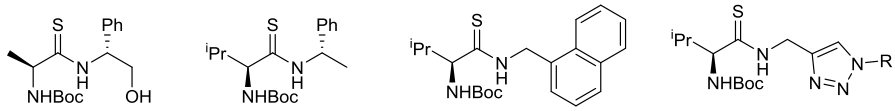


Figure 1.29. Structure of pseudo-dipeptide based ligands **94** and the optimal ligand **95**. This figure also shows the structure of the transition state proposed when LiCl is used (**96**).

The enantioselectivity of this catalytic system was even improved by adding lithium chloride to the reaction mixture. This catalytic behaviour has been explained by the formation of a tight bimetallic transition state, in which the lithium coordinates to both the metal ligand alkoxide and the oxygen of ketone (structure **96**; Figure 1.29).[89] Performing the reaction in a mixture of THF and ^{i}PrOH resulted in higher reaction rates, probably due to an enahance solubility of the various components taking part in the reaction.[89b] These two modifications led to a new protocol that provided higher yields and enantioselectivities up to >99% in the reduction of different aryl ketones.[89b] Unfortunatelly, this methodolgy proved to be less efficient for the reduction of more sterically demanding ketones, which were reduced with high enantioselectivity, albeit in low yields. In this respect, a new protocol has been recently reported in which several sterically hindered ketones can be reduced with ligand **95**, in moderate to high yields (45 - 98%) and with good to excellent ee values (88->99%).[99m] At the same time, another new catalytic protocol for the asymmetric reduction of propargylic ketones has been reported.[99l] Alkynones substituted with aromatic, heteroaromatic, aliphatic, and silyl protecting groups were all tolerated under the reaction conditions to afford propargylic alcohols in good to excellent yields and enantioselectivities (up to 99 % yield an up to >99% ee). Finally, ligand **95** has been also used in two types of tandem reactions involving the ATH process: (a) the ruthenium-catalyzed tandem isomerization/ATH of racemic allylic alcohols into the corresponding enantiomerically enriched saturated alcohols (ee's up to 93%),[99j] and (b) the tandem α-alkylation/asymmetric transfer hydrogenation of acetophenone derivatives with primary alcohols, which results in the corresponding secondary alcohols with an elongation of the alkyl chain (ee's up to 89%).[99k]

The central amide of ligands **94** was converted into the corresponding thioamide with the aim of increasing the acidity of this functionality, and consequently the stability of the catalytically active metal complex.[100] Thioamide ligand **97** (Figure 1.30) was tested in the Ru-catalyzed ATH of acetophenone providing the corresponding alcohol in only 39% conversion and 20% ee of the opposite enantiomer than its corresponding pseudodipeptide. The different catalytic behavior between pseudo-dipeptide and thioamide ligands was attributed to a different coordination manner of each ligand class. While pseudo-dipeptide ligands would coordinate in a tridentate mode, thioamide ligands would coordinate in a bidentate fashion, through the nitrogen and the sulphur atoms (Figure 1.31).[101] After catalyst optimization it was shown that catalytic performance was best without the hydroxyl group in the ligand structure, and using $[RhCl_2Cp^*]_2$ as catalyst

precursor in presence of LiCl. The presence of a bulky group at the α position of the amino acid and an aromatic substituent at the C-terminus further enhance the catalytic performance. Hence, enantioselectivities up to 97% ee were achieved in the reduction of several aryl ketones by using ligand **98** (Figure 1.30).[100] It was observed that ligands containing only one stereogenic centre also provided excellent enantioselectivities in the reduction of different aryl ketones (e.g ligand **99**, Figure 1.30).[101,102] Finally, the aromatic substituent of the C-terminus was substituted by a triazole ring, yielding ligands **100** (Figure 1.30).[103] These ligands showed higher catalytic activities in the reduction of acetophenone rather than previously reported amino acid base ligands. However, the asymmetric induction was somewhat lower (ee's up to 92%).



97, 20 % ee (*R*) **98**, ee's up to 97% **99**, ee's up to 97% **100**, ee's up to 92%

Figure 1.30. Amino acid base thioamide ligands **97**-**100**.

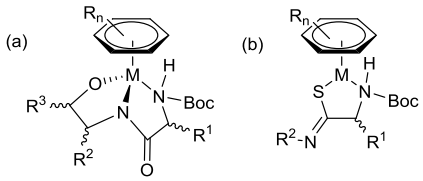


Figure 1.31. Coordination modes of pseudodipeptide (a) and thioamide ligands (b).

Other hydroxyamide ligands have been used in asymmetric transfer hydrogenation of ketones, most of them derived from L-proline. However, all induced lower asymmetric induction than successful ligands reported by Adolfsson and coworkers.[104]

In 2011, our group in collaboration with Adolfsson's group, developed a new class of furanoside pseudodipeptide ligands **101**-**110a** (Figure 1.32) for the enantioselective Ru-catalyzed transfer hydrogenation of ketones.[105] These ligands are related with ligands **94** (Figure 1.28) but the amino alcohol moiety has been replaced by a sugar amino alcohol derived from D-glucose. Interestingly, it was found that the enantioselectivity is controlled exclusively by the sugar moiety, which enables the use of inexpensive achiral or racemic α-amino acid derivatives. It was observed that the configuration of C-3 had no effect in the catalytic performance. As previously observed with ligands **94**, the use of LiCl as an additive had a positive effect on both activity and selectivity (see Figure 1.29). Enantioselectivities from 98 to >99% and high conversions were obtained in the ATH of a wide range of different sterically and electronically substituted aryl ketones. The catalytic performance of ligands **101**-**110a** was even better than in the Ru-catalyzed ATH of ketones with previous successful ligands **94**.

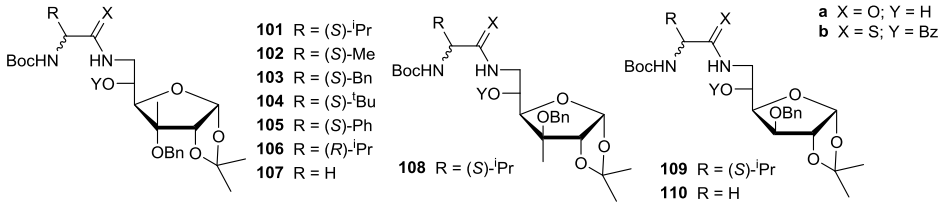


Figure 1.32. Sugar-based pseudodipeptide ligands **101**-**110a** and thioamide ligands **101**-**110b**.

After this breakthrough, ligands **111**-**114a** (Figure 1.33), which contain a 1,3-amino alcohol sugar core instead of the classical 1,2-amino alcohol sugar motif, were prepared and evaluated in the Ru-catalyzed ATH of ketones.[106] Unfortunately, all ligands provided low activities (conversions from 3% to 14%) and enantioselectivities (ee's from 0% to 18%). This catalytic performance was explained by the coordination mode of ligands-type **94** (Figure 1.31; (a)). Upon coordination to the ruthenium center, the new pseudodipeptide ligand library **111**-**114a** forms a six-membered chelate, which is less favoured than when 1,2-amino alcohols are used (which form a more stable five-membered chelate). Thus, catalyst decomposition would take place after only a few turnovers. In order to improve catalytic performance, thioamide ligands **111**-**114b** were synthesized from ligands **111**-**114a** (Figure 1.33), with the aim of obtaining the same coordination mode than with thiomide ligands **97**-**100** (Figure 1.31; (b)). Results were best when using $[RhCl_2Cp^*]_2$ as a metal source. After evaluation of all ligand parameters in the Rh-catalyzed ATH, enantioselectivities up to 99% ee were achieved in the reduction of a broad range of aryl ketones. It should be noted that, in contrast to the previously reported hydroxyamide ligands **101**-**110a**, both enantiomers of the alcohol product can be afforded by simply changing the absolute configuration of the thioamide substituent.

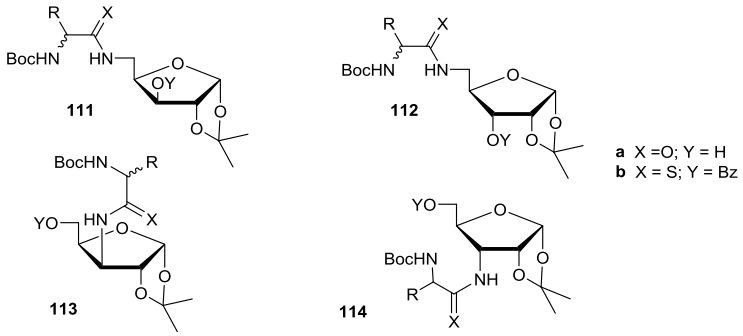


Figure 1.33. D-glucose and D-xylose based pseudodipeptide ligands (**111**-**114a**) and thioamide ligands (**111**-**114b**).

Later, thioamide ligands (ligands **101**-**110b**; Figure 1.32) were synthesized by replacing the oxygen atom with a sulfur atom in the previous ligands **101**-**110a**. As in the case of thioamide ligands **111**-**114b**, the application of new ligands **101**-**110b** in the Rh-catalyzed ATH of acetophenone gave access to both enantiomers of the reduced alcohol with excellent enantioselectivities.[107] Furthermore, the new thioamide ligand library (second generation) allowed to expand the substrate scope which could be reduced with the successful pseudodipeptide ligands **101**-**110a** (first generation). Thus, very challenging

heteroaromatic ketones of industrial interest can be hydrogenated in enantioselectivities up to 99%. Therefore, this new generation of ligands overcomes the limitations of the first-generation of successful ligands **101**-**110a**.

More recently, our group has reported the synthesis and application of a library of pyranoside-based hydroxyamide (**115**-**117a**) and thioamide ligands (**115**-**117b**) (Figure 1.34) in the ATH of ketones.[108] Hydroxyamide ligands **115**-**117a** gave poor catalytic activities using both types of catalyst precursors $[Ru(Cl_2(p\text{-cymene})]_2$ and $[RhCl_2Cp^*]_2$. This catalytic behavior was attributed to the high rigidity of the pyranoside backbone, which hinders its coordination to the metal center. On the contrary, in the previously reported hydroxyamide furanoside ligands **115**-**117a** (Figure 1.32), the amido group is attached to the flexible primary carbon, which allows the perfect coordination of the three groups. Both activity and enantioselectivity were considerably improved when the thioamide ligands **115**-**117** were used in combination of $[RhCl_2Cp^*]_2$ in the reduction of acetophenone (up to 88% conv. and 99% ee). Ligands **115**-**116b**, which contains the thioamide group at the C-2 position, produced better activities and enantioselectivities than ligands **117b**, probably because in these latter ligands there is a higher steric congestion around the metal center. As observed for other thioamide ligands, the sense of enantioselectivity is governed by the absolute configuration of the thioamide substituent. Thus, by changing the absolute configuration of this substituent both enantiomers of the alcohol products were obtained in high enantiopurities. By carefully selecting the ligand components, excellent enantioselectivities (up to >99% ee) were achieved for a wide range of ketones, including the less studied heteroaromatics and challenging aryl/fluoroalkyls. In addition, the efficiency of these Rh-pyranoside-based thioamide catalysts is even higher than their furanoside-based thioamide analogues, since they proved to be more active and enantioselective and tolerate a broader substrate scope.

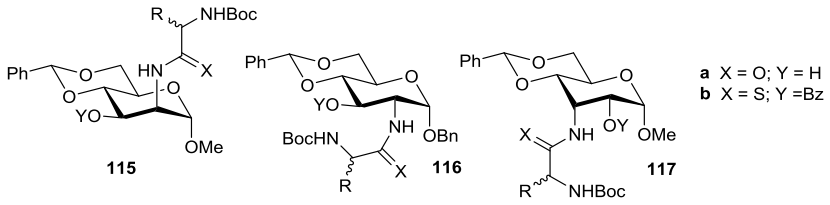


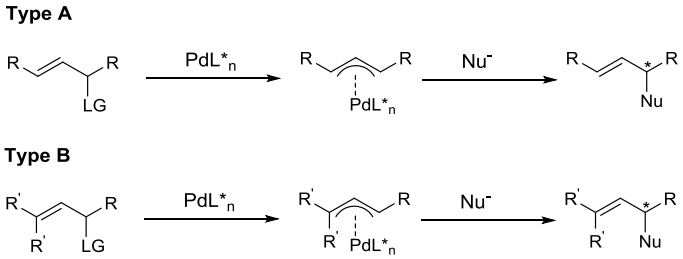
Figure 1.34. Pyranoside-based α-amino acid hydroxamide/thioamide ligands **115**-**117.**

1.3. Asymmetric Pd-catalyzed allylic substitution

Enantioselective Pd-catalyzed allylic substitution is an important synthetic strategy for the construction of asymmetric carbon-carbon and carbon-heteroatom bonds. Besides having a high level of asymmetric induction, the fact that it is tolerant to a wide range of functional groups means that it is an attractive option for application in the synthesis of optically active compounds.[1,38b,109]

In this process, an allylic racemic substrate which contains a leaving group (LG), normally an acetate or carbonate is attacked by a nucleophile (typically a carbon or nitrogen nucleophile). Scheme 1.8 shows two important classes of asymmetric allylic

substitutions depending on the kind of substrate used. Type A reactions start from a racemic substrate (linear or cyclic) and proceed via symmetrical allyl systems. In this case, the enantioselectivity is determined by the regioselectivity of the nucleophilic attack and therefore depends on the ability of the chiral ligand to differentiate between the two allylic termini.[109] In type B reactions, racemic or prochiral substrates with two identical geminal substituents at one of the allylic termini react via the π-allyl intermediate. In this case, enantioselection can occur either in the ionization step, leading to the allyl intermediate, or in the nucleophilic attack step. For these latter substrates, not only does the eantioselectivity of the process need to be controlled, but the regioselectivity is also a problem because a mixture of regioisomers may be obtained.[109]



Scheme 1.8. Asymmetric allylic substitution reaction with two different kind of substrates.

In this reaction, the range of substrates tested (linear or cyclic) is quite wide (Figure 1.35). However, 1,3-diphenylprop-2-enyl acetate **S1** (Figure 1.35) is widely used as a model substrate for testing new ligands. With regard to the metal source, a variety of transition metal complexes derived from Pd, Ni, Ru, Rh, Ir, Mo, W and other elements are known to catalyze allylic substitutions. However, the most widely used catalysts are palladium complexes.[1,109] A wide range of carbon-stabilized nucleophiles bearing carbonyl, sulfone, nitrile or nitro groups have been used in this process, being dimethyl malonate the standard nucleophile for testing new catalysts. There are only few examples of enantioselective reactions with non-stabilized carbon-nucleophiles such as diorganozinc or Grignard reagents. Regarding heteroatom-stabilized nucleophiles, both N- and O-nucleophiles have been used in this process. While several amines such as primary and secondary alkyl amines, aryl amines or nitrogen heterocycles have been extensively employed as nucleophiles, Pd-catalyzed allylic etherification have only been efficiently performed in the presence of phenols. Aliphatic alcohols have found to be poor nucleophiles for such reactions.[109f]

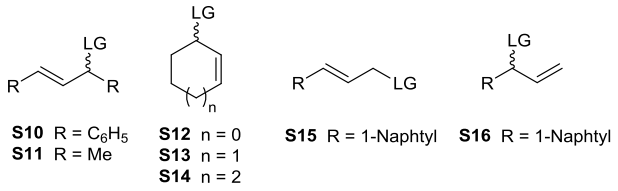
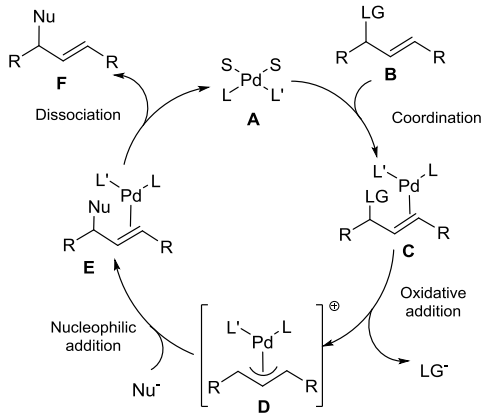


Figure 1.35. The most common substrates used in the enantioselective allylic substitution.

1.3.1. Mechanism

The catalytic cycle for Pd-catalyzed asymmetric allylic substitution with stabilized nucleophiles is well stablished and involves four steps (Scheme 1.9).[109] The first step is the coordination of an allylic substrate **A** to the catalytic precursor **B**, which enters to the cycle at the Pd(0) oxidation level. Both Pd(0) and Pd(II) complexes can be used as precatalysts because Pd(II) is easily reduced in situ by the nucleophile to the Pd(0) form. The most widely used precursors are $Pd_2(dba)_3.dba_2$ (dba = dibenzylideneacetone), $Pd(OAc)_2$ and $[Pd(\eta^3\text{-}C_3H_5)(\mu\text{-}Cl)]_2$. The next step is the oxidative addition of the complex **C** to form the π-allyl intermediate **D**. The product of this oxidative addition has two positions that are susceptible to a nucleophilic attack (C-1 and C-3). After nucleophilic addition, an unstable Pd(0)-olefin complex **E** is produced, which readily releases the final product **F**.[109] The rate-limiting step of this catalytic process can be either the oxidative addition or the nucleophilic substitution, depending on the relative height of their respective transition states. It is known that in the case of 1,3-diphenylated susbstrate **S10**, which forms the more stable Pd π-allyl complex upon oxidative addition, the nucleophilic attack is the rate determining step.[109f]



L,L' = mono or bidentate ligand; S = solvent or vacant; LG = leaving group; Nu = nucleophile

Scheme 1.9. Accepted mechanism for Pd-catalyzed allylic substitutions.

It is accepted, that the enantioselectivity of the process is controlled by the external nucleophilic attack on the most electrophilic allylic carbon terminus of the π-allyl intermediate **D**.[1b,38b,109] Hence, the π-allyl intermediate **D** plays an important role in the catalytic cycle and is the intermediate that controls regio- and enantioselectivity. This intermediate can be isolated in absence of nucleophiles and it is known, that allyl complex type-**D** can show a dynamic behavior in solution, which leads in a mixture of isomers (Figure 1.36). Among the best known process, the $\eta^3\text{-}\eta^1\text{-}\eta^3$ isomerization leads to the *syn*/*anti* interconversion and the apparent "allyl rotation" leads to an *endo*/*exo* isomerisation. The palladium-allyl exchange, although usually slow compared to the other mechanisms, results in an inversion of configuration on all three allyl carbons.[109]

If we assume that the reactions rates are similar for all possible isomers, a single isomer needs to be formed if enantioselectivities are to be high. Both the oxidative

addition and the nucleophilic attack generally occurs stereoselectively with inversion of configuration. Therefore, if the configuration of the intermediate allyl complex is not changed by isomerisation, the overall process **A** to **F** proceeds with retention of configuration; for instance, the nucleophile is introduced on the same side of the allyl plane that was occupied by the leaving group (LG).[110]

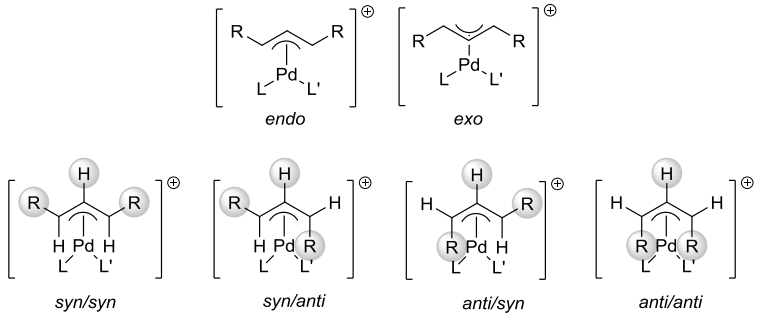


Figure 1.36. Possible isomers adopted by the Pd-allyl complex **D**.

1.3.2. Ligands

Unlike the asymmetric hydrogenation process, few diphosphines have provided good enantioselectivities in allylic substitutions. Though high enantioselectivities can be obtained in certain cases for instance, with **BINAP** and **CHIRAPHOS** (Figure 1.2), the scope of standard diphosphines in this process seems limited.[1,109]

Most of the successful ligands reported to date for this process have been designed using three main strategies. The first one, developed by Hayashi and coworkers, was the use of a secondary interaction of the nucleophile with a side chain of the ligand to direct the approach of the nucleophile to one of the allylic terminal carbon atoms (**118**;Figure 1.37).[110] The second one, delevoped by Trost and co-workers, was to increase the ligand's bite angle in order to create a chiral cavity in which the allyl system is perfectly embedded (**119**; Figure 1.37). This idea paved the way for the successful application of ligands with large bite angles for the allylic substitution of sterically undemanding substrates.[111] Despite historically this rationalization has being generally accepted, recently, Norrby in conjunction with Lloyd-Jones has found out another explanation of the enantiocontrol achieved with Trost's ligand, by exploring the nucleophilic attack of malonate to the corresponding Pd-allyl complex, using DFT calculations.[112] Such calculations prove the existence of an H-bonding interaction between the enolate oxygen of the malonate and the amide NH on the concave surface of Pd-allyl complex, directing the nucleophilic attack to one of the two allylic termini. Therefore, the enantiocontrol obtained with Trost's ligand (**119**) would be also consequence of an interaction between the nucleophile and the ligand, as in the case of Hayashi's ligand (**118**), and not just because of the chiral cavity provided by the ligand scaffold. Regarding the third strategy, developed by Helmchen's, Pfalz's and Williams' groups, the use of heterodonor ligands results in an electronic discrimination of the two allylic terminal carbon atoms due to the different *trans* influences of the donor groups (Figure 1.37).[113] This made it possible to successfully use a wide range of heterodonor ligands (mainly P,N-ligands) in allylic substitution reactions.[1,109] More recently,

we found that the use of biaryl phosphite-containing heterodonor ligands is highly advantageous by overcoming the most common limitations of this process, such as low reaction rates and high substrate specificity.[114,115] Introducing a phosphite in the ligand design was beneficial because of its large π-acceptor ability, which increases reaction rates, and because of its flexibility that allows the catalyst chiral pocket to adapt to both hindered and unhindered substrates. In addition, the presence of a biaryl phosphite moiety was also beneficial in the allylic substitution of more challenging monosubsituted substrates. Regioselectivity towards the desired branched isomer in this substrate class increases thanks to the π-acceptor ability of the phosphite moiety, which decreases the electron density of the most substituted allylic terminal carbon atom via the *trans* influence, favoring the nucleophilic attack to this carbon atom.[114]

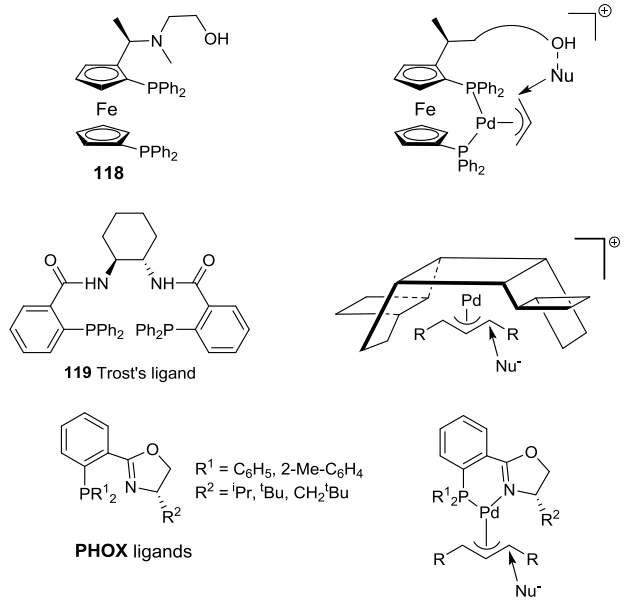


Figure 1.37. Representative ligands developed for the Pd-catalyzed allylic substitution reaction.

Following the third strategy, several mixed bidentate donor ligands (P-N[109,115,116], P-S[4,117], N-S[4,118] and P-P'[21c,119]) have been developed for Pd-allylic substitution reactions. In the following sections we collect the most successful applications of P-N and P-S ligands for this catalytic process.

1.3.2.1. Phosphorus-nitrogen ligands

Inspired by the early work done by Pfaltz, Helmchen and Williams, several successful phosphorus-oxazoline ligands have been developed for this process. Later, the oxazoline moiety has been replaced with other sp^2- and also sp^3-nitrogen donor groups. Figure 1.38 shows the most representative successful ligands reported to date for asymmetric Pd-catalayzed allylic substitutions.

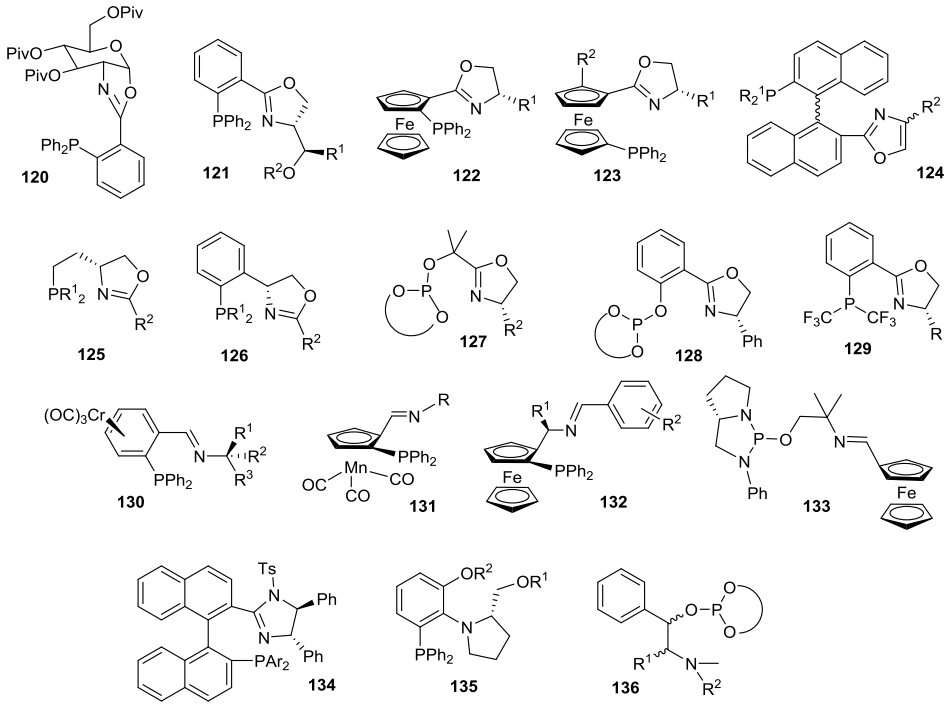


Figure 1.38. Selected successful P,N-ligands applied in the asymmetric Pd-catalyzed allylic substitution reaction.

Modification on the substituent of the oxazoline ring led to ligands **120**[120] and **121**[121] (Figure 1.38). Both ligands provided similar high enantioselectivities than **PHOX** ligands in the Pd allylic substitution of model substrate **S10** (up to 98 % and up to >99% ee, respectively). However, only moderate enantioselectivities were obtained in the allylic substitution of less sterically demanding substrates such as linear substrate **S11** (ee's up to 69% with ligand **120**) or cyclic susbstrate **S13** (ee's up to 59% with ligand **121**).

A ferrocenyl substituent at the oxazoline ring was introduced in ligands **122**[122] and **123**[123] (Figure 1.38) instead of a phenyl ring. Both ligand families provided excellent results in the Pd-allylic alkylation of model substrate **S10** with dimethyl malonate (ee's up to 99% ee and up to 95% ee, respectively). The authors found that the planar chirality is decisive in exerting control over both absolute configuration and enantiomeric excess.

The groups of Ikeda and Pregosin developed ligands **124** by introducing an enantiomerically pure binaphtyl moiety (Figure 1.38).[124] These ligands provided excellent enantioselectivities (ee's up to 97%) in the test reaction. The authors found that the configuration of the substituted product was mainly determined by the configuration of the binaphtyl moiety.

Phosphine-oxazoline ligands **125**[125] and **126**[126] (Figure 1.38) were also successfully applied in the Pd-allylic alkylation reaction of model substrate **S10** (ee's up to 98%). Ligand **125** also provided promising enantioselectivties in the allylic substitution of unhindered substrate **S11** (ee's up to 80%) and the cyclic substrate **S13** (ee's up to 79%).[125]

Phosphite-oxazoline ligands **127** (Figure 1.38) were designed to overcome the problem of regioselectivity in the allylic alkylation of monosubstituted linear substrates.[127] An excellent combination of regioselectivities (up to 95%) towards the desired branched isomer and enantioselectivties (up to 94%) were achieved. Despite this success these ligands produced moderate results for hindered (ee's up to 60% for **S10**) and unhindered (ee's up to 70% for **S13**) disubstituted substrates.

With the aim of finding more versatile phosphite-oxazoline ligands, a decision was made to take one of the most successful ligand families for this process (**PHOX** ligands, Figure 1.38), and replace the phosphine group by a bulky diphenyl phosphite moiety (ligands **128**; Figure 1.38).[128] The application of these ligands in the asymmetric Pd-catalyzed allylic substitution was very successful. Excellent activities (TOF's > 2400 $(h)^{-1}$), regio (up to 99%) and enantioselectivties (ee's up to >99%) were obtained for hindered and unhindered disubstituted and also monosubstituted substrates. Very recently, the range of substrates and nucleophiles used with ligands **128** has been expanded, maintaining the excellent enantioselectivities. Furthermore, experimental and theoretical studies showed that ligands **128** are able to tolerate a wide substrate scope due to their ability to adapt the size of the substrate-binding pocket to the reacting substrate, since the coordinated ligand in all reactions adopts the *Sa*,*S* configuration.[115e]

After this breakthrough, other biaryl phosphite-oxazoline ligands have been developed. For instance, ligands **26**[129] and **27** (X = O)[130] (Figure 1.12) have been efficiently applied in the Pd-catalyzed allylic substitution of a broad range of mono- and disubstituted hindered and unhindered linear and cyclic substrates. The replacement of the oxazoline moiety in ligands **27** by a thiazoline ring (ligands **27**, X = S; Figure 1.12) has expanded the range of unhindered allylic substrates that can be efficiently catalyzed with this ligand family.

Recently, the strong π-accepting ligands **129** (Figure 1.38) have also provided high regioselectivities (up to 96%) and enantioselectivities (up to 94%) in the Pd-catalyzed alkylation of monosubstituted allyl substrates.[131]

Other sp^2-nitrogen donor groups have also been incorporated in heterodonor P,N-ligands. In this respect, several phosphorus-imine ligands have been developed and showed to be efficient in Pd-allylic substitution reactions. For instance, enantioselectivities up to 98% ee were obtained with ligands **130**-**133** (Figure 1.38) in the Pd-alkylation of model substrate **S10**.[132] More recently, phosphine imidazoline ligands have been also developed. For example, ligand **134** (Figure 1.38) provided high yields and enantioselectivities in the substitution of **S10** with dimethyl malonate and 1-fluorobis-(phenylsulfonyl)methane (ee's up to 96% and 98%, respectively).[133] P,N-ligands containing a pyridine group as sp^2-N donor group have also been developed (see section 1.3.2.1.1).

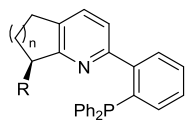
Finally, sp^3-nitrogen containing ligands have been also applied in the Pd-allyic alkylation reaction with great success. Generally, all these ligands have provided high enantioselectivities (ee's up to 99%) in the Pd-allylic alkylation of model substrate **S1** (e. g. ligands **135**,[134] Figure 1.38). Very recently, ligand **136** (Figure 1.38) has been proved to be very efficient in the Pd-catalyzed allylic substitution of several substrate types (hindered and unhindered) with a wide range of C-, N- and O- nucleophiles (enantioselectivities up to 99%).[115d]

1.3.2.1.1. Phosphorus-pyridine ligands

The incorporation of a pyridine group instead of an oxazoline moiety is an alternative for synthesizing more robust P,N-ligands. Although this ligand class has been less studied rather than oxazoline containing ligands, there are some examples in the literature of their application in the asymmetric Pd-catalyzed allylic substitution.

Phosphine-pyridine ligands

In 1999, phosphine-pyridine ligands **137** were developed for the Pd-catalyzed allylic alkylation reaction.[135] Palladium complex of ligand **137b** was found to be an effective catalyst for the alkylation of 1,3-diphenylated (98% ee) and 1,3-dimethylated (96% ee) substrates.



137

a n = 1; R = Ph
b n =1; R = ^{i}Pr
c n = 1; R = $CMe_2OSiMe_2{}^{t}Bu$
d n = 2; R = Ph
e n =2; R = ^{i}Pr
f n = 2; R = $CMe_2OSiMe_2{}^{t}Bu$

Figure 1.39. Phosphine-pyridine ligands **137**.

Phosphine-pyridine ligands **28**-**29a** (Figure 1.13) were also applied in the Pd-catalyzed allylic substitution.[61b] These ligands were used in the alkylation and amination of the standard substrate **S10**, providing good yields and enantioselectivities (96% ee and 87% ee, respectively).

Ligands **34** (Figure 1.15) were evaluated in the Pd-catalyzed allylic alkylation of model substrate **S10** with different nucleophiles.[64] The alkylated products were afforded in high yields and enantioselectvities up to 95% ee.

[2,2]-Paracyclophane derived ligands **138a**-**b** possessing planar chirality have also been investigated in the model Pd-alkylation reaction.[136] Chelate P,N-type π-allylpalladium and P,P-type π-allylpalladium species involving two molecules of the ligand were detected to be in equilibrium. Palladium-complex with ligand **138b** was found to be more stable due to the formation of a more flexible six-member chelate ring. However, although ligand **138b** induced higher enantioselectivities than ligand **138a**, only a maximum of 58% ee was obtained. Later, with the idea of tuning structural flexibility and rigidity, ligands **139**-**140**, which are also derived from [2,2]-paracyclophane, were designed and synthesized. These ligands were tested in the Pd-alkylation of **S10** using dimethyl malonate.[137] High yields and enantioselectivities (i. e. 99% yield, 97% ee) were observed while using ligands bearing matched planar and central chirality.

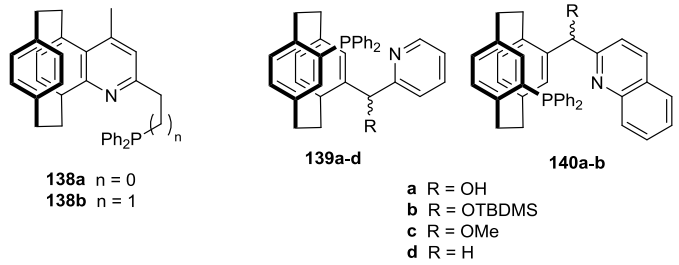


Figure 1.40. [2,2]-paracyclophane derived ligands **138-140** possessing planar chirality.

Phosphinite-pyridine

As far as we know only one phosphinite-pyridine ligand family have been applied in the asymmetric Pd-catalyzed allylic substitution. Ligands **41** (Figure 1.19) were applied in the alkylation of the model substrate **S10** with dimethyl malonate, achieving enantioselectivities up to 95% ee.[70] *Trans*- and *cis*-ligands **41** all gave the product with the same configuration. It was suggested that the absolute configuration of the product was controlled by the configuration of the stereogenic pyridyl-bearing carbon of the ligands.

Phosphite-pyridine ligands

Two families of phosphite-pyridine ligands have been developed and applied in this catalytic process. The first one is composed by ligands **141**-**144** (Figure 1.41).[138] The addition of BuLi was needed in order to achieve high enantioselectivities (ee's up to 95%) in the alkylation of model substrate **S10** with different nucleophiles. However, the alkylation of the less sterically demanding substrate **S13** proceeded in lower yield and enantioselectivity (ee's up to 80%). Results indicated that the configuration of the substituted products is highly controlled by the configuration of the chiral piridyl alcohol.

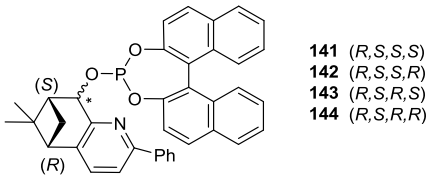


Figure 1.41. Phosphite-pyridine ligands **141**-**144**.

The previously mentioned ligands **47**-**54** (Figure 1.23) were successfully applied in asymmetric allylic substitution reaction.[115b] It was found that the introduction of an enatiopure biaryl phosphite moiety is crucial for achieving high enantioselectivities. Hence, by correctly chosing the ligand components, high enantioselectivities were achieved in the substitution of several di- and trisubstituted substrates with several C-, N- and O-nucleophiles, including the less studied α-substituted malonates, β-diketones and alkyl alcohols. Of particular note were the high enantioselectivities (up to >99%) and high activities obtained for trisubstitued substrates. The potential application of allylic substitution by using functionalized malonates was demonstrated by the practical synthesis

of chiral carbocyclic compounds using a simple sequential allylic alkylation and ring-closing metathesis reactions.

1.3.2.1.2. Phosphorus-triazole ligands

As previously mentioned, 1,2,3-triazoles are of interest for the synthesis of P,N-ligands tue to their simple and benign preparation. However, there are only two reports of the application of triazole containing P,N-ligands in Pd-catalyzed allylic substitutions. In 2007 ligands **145** and **146** (Figure 1.42) were evaluated in the asymmetric Pd-catalyzed allylic alkylation of model substrate **S10** with dimethyl malonate.[139] Ligand **145** afforded the substituted product in moderate enantioselectivity (79% ee), while ligand **146** was not effective for the reaction, giving the product in low enantipurity (10% ee).

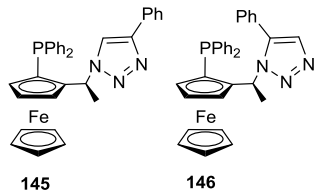


Figure 1.42. Triazole-phosphine ligands **145** and **146**.

Later, phosphine-triazole ligands **148** (Figure 1.43) were synthesized with the aim of supporting phosphinoimidazoline **147** (Figure 1.43) onto polymer supports for easy recovery and recycling. However, the application of new ligands **148** in allylic substitution reactions showed an improved enantioselectivity with respect to analogous ligands lacking the triazole unit (up to 99% ee vs 80% ee). A combined NMR and DFT study showed that these P,N-ligands most likely coordinate to palladium through the triazole N-3 nitrogen atom. The performance of these ligands was also examined in the alkylation of trisubstituted acetates with dimethyl malonate (up to 99%) and in the amination of substrate **S10** with different N-nucleophiles (up to 99%).

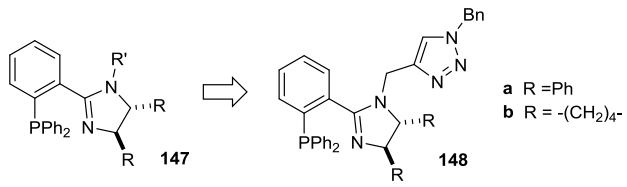


Figure 1.43. Phosphinoimidazoline ligands **147** and phosphino-triazole ligands **148**.

1.3.2.2. Phosphorus-thioether ligands

Although P-S ligands have been less studied compared with P-N ligands, there are some successful examples of their application in the literature. In the next section, the most successful P-S ligands reported to date will be discussed.

Phosphine-thioeter ligands

Among all the combinations of P-S ligands that have been tested in enantioselective Pd-catalyzed allylic substitutions (e.g. phosphine-thioethers, phosphinite-thioethers or phosphite-thioethers), phosphine-thioether ligands have been the most widely studied. In

particular, several chiral phosphine-thioether ferrocene based ligands has been developed for this process.

The first example of the application of phosphine-thioether ligands containing a ferrocenyl moiety in the Pd-allylic alkylation to the model substrate **S10** was developed by Albinati and Pregosin (Figure 1.44) in 1996.[140] Ligand **149** bearing a thyoglicose funcionality afforded the alkylated product with an enantioselectivity of 88%. Changing the carbohydrate substituent for a cyclohexyl (**150a**) or an ethyl group (**150b**) (Figure 1.44) resulted in a dramatic decrease in the enantioselectivity (67% ee and 34% ee, respectively). Additionally, the replacement of the ferrocene group by a phenyl ring on ligands **151a**-**b** (Figure 1.44) resulted in a low asymmetric induction (ee's up to 64%).[141] Thus, the combination of the two stereogenic fragments was crucial for achieving good levels of enantioselectivity. Low enanantiomeric excesses were also obtained with a similar thioether-phosphine ligand **152** using a stereogenic norborneol fragment (Figure 1.44), but the authors attributed their catalytic performance to the chain size between the sulphur donor and the stereogenic unit.

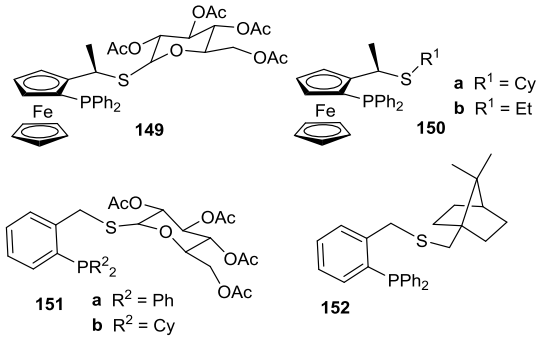


Figure 1.44. Chiral phosphine-thioether ligands **149**-**152**.

The catalytic results using ferrocenyl phosphine-thioether ligands **153**-**157** (Figure 1.45) indicated that enantioselectivity is better when the phosphine group is attached to the Cp ring (ligands **153**-**155**) rather than when is attached to the thioether unit (ligands **157** and **157**) (Figure 1.45). Furthermore, by comparing ligands **153**-**155**, it can be seen that enantioselectivities are not affected by the presence of an additional stereogenic unit or by the length of the thioether chain (Figure 1.45). The structural studies of a 1,3-diphenylallyl palladium complex containing ligand **153a**, [Pd(η^3-1,3-PhC_3H_3Ph)(**153a**)]PF_6, indicate that the small substituents on thioether groups favor the nucleophilic attack in the *cis* position to the S-donor moiety (Figure 1.45).[142]

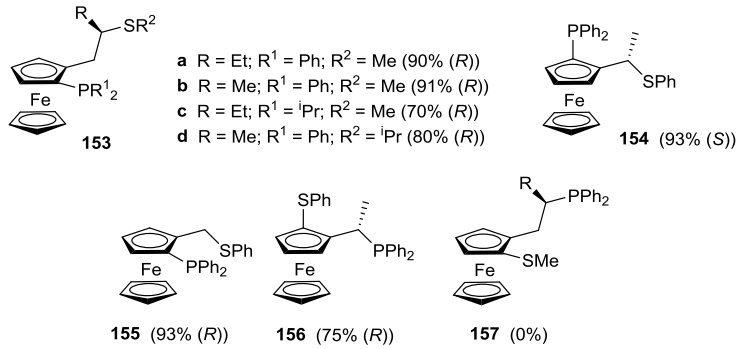


Figure 1.45. Ferrocenyl thioether-phosphine ligands **153**-**157**. This figure also shows the enantioselectivities obtained in the Pd-catalysed asymmetric allylic alkylation of dimethyl malonate to **S10**.

Carretero et. al. reported a readily available family of enantiopure phosphine-thioether ferrocenes (Figure 1.46), having exclusively planar chirality. Ligands **158** and **159** were efficiently applied in the palladium-catalyzed allylic substitution of the model substrate **S10** (ee's up to 97%).[143] Catalytic results showed that ligands **158b**-**c** containing electronwithdrawing phosphines (Figure 1.46) provided high enantioslectivities in significantly shorter reaction times (20 min). A less sterically demanding thioether substituent in ligand **159** (Figure 1.46) resulted in a dramatically drop of the enantioselectivity (40% ee). Ligands **158** and **159** were also applied in the Pd-catalyzed allyllic amination achieving the best ee's with ligands **158f**-**g** containing bulky phosphines (Figure 1.46) (ee's up to 99.5%). The authors also performed X-ray diffraction analyses and NMR studies of the Pd-allyl intermediates, proving the formation of a P,S-bidentated ligand and explaining the enantioselectivity obtained. It was concluded that the nucleophilic attack takes place *trans* to the phosphorus donor atom and the bulky thioether substituent plays an important role in enhancing the reactivity of the *endo*/*exo* intermediate that gives the obtained product enantiomer.

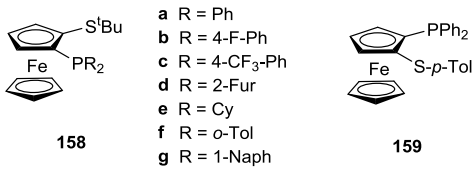


Figure 1.46. Ferrocenyl thioether-phosphine ligands **158** and **159** developed by Carretero et. al..

Recently, a new class of ferrocenyl phosphine-thioether ligands with heterocyclic scaffolds has been reported by Chan and coworkers (Figure 1.47). Ligands **160**-**161** were initially applied in the enantioselective Pd-catalyzed indole alkylation of the 1,3-diphenylated substrate **S10**, achieving enantioselectivities up to 96% with ligand **161**, irrespective of the steric and electronic nature of indoles.[144] Later, ligands **160**-**162** (Figure 1.47) were applied in Pd-catalyzed allylic alkylation reactions using several malonate nucleophiles, providing enantioselectivities up to 96% ee with ligand **161**. Privileged ligand

161 was also examined in the Pd-allylic alkylation of cyclic allylic acetates and unsymmetrical allylic substrates, obtaining enantioselectivities up to 87% ee.[145]

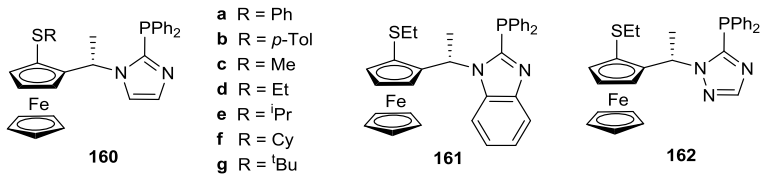


Figure 1.47. Phosphine-thioether ligands **160**-**162** based on ferrocene and heterocyic scaffolds.

A novel phosphine-thioether ligand family based on a triazoleferrocenylethyl backbone was synthesized and applied in Pd-catalyzed allylic alkylations, etherifications and aminations. **ThioClickFerrophos** ligands **163a**-**f** (Figure 1.48), in which the thioether moiety is directly attached to the ferrocene unit, were screened in the Pd-catalyzed allylic alkylation of substrate **S10** using dimethyl malonate. The best enantioselectivities were obtained with ligand **163e** (up to 90% ee). It should be pointed out that ligand **163e** was able to efficiently catalyze the etherification between substrate **S10** and different electronically substituted benzyl alcohols (ee's and yields ranging from 74 to 82% and from 85 to 99%, respectively).[146]

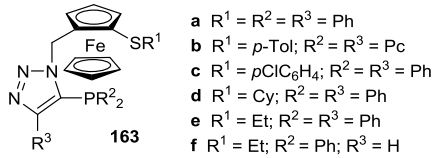


Figure 1.48. ThioClickFerrophos ligands **163**.

The axially chiral 1-1'-binaphtyl backbone has been also widely used in the ligand design for the asymmetric Pd-catalyzed allylic substitution reaction. Phosphine-thioether ligands **BINAPS 164a**-**d** (Figure 1.49) derived from enantiopure **BINOL** have been reported by Kang[147], Gladiali[148] and Shi[149] with different alkyl groups on the sulfur atom. Kang and co-workers reported 91% ee for the product of usual allylic alkylation test by using ligand **164a**. Gladiali tested the isopropyl derivative **164b**, which led to the corresponding compound in quantitative yield in 60% ee. Shi obtained 77% and 33% ee, respectively, by using ligands **164c** and **164d**. Interestingly, they obtained a reversal of enantioselectivity between ligands **164a**, **164c**, and **164b**, **164d**. X-ray analyses and NMR studies confirmed a P,S-coordination as a metallocyle in a pseudo-boat-seven-membered arrangement. The steric bulkiness of alkyl groups on the sulfur atom seems to be responsible for the observed reversal of enantioselectivity by favoring one or the other diastereomeric π-allyl complex. Recently, Hagiwara and coworkers have reported for the first time the synthesis of the aryl-thioether substituted **BINAPS** ligands **164e**-**h** and their alkyl counterpart **164i**.[150] After a first examination of ligand **164e** in the test reaction with **S10** (90% yield, 95% ee), ligands **164e**-**i** were tested in the enantioselective Pd-catalyzed allylic alkylation of indoles. Tunning of the structural properties of the sulfur substituent was an effective stereocontrol tactic. Therefore, **164f** provided enantioselectivities up to 95% using different sterically and electronically substituted indoles.

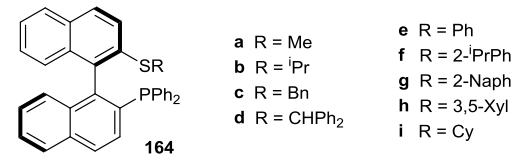


Figure 1.49. Phosphite-thioether **BiNAPS** ligands **164**.

Very recently, the synthesis of another axially chiral thioether-phosphine ligand has been reported.[151] Ligands **165** (Figure 1.50), containing an enantiopure biphenyl backbone, have been applied in the asymmetric Pd-catalyzed allylic substitution of model substrate **S10** using dimethyl malonanate and indole as nucleophiles. These ligands showed in both cases comparable efficiency with regard to their binaphtyl homologues (**164**) above mentioned (ee's up to 94% were obtained with ligands **165**).

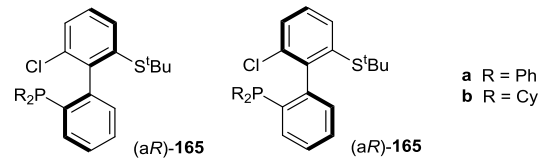


Figure 1.50. Axially chiral biphenyl-based phosphine-thioether ligands **165**.

Nakano and Hongo were the first to test the ability of oxathiane-type ligands to perform Pd-catalyzed allylic substitutions. They initially synthesized ligands **166**-**168** (Figure 1.51) and successfully used them in alkylation and amination reactions of substituted allyl acetates. Norbornane-based phosphine-oxathiane ligand **166** gave the highest level of enantioselectivity (ee's up to 94%) in the test reaction. Ligand **166** was also useful in the analogous allylic amination with either benzyl amine or potassium phtalamide providing enantioselectivities up to 90%.[152] Later, taking into account the good catalytic performance obtained with ligand **166**, Nakano et. al reported a novel polymer-supported P-S type ligands **169a**-**e** (Figure 1.51) and applied them in Pd-catalyzed asymmetric alkylations and aminations. Excellent enantioselectivities were obtained in both processes (up to 96 ee% in alkylation reactions and up to 99% ee in amination reactions).[153] Additionally, the same authors developed a new xylofuranoside-based phosphinoxathiane ligand **170** (Figure 1.51), that provided also high enantioselectivities in the enantioselective Pd-catalyzed allylic substitution of **S10** (ee's up to 91%).[154]

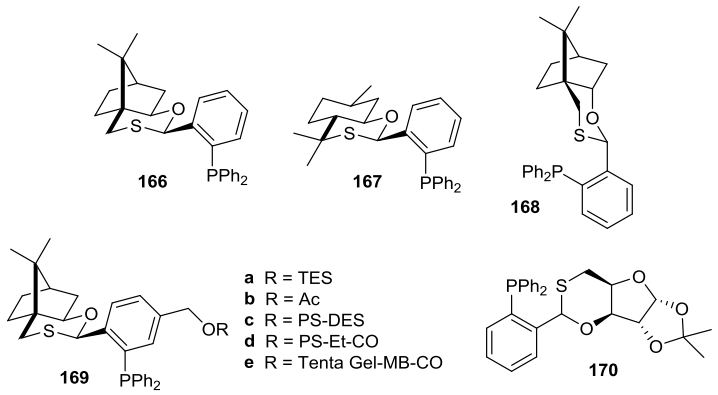


Figure 1.51. Phosphinooxathiane ligands **166**-**170**.

Cyclopropane-based phosphine-thioether ligands **17**-**19** (Figure 1.9) and related ligands **171**-**175** (Figure 1.52) were applied in the palladium-catalyzed allylic alkylation of **S10** with dimethyl malonate. Varying the ligand substituents on the phosphorus, sulfur and carbon chain revealed ligand **18** (Figure 1.9) to have the optimal configuration for this reaction, giving the product in high yield and with good enantioselectivity (93% ee).[29]

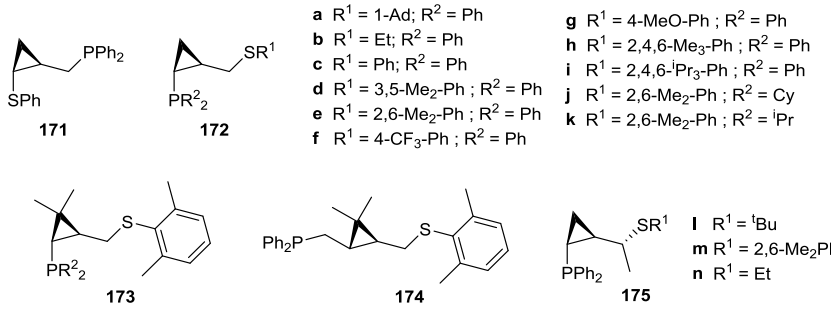


Figure 1.52. Cyclopropane-based thioether-phosphine ligands **171**-**175**.

A series of (*S*)-proline-derived phosphine ligands bearing thioether and selenoether functionalities (**176**-**180**; Figure 1.53) were prepared and used in the test Pd-catalyzed asymmetric allylic alkylation. It was observed that an increase of the steric hindrance around the sulfur atom in ligands **178a**-**g** resulted in higher values of enantioselectivity, with a maximum of 88% ee for the ligand bearing a sterically hindered naphtyl group (**178g**). It should be noted that ligands **177** and **179**, bearing a selenium atom instead of sulfur, also induced good levels of enantioselectivities (ee's ranging from 79% to 86%).[155]

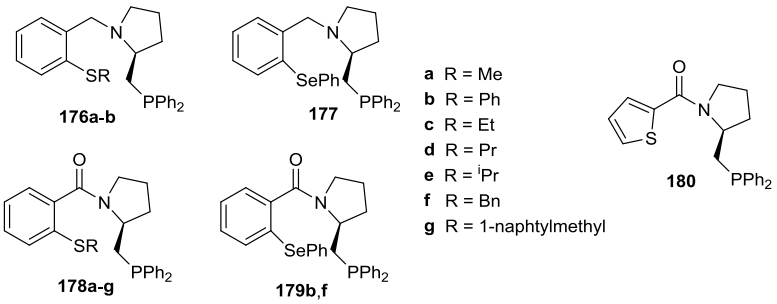


Figure 1.53. (*S*)-Proline-derived chiral ligands **176**-**180**.

Two families of *P*-chirogenic phosphine-thioether ligands have been developed for the asymmetric Pd-catalyzed allylic substitution process. The first one was reported in 2001 by Imamoto and coworkers (ligands **181**, Figure 1.54).[156] By changing the substituents on the phosphorus and sulfur atoms, ee's up to 90% were obtained in the model reaction using different malonates. Very recently, a second family of *P*-chirogenic phosphine-sulfide has been developed (ligands **182**, Figure 1.54).[157] Ligands **182** have been applied in the Pd-catalyzed allylic alkylation of substrates **S10**, **S11** and **S13** (Figure 1.35). Excellent enantioselectivities were achieved in the alkylation of model substrate **S10** (ee's up to 96%). In contrast, low-to-moderate enantioselectivities were obtained in the case of the more challenging substrates **S11** and the **S13** (ee's up to 66% and up to 34%, respectively). These ligands have been also applied in the Pd-catalyzed allylation of benzyl amine, leading to the *N*-benzyl product with enantioselectivities ranging from 37% to 89% ee. In all cases enantioselectivity was strongly dependent upon the substituents on the phosphorus atom and significantly less dependent upon those on the sulfide moiety.

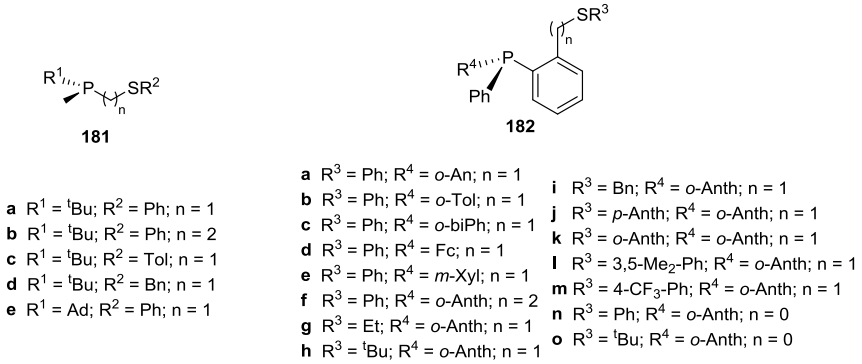


Figure 1.54. *P*-chirogenic phosphine-thioether ligands **181** and **182**.

Phosphinite-thioether ligands

The first application in the Pd-catalyzed allylic substitution of a family of mixed thioether-phosphinite ligands was reported by Evans and coworkers.[158] Ligands **2**-**4** (Figure 1.4), also applied in the Rh-catalyzed hydrogenation of enamides,[24] and related ligands **183**-**188** (Figure 1.55) were successfully applied in the allylic substitution of several linear and cyclic substrates. After a systematic variation of the ligand substituents at sulfur,

phosphorus, and backbone, ligands **2g** and **3g** were found to be optimal in the Pd-catalyzed allylic substitution of **S10** with dimethyl malonate and benzyl amine in high yield and excellent enantioselectivities (91-98% ee) (Figure 1.56). Hence, ligand **3g** contains a bulky substituent in both backbone and thioeher group that controls the sulfur inversion. A similar optimization of the ligand structure for the Pd-catalyzed allylic substitution of cycloalkenyl acetates showed that **186c** afforded the highest enantioselectivities (91-97% ee) (Figure 1.57). Moreover, sulfur and nitrogen containing heterocyclic substrates underwent enantioselective allylic alkylation and amination using ligand **186c** to afford 3-substituted piperidines and dihydrothiopyrans in enantioselectivities up to 94% ee(Figure 1.57). The regioselective allylic alkylation of trisubstituted propenyl acetates was also explored with ligands **2g** and **3g**, affording high yields and asymmetric induction up to 94% ee (Figure 1.56). The authors could furthermore prove the contribution of sulfur in the coordination of the palladium by X-ray analysis of crystals of these organometallic complexes.

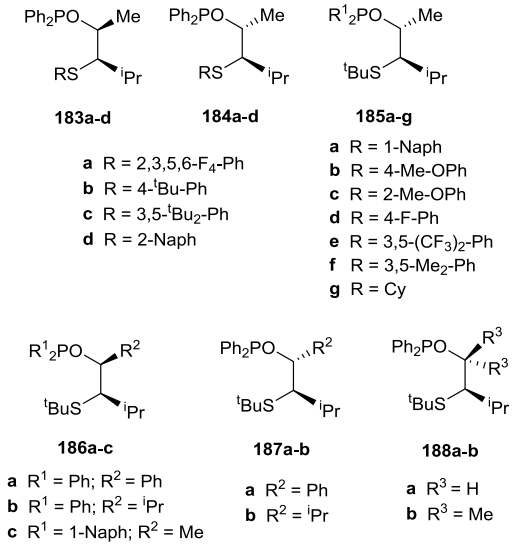


Figure 1.55. Phosphinite-thioether ligands **183**-**188** developed by Evans and coworkers.

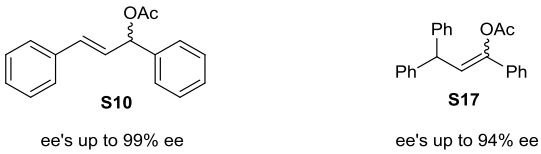


Figure 1.56. Summary of the best results obtained by using ligands **2**-**3g** in the Pd-allylic alkylation and amination of symmetrical and unsymmetrical linear substrates **S10** and **S17**.

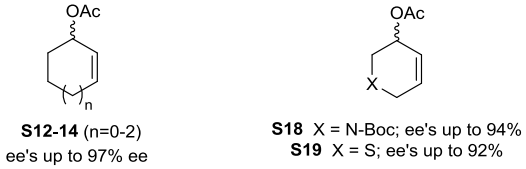


Figure 1.57. Summary of the best results obtained by using ligands **186c** in the Pd-allylic alkylation and amination of cyclic and heterocyclic substrates **S12**-**S14** and **S18**-**S19**.

The series of above mentioned furanoside phosphinite-thioether ligands **5** (Figure 1.5) and ligands **189** (Figure 1.58) bearing a wider variety of thioether susbtituents, were applied in the Pd-catalyzed allylic substitution of mono- and disubstituted linear and cyclic substrates (ee's up to 95%).[159] These ligands contained several thioether substituents with different electronic and steric properties. The authors found that this substituent has an important effect on catalytic performance. Enantioselectivities were best when the bulkiest ligands **5c** and **189a** were used.

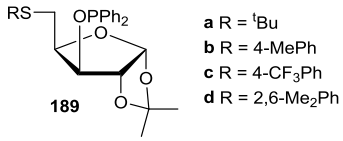


Figure 1.58. Phosphinite-thioether ligands **189** with a furanoside backbone.

At the same time, the phosphinite-thioether ligands **6** and **7** with a pyranoside backbone (Figure 1.6) were successfully applied in the Pd-catalyzed allylic substitution of 1,3-diphenylprop-2-enyl acetate (ee's up to 96%). Highest enantioselectivities were obtained when bulky *tert*-buthyl group was present in the thioether moiety. Both enantiomers of the products were obtained by using ligand **7b**.[26a,b,160]

More recently, Pericàs and coworkers applied the previously mentioned phosphinite-thioether ligands **9a**-**n** (Figure 1.7) and related ligands **190a**-**f** and **191a**,**e** (Figure 1.59), to Pd-catalyzed allylic substitution reactions.[161] After an iterative optimization of four different structural parameters (the skeletal aryl group, the thioether substituent, the ether moiety and the relative configuration of the chiral centers), highly active and enantioselective ligands were identified. In this way, ligands **190a** and **191b** provided excellent enantioselectivities in the reaction of **S10** using dimethyl malonate (up to 99%), benzyl amine (up to 95%), and a much less common O-nucleophile, such as benzyl alcohol (up to 94%), in very short reaction times (20 min-4h, 2h-16h and 3h, respectively).

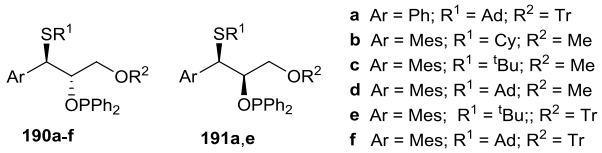
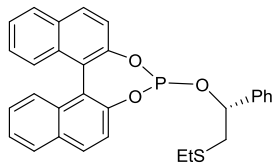


Figure 1.59. Arylglicidol derived thioether-phosphinite ligands **190** and **191**.

Phosphite-thioether ligand

Several combinations of P-S ligands, mainly phosphine thioether and phosphinite-thioether, have been studied and proven to be effective, but less attention has been paid to catalysts containing phosphite-thioether ligands.

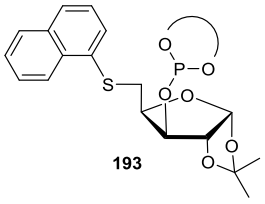
The first one was the binaphtylphosphite-thioether ligand **192** (Figure 1.60), reported by Pregosin and coworkers. Yields up to 70% were reached, but in all cases, both the regio- and enantioselectivities were moderate.[162]



192

Figure 1.60. Binaphtylphosphite-thioether ligand **192**.

In 2001 thioether-phosphite ligands **56**-**58a** and **56d** with a furanoside backbone (Figure 1.25) were applied in the Pd-catalyzed allylic alkylation and amination substitution reactions providing only moderate enantioselectivities (up to 58% and 67% ee, respectively).[163] It was not until 2014 that the high efficiency of this sugar-based backbone has been demonstrated in this catalytic process. Ligands bearing bulkier thioether substituents (**62**, Figure 1.25; **193**, Figure 1.61) and enantiopure biaryl-phosphite moieties (**e** and **f**, Figure 1.25) and also their analogous ligands having the opposite configuration in C-3 (**63** and **66**, Figure 1.25) have been successfully applied in the Pd-catalyzed allylic substitution.[5c] Ligand **193f** was found to have the optimal ligand parameters for the Pd-allylic substitution of both linear and cyclic substrates **S10** and **S13** using dimethyl malonate (>99% and 96% ee, respectively). The privileged ligand **193f** has been efficiently used in the Pd-allylic substitution of different hindered and unhindered substrates with a large number of nucleophiles, including synthetically useful functionalized malonates, β-diketones, and allyl alcohols (ee's up to >99%) (Figure 1.62). Furthermore, the potential application of this P,S-system has been proven by simple tandem reactions, involving allylic alkylation/ring-closing metathesis or allylic alkylation/cycloisomerization of 1,6-enyne reactions, with no loss of enantiomeric excess.



193

Figure 1.61. Phosphite-thioether ligands-type **193**.

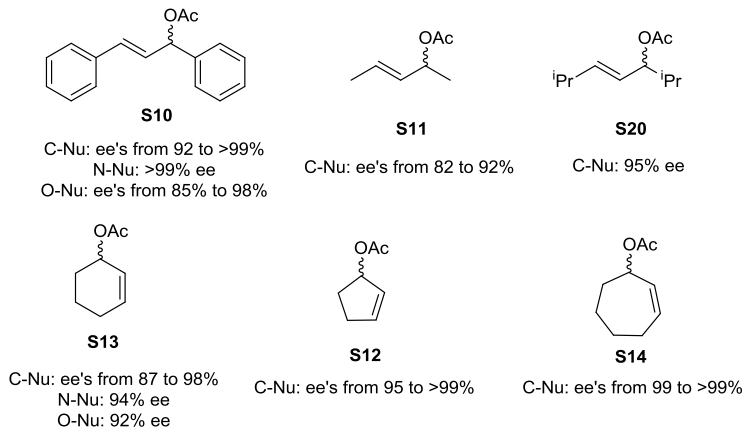


Figure 1.62. Summary of the excellent enantioselectivities obtained in the Pd-allylic substitution of hindered and unhindered substrates with several C-, N- and O-nucleophiles, using Pd-**193f** system.

N-phosphine-thioether ligands

In 2006 Chan and coworkers developed a series of ferrocene *N*-phosphine-thioether ligands **194a**-**c** (Figure 1.63) and successfully applied them in the asymmetric allylic substitution of **S10** (ee's up to 93%).[164] Later, the same authors expanded this family with ligands containing bulkier thioether substituents (**194d**-**e**) (Figure 1.63). Ligands **194a**-**e** were tested in the Pd-catalyzed allylic substitution of substrate **S1** with aliphatic alcohols. Ligand **194e** was found to be highly efficient in terms of activity and enantioselectivities. Thus, high yields and excellent enantioselectivities (from 77 to 96% ee) were obtained in the Pd-catalyzed allylic etherification of **S10** with a broad range of aliphatic alcohols.[165]

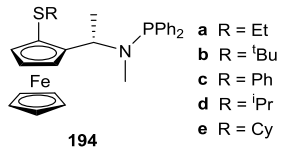
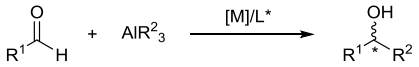


Figure 1.63. Ferrocene N-thioether-phospine ligands **194**.

1.4. Asymmetric Ni-catalyzed trialkylaluminum 1,2-addition to aldehydes

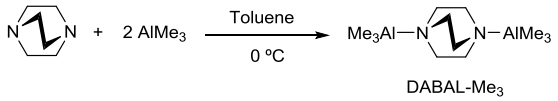
Nucleophilic 1,2-addition of organometallic reagents to carbonyl compounds constitutes one of the most fundamental operations in organic synthesis for the formation of chiral secondary alcohols.[166] Many chiral alcohols are highly valuable intermediates for preparing chiral pharmaceutical and agricultural compounds. In this context, catalytic addition of dialkylzinc reagents to aldehydes as a route to chiral alcohols has attracted much attention. Among alkylating reagents, trialkylamunium compounds are most interesting than other organometallic reagents because they are economically available in industrial scale from aluminum hydride and olefins. Moreover, they present a high

functional group tolerance because of their moderate reactivity.[167] Despite these advantages, their use is rare.[168,169] In this respect, the few successful catalysts developed for the enantioselective addition of trialkylaluminum to aldehydes can be grouped in two types. The first group consists in the titanium complexes bearing chiral diols or *N*-sulfonylated amino alcohols. These catalysts usually afford high enantioselectivities, but the high catalysts loadings (10-20 mol%) and the slow turnover rates hamper their potential utility.[168] The second ones, developed by Woodward and coworkers in 2005, are the nickel complexes that provide enantioselectivities similar to those using titanium complexes but with lower catalyst loadings (0.05-1 mol%).[169a-c,e]



Scheme 1.10. Metal-catalyzed 1,2-addition of trialkylaluminum reagents to aldehydes.

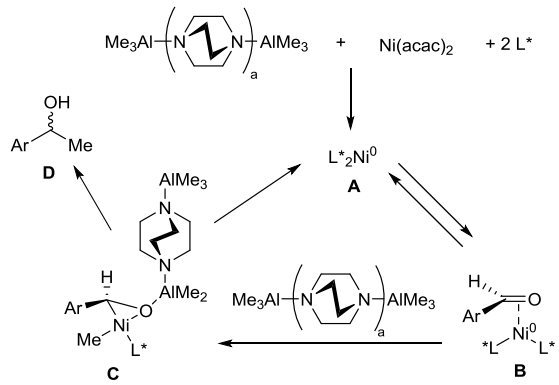
Several aldehydes, such as aryl-, alkyl- and vinyladehydes, have been tested as substrates. However, benzaldehyde has been the substrate of choice for testing new ligands. The aluminum source is also an important parameter for achieving high catalytic activity and enantioselectivity. Traditionally, commercially available trialkylaluminum reagents have been generally used. However, these reagents are often contaminated with oxo-containing by-products formed through accidental exposure to traces of air and moisture, and consequently, their reactivity becomes modified.[170] In this respect, the group of Woodward reported the preparation of DABAL-Me_3 (Scheme 1.11) as a new air-stable $AlMe_3$ adduct that is easily formed from the exposure of neat $AlMe_3$ to DABCO (1,4-diazobicyclo[2,2,2]octane).[169a]



Scheme 1.11. Formation of DABAL-Me_3.

1.4.1. Mechanism

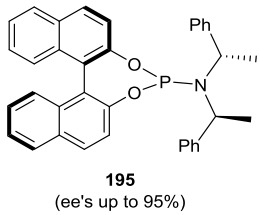
The tentative mechanism proposed for the Ni-catalyzed 1,2-addition of trimethylaluminuim reagents to aryl aldehydes is shown in Scheme 1.12.[169b] The reductive generation of the active Ni(0)-catalyst **A** is followed by the formation of a π-aldehyde complex **B**, as showed possible by the seminal work of Walther who crystallized Ni(η^2-O=CHAr)$PCy_3)_2$ (Ar = Ph, 2,4-$(MeO)_2C_6H_3$).[171] Then aluminum Lewis acid promotes the oxidative addition of the ketone complex **B** and produces Ni(II)-complex **C**. Finally, by reductive elimination, complex **C** releases the final product **D** and the catalytically active species **A** is regenerated.



Scheme 1.12. Proposed catalytic cycle for the Ni-catalyzed 1,2-additon of DABAL-Me_3 (a = 1) or $AlMe_3$ (a = 0) to aromatic aldehydes.

1.4.2. Ligands

Woodward and coworkers reported the first asymmetric Ni-catalyzed 1,2-addition of trialkylaluminum reagents to aldehydes using phosphoramidite and monophosphine ligands. High yields and enantioselectivities (ee's up to 95%) were obtained using monophosphoramidite ligand **195** (Figure 1.64) and DABAL-Me_3 as alkylating reagent. Only 1 mol% of the catalyst precursor [$Ni(acac)_2$] was needed.[169a] To further expand the range of ligands and performance of this asymmetric process, other phosphorus-based ligands have been developed, which are summarized in the following sections.



195
(ee's up to 95%)

Figure 1.64. Monophosphoramidite ligands **195**.

1.4.2.1. P-donor ligands

Phosphite ligands

Carbohydrate-based monophosphite ligands **196**-**200** (Figure 1.65), derived from D-glucose, D-galactose and D-fructose, have been successfully applied in the asymmetric Ni-catalyzed 1,2-addition of several aryl aldehydes.[169c] By judicious choice of ligand components, enantioselectivities up to 94% were achieved with glucofuranoside ligand **196c**. Later, ligands **196** and **197** were further modified by introducing new substituents with different electronic and steric properties at C-3 of the sugar backbone (ligands **201**-**206**, Figure 1.65).[169g] Unfortunately, the introduction of a methyl substituent at C-3 of the furanoside backbone in ligands **196** didn't improve the enantioselectivities. In contrast, in ligand **197**, this change was highly advantageous in terms of enantioselectivity (ee's from

44% (R) to 75% (S) when using benzaldehyde as a substrate). Thus, by using ligand **202**, ee values up to 94% and high activities with several aryl adehydes were obtained.

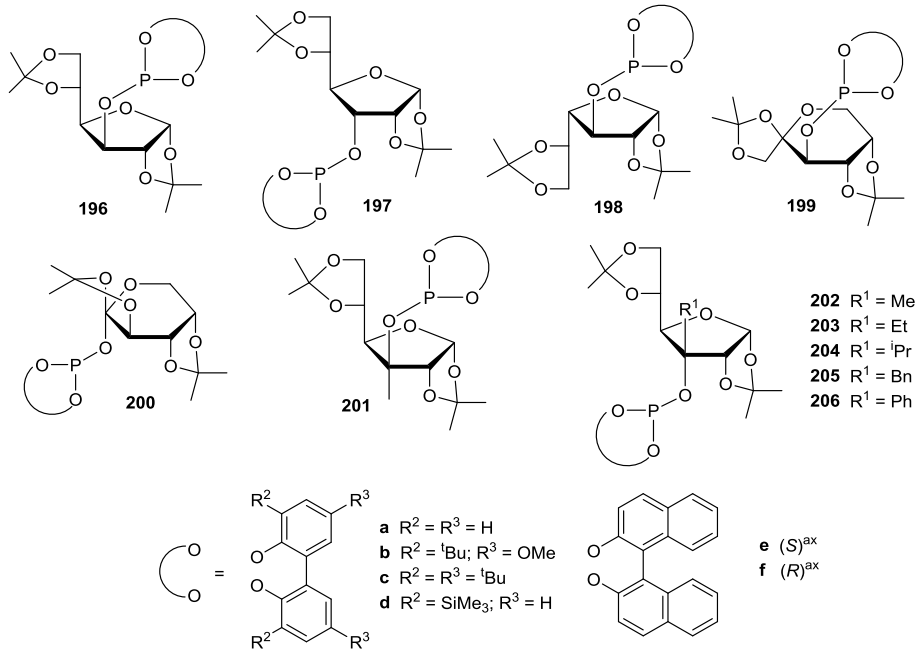


Figure 1.65. Carbohydrate-based monophosphite ligands **196**-**206**.

Phosphoramidite ligands

Our group screened the modular sugar-based monophosphoramidite ligand library **207**-**211** (Figure 1.66), related to phosphite ligands **196**-**200** (Figure 1.65), for the Ni-catalyzed trialkylaluminum addition to several aldehydes.[169e] By carefully selecting all ligand components, ligand **207d** was found to provide good enantioselectivities (ee's up to 78%) and high activities in the 1,2-addition of several aryl aldehydes. However, phosphoramidite ligands **207**-**211** induced lower levels of asymmetric induction than the corresponding phosphite counterparts **196**-**200** (ee's up to 78% vs 94%).

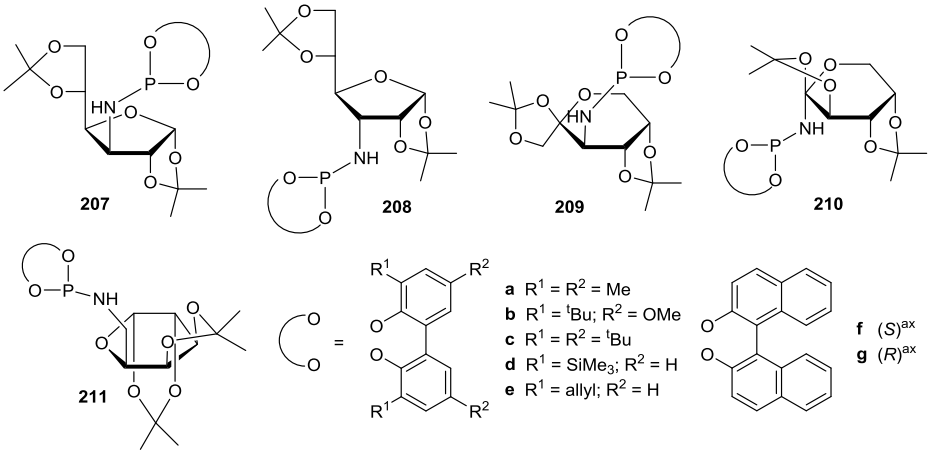


Figure 1.66. Carbohydrate-based monophosphoramidite ligands **207**-**211**.

1.4.2.2. Heterodonor ligands

P-P' and P-N ligands

The previously mentioned carbohydrate-based phosphite-oxazoline ligands **26** (Figure 1.12) and phosphite-phosphoramidite **212** ligands (Figure 1.67) were applied in the asymmetric Ni-catalyzed 1,2-addition of trialkylaluminum reagents to aldehydes giving poor-to-moderate enantioselectivities (ee's up to 59%).[169d]

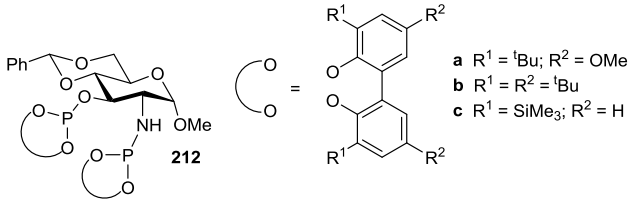


Figure 1.67. Carbohydrate-based phosphite-phosphoramidite ligand library **212**.

Recently, our group tested the phosphite-phosphoramidite **213**-**216** ligand library (Figure 1.68) in the asymmetric Ni-catalyzed trialkylaluminum addition to aldehydes.[169f] High activities and enantioselectivities (ee's up to 84%) were obtained. These ligands constitute the first successful application of bidentate ligands in the asymmetric Ni-catalyzed trialkylaluminum addition of several aldehydes.

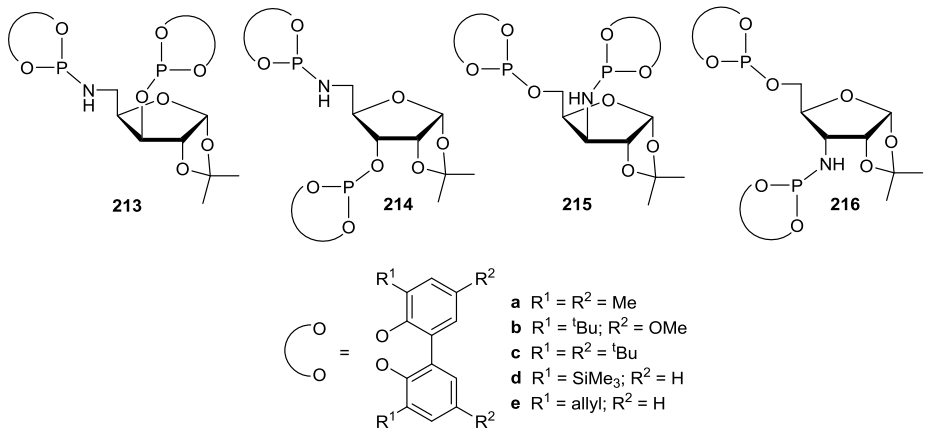


Figure 1.68. Carbohydrate-based phosphite-phosphoramidite ligands **213**-**216**.

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UNIVERSITAT ROVIRA I VIRGILI
SCREENING OF MODULAR AND READILY AVAILABLE LIGAND LIBRARIES FOR C-X (X=H, C, N AND O) BOND FORMING REACTIONS. THE USE OF DFT STUDIES FOR CATALYSTS OPTIMIZATION
Jèssica Margalef Pallarès

Chapter 2

Objectives

UNIVERSITAT ROVIRA I VIRGILI
SCREENING OF MODULAR AND READILY AVAILABLE LIGAND LIBRARIES FOR C-X (X=H, C, N AND O) BOND FORMING REACTIONS. THE USE OF DFT STUDIES FOR CATALYSTS OPTIMIZATION
Jèssica Margalef Pallarès

2. Objectives

This thesis focuses on the synthesis of new chiral ligand libraries from readily available compounds, in order to develop robust and efficient catalytic systems and apply them in relevant asymmetric catalytic processes.

The more specific aims are:

1. To synthesize and apply carbohydrate-derived phosphite-thioether/selenoether ligands **L1-L23a-g** (Figure 2.1) in the following metal-catalyzed reactions: a) Rh- and Ir-catalyzed hydrogenation of functionalized and minimally functionalized olefins; b) Pd-catalyzed allylic substitution reactions; and c) asymmetric Ni-catalyzed 1,2-addition of trialkylaluminium reagents to aldehydes.

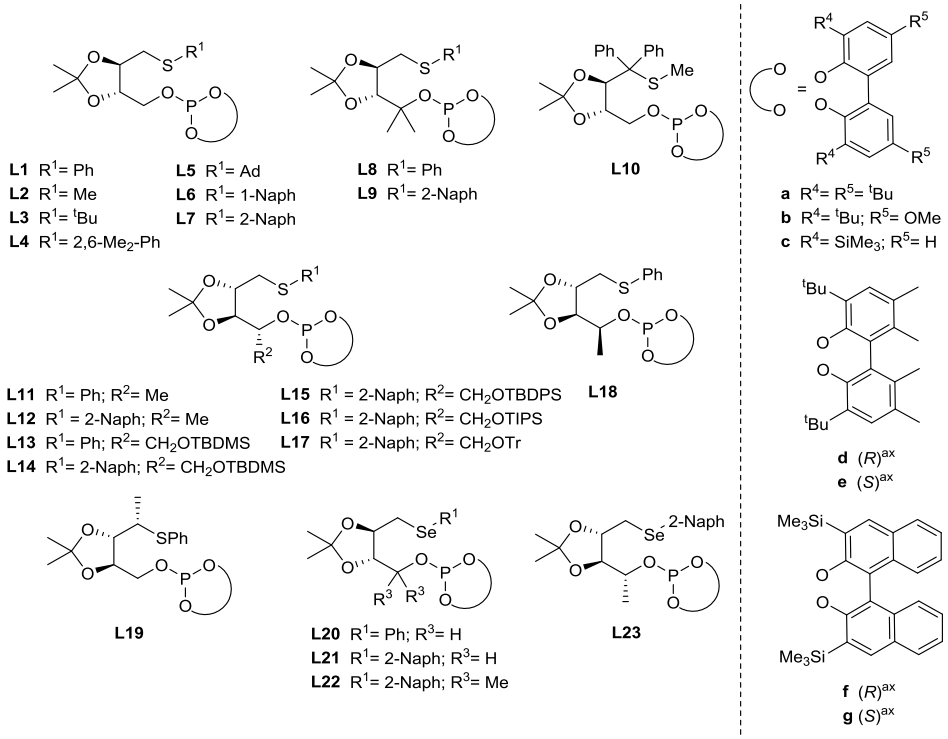

Figure 2.1. Carbohydrate-derived phosphite-thioether/selenoether ligand library **L1**-**L23a**-**g**.

2. To apply furanoside-based phosphite/phosphinite-thioether ligand library **L24**-**L40a**-**l** (Figure 2.2) in Pd-catalyzed allylic substitution reactions. A DFT study has been performed in order to better understand their cataliytic behaviour.

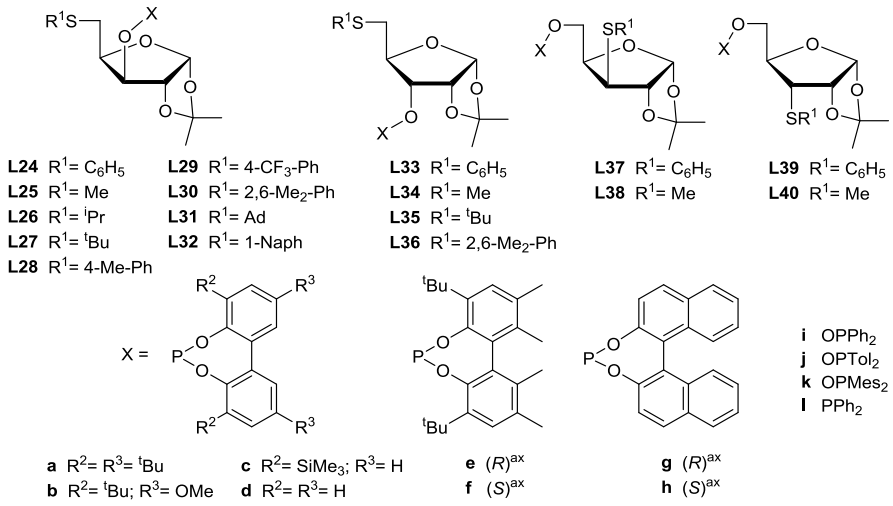

Figure 2.2. Carbohydrate-based phosphite/phosphinite-thioether ligand library **L24**-**L40a**-**l**.

3. To synthesize and apply phosphite/phosphinite-thioether ligand library **L41**-**L50a**-**g** (Figure 2.3) in the Ir-catalyzed hydrogenation of minimally functionalized olefins. A DFT study has been performed and used for further optimization of the ligand backbone.

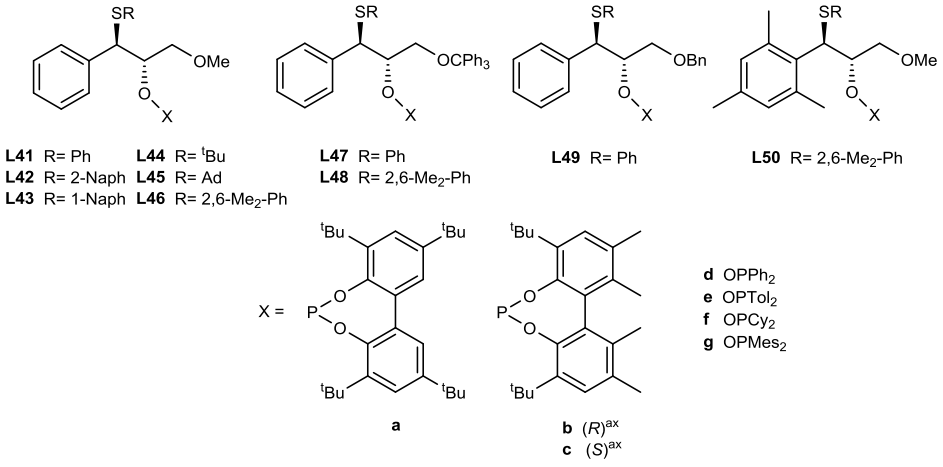

Figure 2.3. Phosphite/phosphinite-thioether ligand library **L41**-**L50a**-**g**.

4. To synthesize and apply phosphite/phosphinite-thioether ligand library **L51**-**58a**-**g** (Figure 2.4) in the asymmetric Ir-catalyzed hydrogenation of minimally functionalized olefins and in Pd-catalyzed allylic substitution reactions.

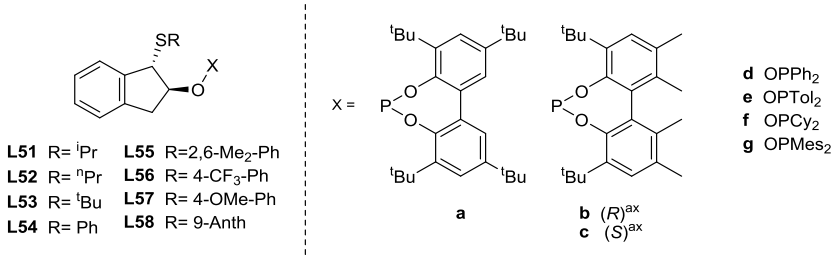

Figure 2.4. Phosphite/phosphinite-thioether ligand library **L51**-**58a**-**g**.

5. To synthesize and apply glucopyranoside phosphite-pyridine ligand library **L59**-**L60a**-**f** (Figure 2.5) in the asymmetric Ir-catalyzed hydrogenation of minimally functionalized olefins and in Pd-catalyzed allylic substitution reactions.

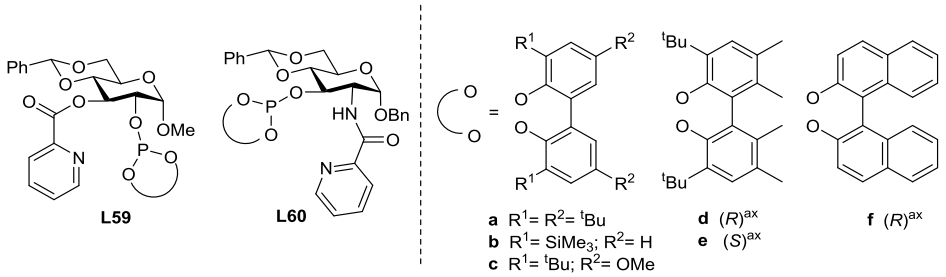

Figure 2.5. Glucopyranoside phosphite-pyridine ligand library **L59**-**L60**-**f**.

6. To synthesize and apply phosphite-triazole ligand library **L61**-**67a**-**c** (Figure 2.6) in the asymmetric Ir-catalyzed hydrogenation of minimally functionalized olefins and in Pd-catalyzed allylic substitution reactions.

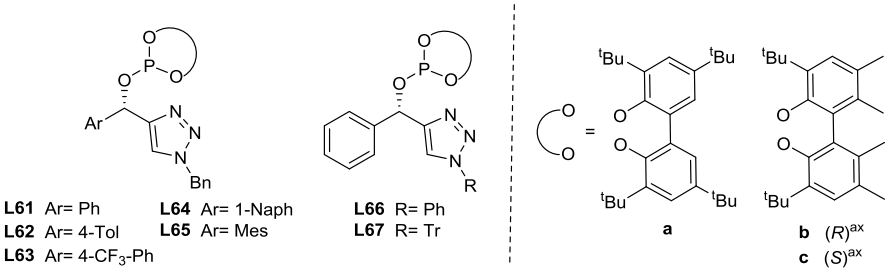

Figure 2.6. Phosphite-triazole ligand library **L61**-**L67a**-**c**.

7. To synthesize and apply hydroxiamide ligand library **L68**-**L70a**-**j** (Figure 2.7) and their corresponding thioamide ligands **L71**-**L73a**-**j** (Figure 2.7) in asymmetric transfer hydrogenation (ATH) of ketones and tandem processes involving ATH reactions.

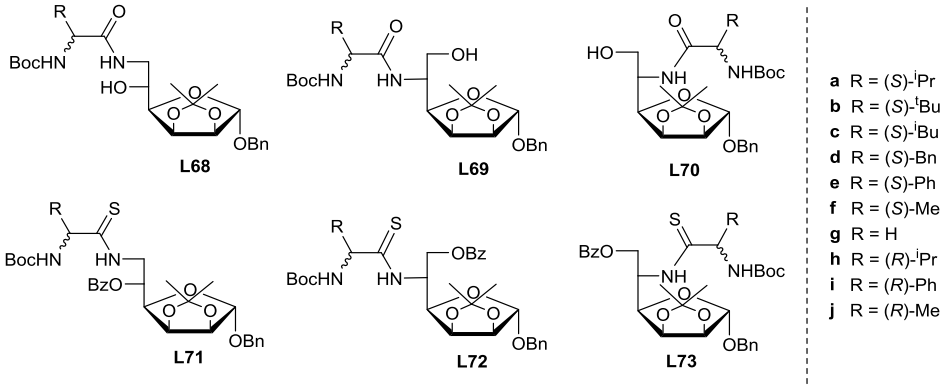

Figure 2.7. Carbohydrate-based hydroxiamide/thioamide ligand library **L68**-**L73a**-**j**.

Chapter 3

Asymmetric hydrogenation reactions

UNIVERSITAT ROVIRA I VIRGILI
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3. Asymmetric hydrogenation reactions

3.1. Background

Because of its high efficiency, operational simplicity and perfect atom economy, asymmetric metal-catalyzed hydrogenation is nowadays one of the most widely used and reliable catalytic methods for the preparation of optically active compounds.

Rh- and Ru- complexes containing chiral ligands with phosphorus and nitrogen donor centers have proven to be the best catalysts for the asymmetric hydrogenation of dehydroamino acid and ester derivatives. As mentioned in the introduction, most of the successful catalysts contain diphosphine and diphosphinite ligands. However, some catalysts containing a group of less electron-rich phosphorus compounds, phosphite and phosphoramidite ligands, have also shown to be effective ligands for asymmetric hydrogenation. On the other hand, mixed chiral P,S-ligands, especially phosphinite-thioether, have also demonstrated their potential utility. In this respect, we report in section 3.2 the synthesis and application of a highly modular phosphite-thioether ligand family (**L1**-**L23a**-**g**) in the asymmetric Rh-catalyzed hydrogenation of α,β-unsaturated carboxylic acid derivatives and enamides. Since both thioether and phosphite moieties are more stable towards oxidation than phosphines, ligands **L1**-**L23a**-**g** present the advantages of being easier to handle than the typical ligands used for this process. Moreover the sulfur atom becomes a stereogenic center when coordinates to the metal center, thus moving the chirality closer to the coordination sphere. By carefully selecting the ligand components, full conversions and high enantioselectivities have been achieved in the reduction of several α- and β-dehydroamino acid esters (up to 98% ee), dimethyl itaconate (up to 79% ee), and a range of α- and β-enamides (up to 95% ee).

On the other hand, Rh- and Ru-catalysts are not able to enantioselectively hydrogenate substrates having no adjacent polar group to direct the reaction. Alternatively, Ir-complexes with chiral P,N-ligands have recently emerged as efficient catalysts for the hydrogenation of unfunctionalized olefins, and their scope is complementary to those of Rh- and Ru-diphosphine complexes. As illustrated in the introduction, the most successful ligands reported for this process have been the phosphine/phosphinite-oxazoline ligands. Later, it was shown that the replacement of the phosphine/phosphinite moiety by a biaryl phosphite group in these P,N-ligands provided greater substrate versatility than previous Ir-phosphine/phosphinite, N catalyst systems. The possibility of changing the nature of the N-donor in these heterodonor ligands has been poorly contemplated. The presence of a thioether moiety in the ligand may be beneficial because of the advantages commented above (robustness and closer chirality to the metal center). In this respect our group reported the first successful application of phosphite-thioether ligands in the Ir-catalyzed hydrogenation of minimally functionalized olefins. A systematic study of the possibilities offered by this new kind of ligands for this process is still needed. On the other hand, another way for obtaining new robust P,N-ligands for this catalytic transformation is to replace the oxazoline moiety by other more stable N-coordinating groups. The use of the more robust pyridine and triazole rings as N-donors would be a good alternative to the

oxazoline group. Some relevant examples of the use of phosphorus-pyridine ligands in Ir-catalyzed hydrogenation of minimally functionalized olefins can be found in the literature. However, little attention has been paid to phosphorus-triazole ligands.

In this respect, we report in this chapter the synthesis and application of a new series of readily accessible and robust phosphorus-thioether, phosphite-pyridine and phosphite-triazole ligand families in the Ir-catalyzed hydrogenation of minimally functionalized olefins. More specifically, in section 3.3 we have applied carbohydrate-derived phosphite-thioether/selenoether ligands **L1**-**L23a**-**g**, described in section 3.2, in the Ir-catalyzed hydrogenation of several minimally functionalized olefins. The highly modularity of these ligands allowed us to identify catalytic systems able to hydrogenate substrates containing poorly coordinative groups (i.e. alkenylboronic esters, α,β-unsaturated amides and esters) and the more challenging disubstituted olefins in high enantioselectivities. It should be noted the excellent enantioselectivities (up to 99% ee) achieved in the hydrogenation of β-aryl enamides, which gave access to 2-aminotetralines and 3-aminochromanes in almost enantiopure form. In section 3.4 a phosphite/phosphinite-thioether ligand family **L41**-**L50a**-**g** has been easily prepared in few steps from readily available enantiopure arylglycidols. They have been successfully applied in the Ir-hydrogenation of a wide range of substrates. Moreover, a DFT study of the transition states involved in this catalytic process allowed identifying the key ligand parameters for achieving high levels of enantioselectivity. We therefore obtained excellent enantioselectivities in the hydrogenation of (*E*)- and (*Z*)-trisubstituted and disubstituted olefins, including α,β-unsaturated enones, tri- and disubstituted alkenylboronic esters and olefins with trifluoromethyl substitutents (ee's up to 99%). In the next section (section 3.5) we present the synthesis of a new indene-based phosphite/phosphinite thioether ligand family (**L51**-**L57a**-**e**). It's remarkable that these ligands are synthesized in only three simple steps. We have made an initial evaluation of these ligands in the Ir-catalyzed hydrogenation of the benchmarck substrates (*E*)- and (*Z*)-trisubstituted and 1,1-disubstituted terminal olefins. Although poor enantioselectivities were obtained for trisubstituted substrates, excellent enantioselectivities were obtained for the disubstituted substrate 3,3-dimethyl-2-phenyl-1-butene (up to 97% ee). In section 3.6 we have synthesized a new family of D-glucopyranoside-based phosphite-pyridine ligands (**L59**-**L60a**-**f**). They have been examined in the iridium-catalyzed asymmetric hydrogenation of poorly functionalized (*E*)- and (*Z*)-trisubstituted alkenes and other challenging substrates (i.e. alkenes with a neighboring polar group or demanding 1,1-di-substituted alkenes). Moderate to good enantioselectivities were obtained (65-90% ee). Finally, in the last section (3.7) a new phosphite-triazole ligand family (**L61**-**67a**-**c**) has been easily synthesized in few simple steps. These ligands have been applied in model (*E*)- and (*Z*)-trisubstituted and 1,1-disubstituted terminal olefins. Although only moderate enantioselectivities could be achieved in the hydrogenation of trisubstituted alkenes, promising enantioselectivities were obtained in the reduction of 3,3-dimethyl-2-phenyl-1-butene (ee's up to 87%).

3.2. Rh-Catalyzed asymmetric hydrogenation of functionalized olefins using phosphite-thioether/selenoether ligands

Jèssica Margalef, Carlota Borràs, Sabina Alegre, Elisabeta Alberico, Oscar Pàmies and Montserrat Diéguez in manuscript to be submitted

***Abstract**: A modular thioether-phosphite ligand library has been synthesized for the Rh-catalyzed asymmetric hydrogenation of α,β-unsaturated carboxylic acid derivatives and enamides. These ligands can be prepared efficiently from easily accessible L-(+)-tartaric acid and D-(+)- mannitol. We found that their effectiveness at transferring the chiral information in the product can be tuned by correctly choosing the ligand components and the substrate. Enantioselectivities were therefore high (ee's up to 98%).*

3.2.1. Introduction

There are many applications in which only one enantiomer has the desired properties while the other enantiomer is either inactive or can give undesirable secondary effects. Consequently, the preparation of enantiomerically pure compounds is growing in several important fields such as pharmaceuticals, agrochemicals, fine chemicals and natural product chemistry. Asymmetric hydrogenation utilizing molecular hydrogen to reduce prochiral olefins has become one of the most efficient asymmetric catalytic methods for constructing chiral compounds.[1] Over many years the scope of this reaction has gradually extended in terms of reactant structure and catalyst efficiency. Chiral homodonor P-donor ligands have played a key role in the success of the enantioselective Rh-catalyzed hydrogenation.[1] Research in this area mainly focuses on the search for new chiral ligands that are readily available from cheap/renewable raw materials and which can hydrogenate a wide range of substrates with high ee's. In this respect ligands derived from the chiral pool have many advantages: they are readily available and highly functionalized, and they have several stereogenic centers. This facilitates the development of chiral ligand libraries in the search for high activities and selectivities for each particular substrate.[2]

Heterodonor P,S ligands also have a potential advantage because specific substrate coordination, mediated by two nonequivalent donor atoms, facilitates the transfer of the chiral information from the catalyst to the hydrogenation product for a wide range of substrates.[3] Despite this, their use in asymmetric hydrogenation has been less developed than other heterodonor ligands such as P,N and P,P' ligands.[1] Among them, thioether-phosphinite ligands have played a dominant role.[4,5,6] In the last decade, a group of less electron rich phosphorus compounds (phosphite and phosphoroamidite ligands) have demonstrated that they are potentially extremely useful in asymmetric hydrogenation.[7] Despite this, to the best of our knowledge, there is only one report on the use of heterodonor thioether-phosphite ligands in this process with moderate results.[5b] More

research is therefore needed to study the possibilities offered by thioether-phosphites as a new class of ligands for this process.

For this purpose in this chapter we report the synthesis and application of a new thioether-phosphite ligand library, derived from inexpensive L-(+)-tartaric acid, and D(+)-mannitol (**L1**-**L23a**-**g**; Figure 3.2.1) in the Rh-catalyzed asymmetric hydrogenation of α,β-unsaturated carboxylic acid derivatives and enamides.

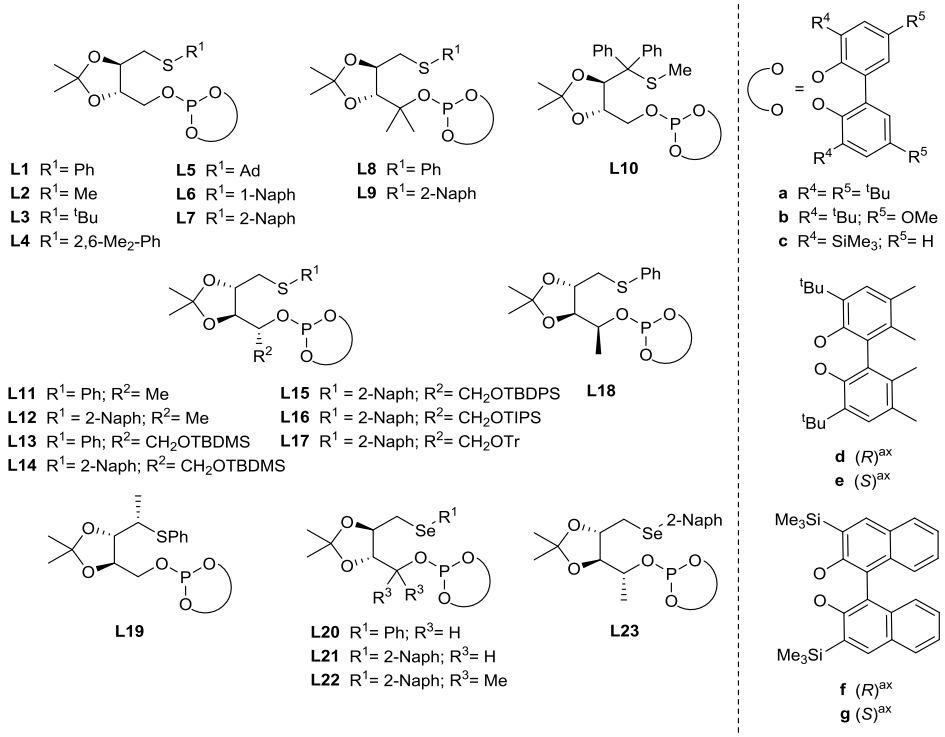


Figure 3.2.1. Sugar-based phosphite-thioether/selenoether ligand library **L1**-**L23a**-**g**.

Another advantage of this ligand library design is its highly modular construction which enables a systematic study of the ligand parameters on catalytic performance. With this library we investigate the effect of systematically varying: (a) the electronic and steric properties of the thioether group (ligands **L1**-**L7**); (b) the substituents and the introduction of a new stereogenic centre in the alkyl backbone chain next to the phosphite moiety (ligands **L1**, **L7**, **L8**-**L9** and **L11**-**L18**); (c) the substituents and the introduction of a new stereogenic centre in the alkyl backbone chain next to the thioether moiety (ligands **L1**, **L2**, **L10** and **L19**); (d) the substituents and configurations in the biaryl phosphite moiety (**a**-**g**); and (e) the replacement of the thioether group by a selenoether moiety. By carefully selecting these elements, we achieved high enantioselectivities and activities in the reduction of a range of prochiral olefins.

3.2.2. Results and discussion

3.2.2.1. Synthesis of ligands

The synthesis of phosphite-thioether/selenide ligands **L1**-**L23a**-**g** is straightforward (Scheme 3.2.1). They were efficiently synthesized from the corresponding easily accessible hydroxyl-thioether/selenoether compounds **5**-**10**, **12**-**14**, **17**-**20**, **22**, **27**-**34**, **37** and **40**. Compounds **1** and **2**, which are easily synthesized from inexpensive natural L-(+)-tartaric acid and D-(+)-mannitol in a multigram scale, were chosen as intermediates for the preparation of ligands because they easily allow to incorporate the desired diversity in the ligand design. For the preparation of hydroxyl-thioether/selenide compounds **5**-**10**, compound **1** was reduced with $LiAlH_4$ to afford intermediate diol **3**, which was treated with 1 equiv of *p*-toluenesulfonyl chloride to produce the desired monotosylated compound **4** (Scheme 3.2.1, step (b)). Subsequent reaction with the corresponding NaSR or Se_2R_2 and $NaBH_4$ provided direct access to the corresponding hydroxyl-thioether/selenides **5**-**10** (Scheme 3.2.1, steps (c and d)). However, in this step the incorporation of bulky thioether substituents proceeded with poor-to-moderate yields even with long reaction times. Therefore, for the preparation of hydroxyl-thioether compounds **12**-**14**, a new alternative route was developed. Monoprotection of **3** using 1 equiv of TBDMSCl and NaH and subsequent reaction with triflic anhydride gave access to monotriflate **11** (Scheme 3.2.1, steps (e and f)). Thioether intermediates **12**-**14** were obtained by treating compound **11** with the corresponding NaSR followed by deprotection of the *tert*-butyldimethylsilyl protecting group using TBAF (Scheme 3.2.1, steps (c and g)).

For the preparation of hydroxyl-thioether/selenide compounds **17**-**19** and **21**, compound **1** was transformed to intermediate **15** by treatment with $NaBH_4$ followed by protection of the alcohol group with TBDMSCl (Scheme 3.2.1, steps (h and i)). Treatment of compound **15** with methyl lithium provided compound **16** (Scheme 3.2.1, steps (j)). Standard deprotection of **16** with TBAF, followed by selective tosylation of the primary alcohol gave acces to the corresponding monotosylated compound ((4*S*,5*R*)-5-(2-hydroxypropan-2-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl 4-methylbenzenesulfona-te. Subsequent reaction with the corresponding NaSR or Se_2R_2 and $NaBH_4$ provided direct access to hydroxyl-thioether/selenides **17**-**19** (Scheme 3.2.1, steps (b, c and d)). For the preparation of hydroxyl-thioether compound **21**, intermediate **15** was treated with PhMgBr to provide the corresponding terciary alcohol, which was then treated with Lawesson's reagents to provide thiol **20** (Scheme 3.2.1, steps (k and l)). Methylation of **15** with MeI followed by deprotection of the silyl group gave access to hydroxyl-thioether **21**.

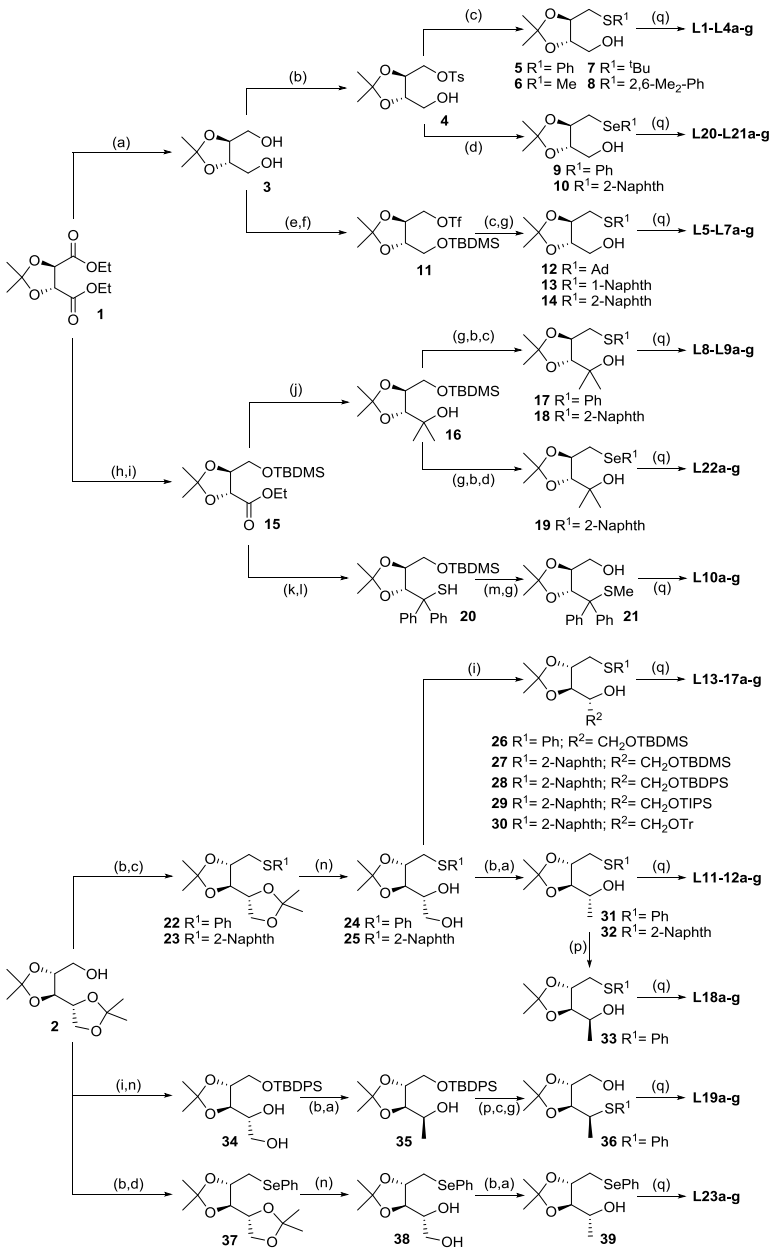
For the preparation of hydroxyl-thioether compounds **26**-**33**, compound **2** was transformed to the desired thioether compounds **22** and **23** by treatment of **2** with 1 equiv of *p*-toluenesulfonyl chloride followed by reaction with the corresponding NaSR (Scheme 3.2.1, steps (b and c)). Subsequent standard acid catalyzed acetal deprotection provided compounds **24** and **25** (Scheme 3.2.1, step (n)).Treatment of **24** and **25** with 1 equiv of the corresponding silyl chloride or trityl chloride gave access to the desired hydroxyl-thioethers **26**-**30** (Scheme 3.2.1, step (i)). Hydroxyl-thioethers **31** and **32** were obtained by treating

compounds **24** and **25** with 1 equiv of *p*-toluenesulfonyl chloride followed by reaction with $LiAlH_4$ (Scheme 3.2.1, steps (b and a)). Inversion of the secondary alcohol of compound **31** to afford the desired hydroxyl-thioethers **32** was achieved using Mitsunobu methodology (Scheme 3.2.1, step (o)).

For the preparation of hydroxyl-thioether compound **36**, compound **2** was transformed to the monoprotected diol **34** by treatment of **2** with 1 equiv of TBDPSCl and NaH and subsequent acetal deprotection using acetic acid (Scheme 3.2.1, steps (I and n)). **34** was selectively monotosylated at the primary alcohol and subsequent reaction with $LiAlH_4$ provided alcohol **35** (Scheme 3.2.1, steps (b and a)). Hydroxyl-thioether **36** was obtained by mesylation of **35** followed by reaction with NaSR and subsequent deprotection of the *tert*-butyldiphenylsilyl protecting group using TBAF (Scheme 3.2.1, steps (p, c and g)).

Hydroxyl-selenide compound **39** was obtained following the same synthetic pathway than for the preparation of hydroxyl-thioether **31**, but using Se_2R_2 and $NaBH_4$ instead of NaSPh.

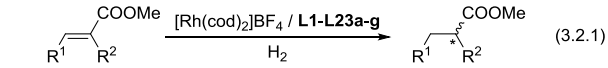
The last step of the ligand synthesis is common for all of them. Therefore, treating the corresponding hydroxyl-thioether/selenides (**5**-**10**, **12**-**14**, **17**-**19**, **21**, **26**-**33**, **36** and **39**) with 1.1 equiv of the desired in situ formed phosphorochloridite ($ClP(OR)_2$; $(OR)_2$ = **a**-**g**) in the presence of pyridine provided easy access to the desired ligands (Scheme 3.2.1, step (q)). All the ligands were purified on neutral alumina under an argon atmosphere and isolated in moderate-to-good yields as white solids. HRMS-ESI spectra were in agreement with the assigned structures. The ^{1}H, ^{31}P and ^{13}C NMR spectra were as expected for these ligands (see Section 3.2.4). One singlet for each compound was observed in the ^{31}P NMR spectrum. Rapid ring inversions (tropoisomerization) in the biphenyl-phosphorus moieties (**a**-**c**) occurred on the NMR time scale because the expected diastereoisomers were not detected by low-temperature ^{31}P NMR.



Scheme 3.2.1. Synthesis of phosphite-thioether/selenoether ligands **L1**-**L23a**-**g**. a) $LiAlH_4$, Et_2O, THF; b) TsCl, Py, CH_2Cl_2; c) NaSR, THF; d) Se_2R_2, $NaBH_4$, THF; e) TBDMSCl, NaH, THF; f) Tf_2O, Py, CH_2Cl_2; g) TBAF, THF; h) $NaBH_4$, EtOH; i) R_3SiCl or TrCl, imidazole, DMF; j) MeLi, THF; k) PhMgBr, THF, Et_2O; l) Lawesson's reagent, toluene; m) MeI, NEt_3, MeOH; n) AcOH (dil); o) DIAD, pNBA, PPh_3, THF then MeOH, NaOH; p) MsCl, NEt_3, CH_2Cl_2; q) $ClP(OR)_2$; $(OR)_2$ = **a**-**g**, Py, toluene.

3.2.2.2. Asymmetric hydrogenation of benchmark dimethyl itaconate S1 and α-dehydroamino acid derivatives S2 and S3

In a first set of experiments we evaluated phosphite-thioether/selenoether ligands **L1**-**L23a**-**g** in the Rh-catalyzed hydrogenation of benchmark dimethyl itaconate **S1** and α-dehydroamino acid derivatives methyl 2-acetamidocinnamate **S2** and methyl 2-acetamidoacrylate **S3** (Equation 3.2.1).



(3.2.1)

S1 R^1= H; R^2= CH_2COOMe
S2 R^1= Ph; R^2= NHAc
S3 R^1= H; R^2= NHAc

Initially, we used the Rh-catalyzed hydrogenation of **S1** to evaluate the potential of the **L1**-**L23a**-**g** ligand library (Table 3.2.1). The results, which are summarized in Table 3.3.1, indicate that enantioselectivities are highly affected by a subtle balance of the thioether/selenoether substituent, the substituents/configurations at the alkyl backbone chain next to the phosphite and next to the thioether/selenoether moieties as well as the configuration of the biaryl phosphite moiety.

The effect of the substituents and configuration of the biaryl phosphite moiety was mainly investigated using **L1a**-**g** (Table 3.2.1, entries 1-7). The results indicated that the presence of substituents at the *para* position of the biaryl phosphite moiety has a positive effect on enantioselectivity (entry 1 and 2 vs 3). In addition, the presence of chiral (*R*)-biaryl moieties (**d** and **f**) is necessary to achieve the highest level of enantioselectivity (entries 4 and 6 vs entries 1-3, 5 and 7).

The results using ligands **L1**-**L7** indicated not only that the enantioselectivity is affected by the thioether substituent, but also that the effect of the configuration of the biaryl phosphite moiety depends on the thioether substituent. Thus, while for ligands **L1**, with a phenyl thioether group, enantioselectivities are better using (*R*)-biaryl phosphite moieties, for ligands **L5**, containing a bulky adamantly thioether group, both (*R*)- and (*S*)-biaryl phosphite moieties led to similar levels of enantioselectivity (entries 17 and 18).

The results using ligands **L8-L19**, containing different substituents and configurations at the carbon adjacent to the phosphite and thioether group, indicated that the presence of two methyl substituents attached to the carbon close to the phosphite moiety had a positive effect on enantioselectivity (ligands **L8**-**L9**; entries 23-28). However, the introduction of either a chiral center at the same position (ligands **L11**-**L18**) or substituents at the carbon adjacent to the thioether moiety (ligands **L10** and **L19**), doesn't improve the enantioselectivities achieved.

Finally, the results using phosphite-selenoether ligands **L20**-**L23** indicated that the introduction of a selenoether group instead of a thioether has a slight positive effect on enantioselectivity.

In summary, the highest enantioselectivity (ee's up to 79%) was achieved using phosphite-selenoether ligand **L22g**, which contains the optimal combination of ligand parameters.

Table 3.2.1. Selected results for the Rh-catalyzed hydrogenation of **S1** using the phosphite-thioether ligand library **L1**-**L23a**-**g**.[a]

Entry	Ligand	% Conv[b]	% ee[b]	Entry	Ligand	% Conv[b]	% ee[b]
1	**L1a**	99	26 (*S*)	30	**L10g**	100	22 (*S*)
2	**L1b**	100	25 (*S*)	31	**L11a**	100	29 (*R*)
3	**L1c**	100	17 (*S*)	32	**L11f**	100	50 (*R*)
4	**L1d**	100	50 (*S*)	33	**L11g**	100	60 (*R*)
5	**L1e**	100	18 (*S*)	34	**L12a**	100	28 (*R*)
6	**L1f**	100	56 (*S*)	35	**L12f**	100	36 (*R*)
7	**L1g**	100	24 (*S*)	36	**L12g**	100	55 (*R*)
8	**L2a**	100	10 (*S*)	37	**L13a**	100	40 (*R*)
9	**L2f**	100	21 (*S*)	38	**L14a**	100	49 (*R*)
10	**L2g**	100	4 (*R*)	39	**L14g**	100	29 (*R*)
11	**L3a**	100	8 (*R*)	40	**L15g**	100	34 (*R*)
12	**L3d**	100	36 (*S*)	41	**L16g**	100	54 (*R*)
13	**L3e**	100	18 (*R*)	42	**L17g**	100	46 (*R*)
14	**L4a**	100	51 (*R*)	43	**L18a**	100	40 (*R*)
15	**L4d**	100	17 (*S*)	44	**L18f**	100	11 (*R*)
16	**L4e**	100	24 (*R*)	45	**L18g**	100	57 (*R*)
17	**L5d**	100	52 (*S*)	46	**L19a**	100	28 (*S*)
18	**L5e**	100	53 (*R*)	47	**L19f**	100	37 (*S*)
19	**L6d**	100	25 (*S*)	48	**L19g**	100	4 (*R*)
20	**L6e**	100	29 (*S*)	49	**L20a**	100	29 (S)
21	**L7d**	100	39 (*S*)	50	**L20f**	100	59 (*S*)
22	**L7e**	100	43 (*S*)	51	**L20g**	100	19 (*S*)
23	**L8a**	100	51 (*S*)	52	**L21f**	100	57 (*S*)
24	**L8d**	100	67 (*S*)	53	**L21g**	100	23 (*S*)
25	**L8e**	100	75 (*S*)	54	**L22f**	100	64 (*S*)
26	**L9a**	100	40 (*S*)	55	**L22g**	100	79 (*S*)
27	**L9f**	100	62 (*S*)	56	**L23f**	100	34 (*R*)
28	**L9g**	100	71 (*S*)	57	**L23g**	100	56 (*R*)
29	**L10f**	100	52 (*S*)				

[a] Reactions conditions: $[Rh(cod)_2]BF_4$ (1 mol%), ligand (1 mol%), **S1** (0.25 mmol), CH_2Cl_2 (2 mL), H_2 (10 bar), 20 h at rt.[b] Conversion and enantiomeric excesses determined by chiral GC.

We next studied Rh-catalyzed hydrogenation of **S2** using **L1**-**L23a**-**g** ligand library (Table 3.2.2). The results again indicate that enantioselectivities are highly affected by a subtle balance of the thioether/selenoether substituent, the substituents/configurations at the alkyl backbone chain next to the phosphite and next to the thioether/selenoether moieties as well as the configuration of the biaryl phosphite moiety. However, the effect of these parameters on enantioselectivity was different from **S1**. Thus, for instance, enantioselectivities not only increased by introducing two methyl substituents at the carbon adjacent to the phosphite moiety (entries 24 and 27 vs 4 and 21) but also by using ligands **L11**-**L17**, with an (*R*)-configurated carbon adjacent to the phosphite group (i.e. entries 31 and 32 vs 6 and 7). Thus, by correctly choosing the ligand parameters, we were able to achieve full conversion and high enantioselectivity (ee's up to 98%) using Rh-**L16g**

catalytic system (Table 3.2.2, entry 41). This result clearly shows the efficiency of using highly modular scaffolds for the ligand design.

Table 3.2.2. Selected results for the Rh-catalyzed hydrogenation of **S2** using the phosphite-thioether ligand library **L1**-**L23a**-**g**.[a]

Entry	Ligand	% Conv[b]	% ee[b]	Entry	Ligand	% Conv[b]	% ee[b]
1	**L1a**	99	48 (*R*)	30	**L10g**	100	29 (*S*)
2	**L1b**	100	40 (*R*)	31	**L11a**	100	60 (*S*)
3	**L1c**	100	30 (*R*)	32	**L11f**	100	84 (*R*)
4	**L1d**	100	68 (*R*)	33	**L11g**	100	93 (*S*)
5	**L1e**	100	21 (*S*)	34	**L12a**	100	59 (*S*)
6	**L1f**	100	78 (*R*)	35	**L12f**	100	89 (*R*)
7	**L1g**	100	64 (*S*)	36	**L12g**	100	96 (*S*)
8	**L2a**	92	21 (*R*)	37	**L13a**	100	55 (*S*)
9	**L2f**	100	42 (*R*)	38	**L14a**	100	58 (*S*)
10	**L2g**	100	19 (*S*)	39	**L14g**	100	95 (*S*)
11	**L3a**	100	9 (*R*)	40	**L15g**	100	96 (*S*)
12	**L3d**	100	55 (*R*)	41	**L16g**	100	98 (*S*)
13	**L3e**	100	35 (*S*)	42	**L17g**	100	95 (*S*)
14	**L4a**	82	8 (*S*)	43	**L18a**	100	16 (*S*)
15	**L4d**	96	28 (*S*)	44	**L18f**	100	95 (*R*)
16	**L4e**	95	11 (*R*)	45	**L18g**	100	70 (*S*)
17	**L5d**	100	59 (*R*)	46	**L19a**	100	13 (*S*)
18	**L5e**	100	51 (*S*)	47	**L19f**	100	34 (*R*)
19	**L6d**	100	54 (*R*)	48	**L19g**	100	63 (*S*)
20	**L6e**	100	18 (*S*)	49	**L20a**	100	39 (*R*)
21	**L7d**	100	83 (*R*)	50	**L20f**	100	75 (*R*)
22	**L7e**	100	16 (*S*)	51	**L20g**	100	64 (*S*)
23	**L8a**	100	36 (*R*)	52	**L21f**	100	81 (*R*)
24	**L8d**	100	96 (*R*)	53	**L21g**	100	23 (*S*)
25	**L8e**	100	34 (*S*)	54	**L22f**	100	90 (*R*)
26	**L9a**	100	29 (*R*)	55	**L22g**	100	48 (*S*)
27	**L9f**	100	91 (*R*)	56	**L23f**	100	85 (*R*)
28	**L9g**	100	34 (*S*)	57	**L23g**	100	92 (*S*)
29	**L10f**	100	61 (*R*)				

[a] Reactions conditions: $[Rh(cod)_2]BF_4$ (1 mol%), ligand (1 mol%), **S2** (0.25 mmol), CH_2Cl_2 (2 mL), H_2 (10 bar), 20 h at rt.[b] Conversion and enantiomeric excesses determined by chiral GC.

We also screened ligands **L1**-**L23a**-**g** in the asymmetric reduction of methyl 2-acetamidoacrylate **S3**. Substrate **S3** is similar to **S2**, but the phenyl group in the latter substrate is lacking; so a different requirement of the ligand parameters may be expected. The results, which are summarized in Table 3.2.3, indicated again that the effect of the ligand parameters on enantioselectivity is different from the hydrogenation of **S1** and **S2**. The main difference can be found in the cooperative effect observed between the configuration of the biaryl phosphite moiety and the substituents in the alkyl chain next to the phosphite moiety. Enantioselectivity is therefore best with ligand **L8e**, with two methyl substituents at the carbon adjacent to the phosphite group, but in contrast to **S2**, with an

(*S*)-biaryl phosphite group (entry 25). As for substrate **S1**, we were able to improve enantioselectivities up to 86% by replacing the sulphur atom in ligand **L8e** by selenium (ligand **L22g**; entry 55).

Table 3.2.3. Selected results for the Rh-catalyzed hydrogenation of **S3** using the phosphite-thioether ligand library **L1**-**L23a**-**g**.[a]

Entry	Ligand	% Conv[b]	% ee[b]	Entry	Ligand	% Conv[b]	% ee[b]
1	**L1a**	100	37 (*R*)	30	**L10g**	100	14 (*S*)
2	**L1b**	100	15 (*R*)	31	**L11a**	100	18 (*R*)
3	**L1c**	100	19 (*S*)	32	**L11f**	100	43 (*R*)
4	**L1d**	100	45 (*R*)	33	**L11g**	100	56 (*S*)
5	**L1e**	100	15 (*R*)	34	**L12a**	100	22 (*R*)
6	**L1f**	100	55 (*R*)	35	**L12f**	100	39 (*R*)
7	**L1g**	100	11 (*R*)	36	**L12g**	100	60 (*S*)
8	**L2a**	100	13 (*R*)	37	**L13a**	100	19 (*R*)
9	**L2f**	100	21 (*R*)	38	**L14a**	100	21 (*R*)
10	**L2g**	100	2 (*S*)	39	**L14g**	100	56 (*S*)
11	**L3a**	100	9 (*S*)	40	**L15g**	100	58 (*S*)
12	**L3d**	100	50 (*S*)	41	**L16g**	100	57 (*S*)
13	**L3e**	100	17 (*R*)	42	**L17g**	100	56 (*S*)
14	**L4a**	100	43 (*S*)	43	**L18a**	100	38 (*R*)
15	**L4d**	100	53 (*S*)	44	**L18f**	100	49 (*R*)
16	**L4e**	100	18 (*R*)	45	**L18g**	100	56 (*S*)
17	**L5d**	100	43 (*S*)	46	**L19a**	100	28 (*R*)
18	**L5e**	100	18 (*R*)	47	**L19f**	100	60 (*R*)
19	**L6d**	100	29 (*R*)	48	**L19g**	100	49 (*S*)
20	**L6e**	100	19 (*R*)	49	**L20a**	100	24 (*R*)
21	**L7d**	99	17 (*R*)	50	**L20f**	100	58 (*R*)
22	**L7e**	100	48 (*R*)	51	**L20g**	100	18 (*R*)
23	**L8a**	100	58 (*R*)	52	**L21f**	100	41 (*R*)
24	**L8d**	100	45 (*R*)	53	**L21g**	100	19 (*R*)
25	**L8e**	100	81 (*S*)	54	**L22f**	100	50 (*R*)
26	**L9a**	100	42 (*R*)	55	**L22g**	100	86 (*S*)
27	**L9f**	100	54 (*R*)	56	**L23f**	100	44 (*R*)
28	**L9g**	100	80 (*S*)	57	**L23g**	100	62 (*S*)
29	**L10f**	100	26 (*R*)				

[a] Reactions conditions: $[Rh(cod)_2]BF_4$ (1 mol%), ligand (1 mol%), **S3** (0.25 mmol), CH_2Cl_2 (2 mL), H_2 (10 bar), 20 h at rt.[b] Conversion and enantiomeric excesses determined by chiral GC.

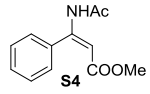
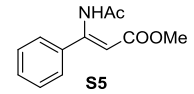
3.2.2.3. Asymmetric hydrogenation of β-dehydroamino acid derivatives S4-S15

We next screened ligands **L1**-**L23a**-**g** in the asymmetric hydrogenation of β-dehydroamino acid derivatives **S4**-**S15**. This is an important class of substrates because their hydrogenation gives rise to chiral β-amino acids, which are structural elements of β-peptides, β-lactam antibiotics, and many other biologically active compounds.[8] A problem often encountered in previously studied hydrogenation methods arises from the different catalytic behaviour attributed to (*Z*)- and (*E*)-isomeric substrates. Generally (*E*)-isomers led

to higher ee values than the corresponding (*Z*)-substrates, which are the major isomers formed in most current synthetic protocols.[9]

In a first set of experiments, we used methyl (*E*)-3-acetamido-3-phenylacrylate **S4** and methyl (*Z*)-3-acetamido-3-phenylacrylate **S5** as substrates to assess the potential of the ligand library **L1**-**L23a**-**g**. The results, which are summarized in Table 3.2.4, indicated that higher enantioselectivities are obtained in the hydrogenation of the more demanding (*Z*)-**S5** than for the (*E*)-analogue **S4**. The sense of enantioselectivity is controlled by the configuration of the biaryl phosphite moiety. Ligands containing an (*R*)-biaryl phosphite group led to (*S*)-products, while the (*R*)-products are achieved using ligands with (*S*)-biaryl phosphite groups (i.e. entry 1 vs 2). In general, ligands containing an (*S*)-biaryl phosphite group (**g**) provide higher enantioselectivities than those containing an (*R*)-biaryl moiety (**f**). Nevertheless, in the reduction of challenging (*Z*)-**S6**, both (*R*)- and (*S*)-biaryl moieties led to similar levels of enantioselectivity (i.e. entries 11 and 12). The results also indicated that the use of ligands **L11**-**L18**, with a chiral carbon adjacent to the phosphite group led to higher enantioselectivities (entries 7-12). In summary, both enantiomers of the hydrogenation product are accessible with similar good enantioselectivities (ee's up to 86%) using Rh-**L18f** and Rh-**L18g** catalytic systems (entries 11 and 12).

Table 3.2.4. Selected results for the Rh-catalyzed hydrogenation of **S4** and **S5** using the phosphite-thioether ligand library **L1**-**L23a**-**g**.[a]

		 **S4**		 **S5**	
Entry	Ligand	% Conv[b]	% ee[b]	% Conv[b]	% ee[b]
1	**L1f**	80	30 (*S*)	60	70 (*S*)
2	**L1g**	90	55 (*R*)	55	79 (*R*)
3	**L2f**	75	12 (*R*)	65	29 (*S*)
4	**L2g**	70	44 (*R*)	45	63 (*R*)
5	**L8f**	100	21 (*S*)	100	75 (*S*)
6	**L8g**	100	25 (*R*)	100	20 (*R*)
7	**L11f**	100	15 (*S*)	100	70 (*S*)
8	**L11g**	100	55 (*R*)	100	86 (*R*)
9	**L12g**	100	60 (*R*)	100	60 (*R*)
10	**L14g**	81	41 (*R*)	100	74 (*R*)
11	**L18f**	100	54 (*S*)	100	80 (*S*)
12	**L18g**	100	44 (*R*)	100	86 (*R*)
13	**L19f**	100	28 (*S*)	100	39 (*S*)
14	**L19g**	100	14 (*R*)	100	49 (*R*)
15	**L22f**	100	22 (*S*)	100	76 (*S*)
16	**L22g**	100	24 (*R*)	100	20 (*R*)

[a] Reactions conditions: $[Rh(cod)_2]BF_4$ (1 mol%), ligand (1 mol%), substrate (0.25 mmol), CH_2Cl_2 (2 mL), H_2 (10 bar), 20 h at rt.[b] Conversion and enantiomeric excesses determined by chiral GC.

We next studied the asymmetric hydrogenation of other (*E*)- and (*Z*)-β-dehydroamino acid derivatives **S6-S15** using Rh-**L18g** catalyst precursor (Figure 3.2.2). We found again that enantioselectivities are better when using (*Z*)-olefines than for (*E*)-olefins. Moreover, enantioselectivities for both substrate types are highly affected by the olefins and ester substituents.

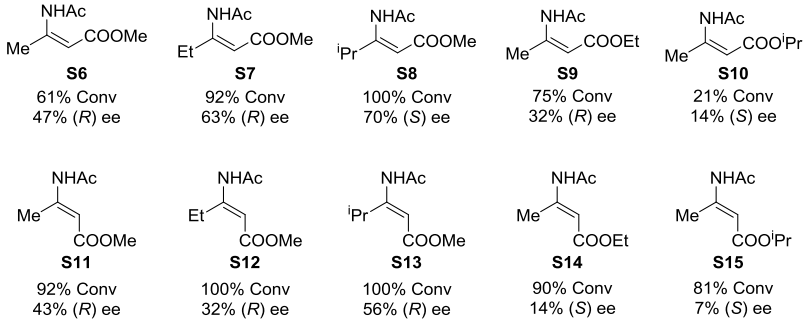
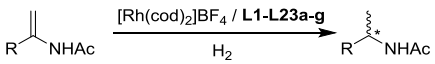


Figure 3.2.2. Asymmetric hydrogenation of β-dehydro amino acid esters **S6**-**S15** using Rh-**L18g** catalyst precursor. Reaction conditions: $[Rh(cod)_2]BF_4$ (1 mol%), ligand (1 mol%), substrate (0.25 mmol), CH_2Cl_2 (2 mL), H_2 (10 bar), 20 h at rt.

3.2.2.4. Asymmetric hydrogenation of α-enamides S16-S20

We subsequently applied ligand library **L1**-**L23a**-**g** in the Rh-catalyzed asymmetric reduction of several enamides (Equation 3.2.2). Enamides are an important class of substrates because their reductions give rise to optically active secondary amines, which are useful building blocks for the synthesis of fine chemicals.[10]



(3.2.2)

S16 R= 4-OMe-C_6H_4
S17 R= 4-F-C_6H_4
S18 R= 4-Me-C_6H_4
S19 R= C_6H_5
S20 R= 2-Naphthyl

In a first set of experiments, we used *N*-(1-(4-methoxyphenyl)vinyl)-acetamide **S16** as substrate to assess the potential of the ligand library **L1**-**L23a**-**g** under standard reaction conditions[11] (i.e. $[Rh(cod)_2]BF_4$ as catalyst precursor, 30 bar H_2 at rt). The results, which are summarized in Table 3.2.5, indicate that again enantioselectivities are highly affected by a subtle balance of the thioether substituent, the substituent at the alkyl backbone chain next to the phosphite moiety as well as the configuration of the biaryl phosphite moiety. However, the effect of these parameters is different from the hydrogenation of **S1**-**S3**. Thus, for instance, although the presence of an (*R*)-biaryl phosphite group led to higher enantioselectivities (entries 4 vs 5), enantioselectivity is hardly unaffected by the different substituents at the biaryl phosphite group (entries 1-3). Once again, either the introduction of two methyl substituents at the alkyl chain next to the phosphite moiety (ligands **L8**-**L9**)

or the use of ligands **L11**-**L17**, with an (*R*)-configurated carbon adjacent to the phosphite group, have a positive effect on enantioselectivity (i.e. entry 7 vs 24 and 40). To sum up, the best enantioselectivities (ee's up to 92%) were obtained using Rh-**L15g** catalyst precursor (entry 40).

Table 3.2.5. Selected results for the Rh-catalyzed hydrogenation of **S16** using the phosphite-thioether ligand library **L1**-**L23a**-**g**.[a]

Entry	Ligand	% Conv[b]	% ee[b]	Entry	Ligand	% Conv[b]	% ee[b]
1	**L1a**	100	32 (*R*)	30	**L10g**	100	58 (*S*)
2	**L1b**	100	30 (*R*)	31	**L11a**	100	70 (*S*)
3	**L1c**	100	31 (*R*)	32	**L11f**	100	75 (*R*)
4	**L1d**	100	54 (*R*)	33	**L11g**	100	63 (*S*)
5	**L1e**	100	31 (*S*)	34	**L12a**	100	70 (*S*)
6	**L1f**	100	51 (*R*)	35	**L12f**	100	67 (*R*)
7	**L1g**	100	40 (*S*)	36	**L12g**	100	72 (*S*)
8	**L2a**	100	15 (*R*)	37	**L13a**	100	87 (*S*)
9	**L2f**	100	19 (*R*)	38	**L14a**	100	86 (*S*)
10	**L2g**	100	12 (*S*)	39	**L14g**	100	90 (*S*)
11	**L3a**	100	33 (*S*)	40	**L15g**	100	92 (*S*)
12	**L3d**	100	14 (*R*)	41	**L16g**	100	89 (*S*)
13	**L3e**	100	29 (*S*)	42	**L17g**	100	91 (*S*)
14	**L4a**	100	19 (*S*)	43	**L18a**	100	59 (*R*)
15	**L4d**	100	8 (*R*)	44	**L18f**	100	81 (*R*)
16	**L4e**	100	19 (*S*)	45	**L18g**	100	46 (*S*)
17	**L5d**	100	52 (*R*)	46	**L19a**	100	14 (*R*)
18	**L5e**	100	30 (*S*)	47	**L19f**	100	27 (*R*)
19	**L6d**	100	59 (*R*)	48	**L19g**	100	35 (*S*)
20	**L6e**	100	29 (*S*)	49	**L20a**	100	35 (*R*)
21	**L7d**	100	25 (*R*)	50	**L20f**	100	54 (*R*)
22	**L7e**	100	19 (*S*)	51	**L20g**	100	43 (*S*)
23	**L8a**	100	13 (*R*)	52	**L21f**	100	48 (*R*)
24	**L8d**	100	84 (*R*)	53	**L21g**	100	36 (*S*)
25	**L8e**	100	11 (*S*)	54	**L22f**	100	80 (*R*)
26	**L9a**	100	46 (*R*)	55	**L22g**	100	29 (*S*)
27	**L9f**	100	84 (*R*)	56	**L23f**	100	79 (*R*)
28	**L9g**	100	13 (*S*)	57	**L23g**	100	90 (*S*)
29	**L10f**	100	46 (*R*)				

[a] Reactions conditions: $[Rh(cod)_2]BF_4$ (1 mol%), ligand (1 mol%), **S16** (0.25 mmol), CH_2Cl_2 (2 mL), H_2 (30 bar), 20 h at rt.[b] Conversion and enantiomeric excesses determined by chiral GC.

We next studied the asymmetric hydrogenation of other α-enamides **S17**-**S20** using Rh-**L15g** as catalyst precursor (Figure 3.2.3). We found that enantioselectivity is hardly affected by the presence of either electron-donating or electron-withdrawing groups at the *para* positions of the aryl group. However, enantioselectivities are best when electron-withdrawing groups are present (i.e. 95% ee for *N*-(1-(4-trifluorophenyl)vinyl)-acetamide **S17**).

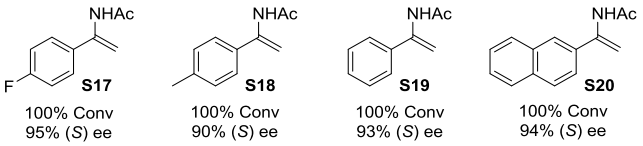


Figure 3.2.3. Asymmetric hydrogenation of α-aryl enamides **S17**-**S20** using Rh-**L15g** catalyst precursor. Reaction conditions: $[Rh(cod)_2]BF_4$ (1 mol%), ligand (1 mol%), substrate (0.25 mmol), CH_2Cl_2 (2 mL), H_2 (30 bar), 20 h at rt.

3.2.2.5. Asymmetric hydrogenation of β-enamides S21-S28

Finally, we explored the hydrogenation of functionalized cyclic β-aryl-*N*-acetyl enamides **S21**-**S28**. The hydrogenation of this substrate class is still a challenge because in contrast to the parent α-enamides most of the Rh- and Ru-catalysts provided low enantiomeric excesses; nevertheless, some successful protocols are available.[12] Thus, for instance, Tang and coworkers have designed a new P-stereogenic diphosphine ligand with deep chiral pockets that has shown high efficiency in the Rh-catalyzed hydrogenation of this substrate class (ee's ranging from 94% to 98%). As a model, we chose *N*-(3,4-dihydronaphthalen-2-yl)acetamide **S21** to assess the potential of the new ligand library. The results are summarized in Table 3.2.6. Again, we can observe that enantioselectivity is affected by the ligands parameters. However, the highest enantioselectivity of the ligand series (up to 90% ee) was achieved using Rh-**L23g** catalytic system.

Table 3.2.6. Selected results for the Rh-catalyzed hydrogenation of **S21** using the phosphite-thioether/selenoether ligand library **L1**-**L23a**-**g**.[a]

Entry	Ligand	% Conv[b]	% ee[b]	Entry	Ligand	% Conv[b]	% ee[b]
1	**L1f**	100	87 (*R*)	10	**L14g**	100	85 (*S*)
2	**L1g**	100	79 (*S*)	11	**L18f**	100	82 (*R*)
3	**L2f**	100	86 (*R*)	12	**L18g**	100	61 (*S*)
4	**L2g**	100	83 (*S*)	13	**L19f**	100	49 (*R*)
5	**L9f**	100	83 (*R*)	14	**L19g**	100	63 (*S*)
6	**L9g**	100	70 (*S*)	15	**L20f**	100	88 (*R*)
7	**L11f**	100	84 (*R*)	16	**L20g**	100	78 (*S*)
8	**L11g**	100	87 (*S*)	17	**L23f**	100	85 (*R*)
9	**L12g**	100	84 (*S*)	18	**L23g**	100	90 (*S*)

[a] Reactions conditions: $[Rh(cod)_2]BF_4$ (1 mol%), ligand (1 mol%), **S21** (0.25 mmol), CH_2Cl_2 (2 mL), H_2 (30 bar), 20 h at rt.[b] Conversion and enantiomeric excesses determined by chiral GC.

We next studied the asymmetric hydrogenation of other β-aryl-*N*-acetyl enamides **S22**-**S28** using Rh-**L23g** catalytic system (Figure 3.2.4). Advantageous, the results indicate that both activities and enantioselectivities are relatively insensitive to the different substitution pattern in the aryl ring. However, the hydrogenation of linear enamide **S28** proceeds with lower enantioselectivities than for the cyclic analogue **S21**. To sum up, Rh-**L23g** catalytic system is therefore able to give access to a range of 2-aminotetralines and 3-aminochromanes in good enantioselectivities (ee's ranging from 81% to 92%).

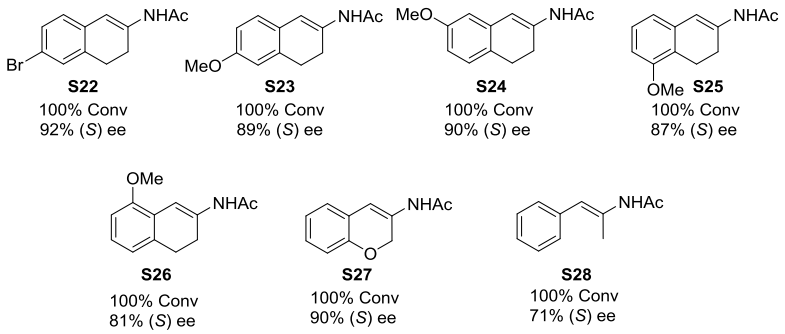


Figure 3.2.4. Asymmetric hydrogenation of α-aryl enamides **S22**-**S28** using Rh-**L23g** catalyst precursor. Reaction conditions: $[Rh(cod)_2]BF_4$ (1 mol%), ligand (1 mol%), substrate (0.25 mmol), CH_2Cl_2 (2 mL), H_2 (30 bar), 20 h at rt.

3.2.3. Conclusions

A modular thioether-phosphite ligand library has been synthesized for the Rh-catalyzed asymmetric hydrogenation of α,β-unsaturated carboxylic acid derivatives and enamides. These ligands can be prepared efficiently from easily accessible L-(+)-tartaric acid and D-(+)-mannitol. The results indicate that enantioselectivity is mainly affected by the substituents in both the thioether/selenoether substituent group and at the alkyl backbone chain next to the phosphite moiety and next to the thioether/selenoether, and the configuration of the biaryl phosphite moiety. However, the effect of these parameters depends on each substrate class. By carefully selecting the ligand components, full conversions and high enantioselectivities have been achieved in the reduction of several α- and β-dehydroamino acid esters (up to 98% ee), dimethyl itaconate (up to 79% ee), and a range of α- and β-enamides (up to 95% ee).

3.2.4. Experimental section

3.2.4.1. General considerations

All syntheses were performed by using standard Schlenk techniques under an argon atmosphere. Solvents were purified by standard procedures. Phosphorochloridites are easily prepared in one step from the corresponding biaryls.[13] Compounds **1**,[14] **2**,[15] **3**,[16] **4**,[17] **5**[17], 2,3-*O*-isopropylidene-1-*O*-(*tert*-butyldimethylsilyl)-L-threitol[18] and 1-deoxy-2,3-*O*-isopropylidene-1-tosyl-D-arabinitol[19] were prepared as previously described. Methyl (*Z*)-*N*-acetylaminocinnamate **S2**,[20] β-dehydroamino acid derivatives **S4**-**S15**[21] and enamides **S16**-**S28**[22] were prepared following literature procedures. All other reagents were used as commercially available. ^1H, $^{13}C\{^1H\}$, $^{31}P\{^1H\}$ NMR spectra experiments were recorded using a 400 MHz spectrometer. Chemical shifts are relative to that of $SiMe_4$ (^1H and ^{13}C) as internal standard or H_3PO_4 (^{31}P) as external standard. ^1H and ^{13}C assignments were done based on ^1H-^1H gCOSY and ^1H-^{13}C gHSQC experiments.

3.2.4.2. Typical procedure for the preparation of phosphite-thioether/selenoether ligands L1-L23a-g

The corresponding phosphorochloridite (1.1 mmol) produced in situ was dissolved in toluene (5 mL), and pyridine (0.3 mL, 3.9 mmol) was added. The corresponding thioether-hydroxyl compound (1 mmol) was azeotropically dried with toluene (3 x 2 mL) and then dissolved in toluene (5 mL) to which pyridine (0.3 mL, 3.9 mmol) was added. The alcohol solution was transferred slowly to a solution of phosphorochloridite. The reaction mixture was stirred at 80°C for 90 min, after which the pyridine salts were removed by filtration. In the case of ligands **L13**-**17a**-**g**, triethylamine was added instead of pyridine (0.5 ml, 3.9 mmol) and the reaction mixture was stirred overnight at 80 °C. In the case of ligands **L8**-**L9**,**22a**-**g**, thriethylamine (0.5 ml, 2.8 mmol) and DMAP (0.11 mmol, 13.4 mg) were added and the reaction mixture was stirred overnight at room temperature. Evaporation of the solvent gave a white foam, which was purified by flash chromatography.

L1a. Yield: 413 mg (65%); SiO_2-flash chromatography (toluene/hexane/NEt_3 = 5:5:0.1). ^{31}P NMR (400 MHz, C_6D_6) δ: 135.7 (s). ^1H NMR (C_6D_6), δ: 1.27 (s, 9H, CH_3, ^{t}Bu), 1.28 (s, 9H, CH_3, ^{t}Bu), 1.29 (s, 3H, CH_3), 1.32 (s, 3H, CH_3), 1.57 (s, 9H, CH_3, ^{t}Bu), 1.59 (s, 9H, CH_3, ^{t}Bu), 2.88 (dd, 1H, $^2J_{H-H}$= 13.6 Hz, $^3J_{H-H}$= 6.4 Hz, CH_2-S), 3.03 (dd, 1H, $^2J_{H-H}$= 13.6 Hz, $^3J_{H-H}$= 5.6 Hz, CH_2-S), 3.93-3.96 (m, 1H, C*H*CH_2O), 4.02 (m, 1H, C*H*CH_2S), 4.08-4.11 (m, 2H, CH_2-O), 6.87-7.60 (m, 9H, CH=). ^{13}C NMR (C_6D_6), δ: 26.9 (CH_3), 27.1 (CH_3), 30.8 (CH_3, ^{t}Bu), 30.9 (CH_3, ^{t}Bu), 31.2 (CH_3, ^{t}Bu), 34.3 (C, ^{t}Bu), 35.3 (C, ^{t}Bu), 35.3 (C, ^{t}Bu), 36.5 (CH_2-S), 64.6 (CH_2-O), 76.5 (*C*HCH_2S), 79.7 (d, *C*HCH_2O, J_{C-P}= 3.8 Hz), 109.4 (CMe_2), 124.1 (CH=), 125.3 (C), 125.7 (CH=), 126.7 (CH=), 128.1 (CH=), 128.7 (CH=), 128.9 (CH=), 129.0 (CH=), 133.2 (C), 136.4 (C), 140.1 (C), 140.2 (C), 146.5 (C), 146.6 (C). MS HR-ESI [found 715.3556, $C_{41}H_{57}O_5PS$ $(M-Na)^+$ requires 715.35.57].

L1b. Yield: 294 mg (46%); SiO_2-flash chromatography (toluene/hexane/NEt_3 = 5:5:0.1). ^{31}P NMR (400 MHz, C_6D_6) δ: 134.3 (s). ^1H NMR (C_6D_6), δ: 1.24 (s, 3H, CH_3), 1.27 (s, 3H, CH_3), 1.45 (s, 9H, CH_3, ^{t}Bu), 1.48 (s, 9H, CH_3, ^{t}Bu), 2.83 (dd, 1H, $^2J_{H-H}$= 13.6 Hz, $^3J_{H-H}$= 6.4 Hz, CH_2-S), 3.02 (dd, 1H, $^2J_{H-H}$= 13.6 Hz, $^3J_{H-H}$= 5.6 Hz, CH_2-S), 3.31 (s, 6H, CH_3-O), 3.90-3.92 (m, 1H, C*H*CH_2O), 3.93-3.97 (m, 1H, C*H*CH_2S), 3.98-4.02 (m, 1H, CH_2-O), 4.12 (m, 1H, CH_2-O), 6.64-7.21 (m, 9H, CH=). ^{13}C NMR (C_6D_6), δ: 26.9 (CH_3), 27.0 (CH_3), 30.6 (CH_3, ^{t}Bu), 35.1 (C, ^{t}Bu), 35.2 (C, ^{t}Bu), 36.6 (CH_2-S), 54.7 (CH_3-O), 64.6 (CH_2-O), 76.2 (*C*HCH_2S), 79.8 (d, *C*HCH_2O, J_{C-P}= 3.0 Hz), 109.4 (CMe_2), 112.9 (CH=), 114.5 (CH=), 125.2 (C), 125.9 (CH=), 128.1 (C), 128.8 (CH=), 128.9 (CH=), 129.1 (CH=), 133.8 (C), 136.3 (C), 137.4 (C), 142.2 (C), 142.3 (C), 156.0 (C). MS HR-ESI [found 663.2514, $C_{35}H_{45}O_7PS$ $(M-Na)^+$ requires 663.2516].

L1c. Yield: 366 mg (60%); SiO_2-flash chromatography (toluene/hexane/NEt_3 = 5:5:0.1). ^{31}P NMR (400 MHz, C_6D_6) δ: 134.5 (s). ^1H NMR (C_6D_6), δ: 0.0 (s, 9H, CH_3, $SiMe_3$), 0.03 (s, 9H, CH_3, $SiMe_3$), 0.88 (s, 3H, CH_3), 0.92 (s, 3H, CH_3), 2.48 (dd, 1H, $^2J_{H-H}$= 13.2 Hz, $^3J_{H-H}$= 5.6 Hz, CH_2-S), 2.64 (dd, 1H, $^2J_{H-H}$= 13.6 Hz, $^3J_{H-H}$= 4.8 Hz, CH_2-S), 3.50-3.54 (m, 1H, CH_2-O), 3.54-3.56 (m, 1H, C*H*CH_2O), 3.56-3.60 (m, 1H, C*H*CH_2S), 3.67-3.71 (m, H, CH_2-O), 6.52-7.03 (m,

11H, CH=). ^{13}C NMR (C_6D_6), δ: 0.0 (CH_3-Si), 27.2 (CH_3), 27.4 (CH_3), 36.9 (CH_2-S), 64.8 (CH_2-O), 76.7 (*C*HCH_2S), 79.9 (d, *C*HCH_2O, $J_{C\text{-}P}$= 3.1 Hz), 109.7 (CMe_2), 125.0 (CH=), 125.6 (C), 126.1 (CH=), 128.4 (CH=), 129.0 (CH=), 129.2 (CH=), 129.5 (C), 131.2 (CH=), 131.3 (CH=), 131.9 (CH=),132.5 (C), 135.5 (CH=), 135.6 (CH=), 136.6 (C), 155.0 (C), 155.1 (C). MS HR-ESI [found 635.1843, $C_{31}H_{41}O_5PSSi_2$ $(M\text{-}Na)^+$ requires 635.1843].

L1d. Yield: 342 mg (54%); SiO_2-flash chromatography (toluene/hexane/NEt_3 = 5:5:0.1). ^{31}P NMR (400 MHz, C_6D_6) δ: 128.7 (s). ^{1}H NMR (C_6D_6), δ: 1.25 (s, 3H, CH_3), 1.27 (s, 3H, CH_3), 1.52 (s, 9H, CH_3, ^{t}Bu), 1.54 (s, 9H, CH_3, ^{t}Bu), 1.64 (s, 3H, CH_3), 1.73 (s, 3H, CH_3), 2.02 (s, 3H, CH_3), 2.04 (s, 3H, CH_3), 2.80 (dd, 1H, $^2J_{H\text{-}H}$= 13.6 Hz, $^3J_{H\text{-}H}$= 6 Hz, CH_2-S), 2.97 (dd, 1H, $^2J_{H\text{-}H}$= 13.6 Hz, $^3J_{H\text{-}H}$= 5.2 Hz, CH_2-S), 3.53-3.59 (m, 1H, CH_2-O), 3.84-3.88 (m, 1H, C*H*CH_2O), 3.94-3.99 (m, 1H, C*H*CH_2S), 4.17-4.23 (m, 1H, CH_2-O), 6.84-7.22 (m, 7H, CH=). ^{13}C NMR (C_6D_6), δ: 16.1 (CH_3), 16.3 (CH_3), 20.0 (CH_3), 26.9 (CH_3), 27.0 (CH_3), 30.9 (CH_3, ^{t}Bu), 31.2 (CH_3, ^{t}Bu), 34.5 (C, ^{t}Bu), 34.6 (C, ^{t}Bu), 36.5 (CH_2-S), 64.4 (CH_2-O), 76.4 (*C*HCH_2S), 79.8 (d, *C*HCH_2O, $J_{C\text{-}P}$= 3.1 Hz), 109.3 (CMe_2), 125.8 (CH=), 127.8 (CH=), 127.9 (CH=), 128.1 (CH=), 128.7 (CH=), 128.9 (CH=), 129.0 (CH=),131.1 (C), 131.5 (C), 131.7 (C), 132.3 (C), 134.5 (C), 134.9 (C), 136.5 (C), 137.0 (C), 137.4 (C), 138.1 (C), 145.8 (C). MS HR-ESI [found 659.2930, $C_{37}H_{49}O_5PS$ $(M\text{-}Na)^+$ requires 659.2931].

L1e. Yield: 317 mg (50%); SiO_2-flash chromatography (toluene/hexane/NEt_3 = 5:5:0.1). ^{31}P NMR (400 MHz, C_6D_6) δ: 126.1 (s). ^{1}H NMR (C_6D_6), δ: 1.19 (s, 3H, CH_3), 1.24 (s, 3H, CH_3), 1.52 (s, 9H, CH_3, ^{t}Bu), 1.54 (s, 9H, CH_3, ^{t}Bu), 1.63 (s, 3H, CH_3), 1.72 (s, 3H, CH_3), 2.01 (s, 3H, CH_3), 2.03 (s, 3H, CH_3), 2.82 (dd, 1H, $^2J_{H\text{-}H}$= 13.6 Hz, $^3J_{H\text{-}H}$= 6.4 Hz, CH_2-S), 2.96 (dd, 1H, $^2J_{H\text{-}H}$= 13.2 Hz, $^3J_{H\text{-}H}$= 4.8 Hz, CH_2-S), 3.56-3.61 (m, 1H, CH_2-O), 3.83-3.88 (m, 1H, C*H*CH_2O), 3.90-3.95 (m, 1H, C*H*CH_2S), 4.13-4.19 (m, 1H, CH_2-O), 6.85-7.23 (m, 7H, CH=). ^{13}C NMR (C_6D_6), δ: 16.1 (CH_3), 16.4 (CH_3), 20.0 (CH_3), 26.7 (CH_3), 27.0 (CH_3), 30.9 (CH_3, ^{t}Bu), 31.2 (C, ^{t}Bu), 36.4 (CH_2-S), 64.4 (CH_2-O), 76.2 (*C*HCH_2S), 79.6 (d, *C*HCH_2O, $J_{C\text{-}P}$= 3 Hz), 109.3 (CMe_2), 125.7 (CH=), 128.1 (CH=), 128.2 (CH=), 128.8 (CH=), 128.9 (CH=), 129.0 (CH=), 131.0 (C), 131.5 (C), 131.6 (C), 132.3 (C), 134.4 (C), 135.0 (C), 136.5 (C), 136.9 (C), 137.4 (C), 138.1 (C), 145.8 (C). MS HR-ESI [found 659.2931, $C_{37}H_{49}O_5PS$ $(M\text{-}Na)^+$ requires 659.2931]..

L1f. Yield: 335.2 mg (47%); SiO_2-flash chromatography (toluene/hexane/NEt_3 = 5:5:0.1). ^{31}P NMR (161.9 MHz, C_6D_6): δ=134.1 (s). ^{1}H NMR (400 MHz, C_6D_6): δ=0.51 (s, 9H, CH_3, $SiMe_3$), 0.55 (s, 9H, CH_3, $SiMe_3$), 1.27 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 2.77 (dd, 1H, CH_2-S, $^2J_{H\text{-}H}$ =13.2 Hz, $^3J_{H\text{-}H}$ =6.0 Hz), 2.95 (dd, 1H, CH_2-S, $^2J_{H\text{-}H}$ =13.6 Hz, $^2J_{H\text{-}H}$ =5.2 Hz), 3.39-3.44 (m, 1H, CH_2-O), 3.72-3.76 (m, 1H, C*H*CH_2O), 3.94-3.99 (m, 1H, C*H*CH_2S), 4.29-4.35 (m, 1H, CH_2-O), 6.85-7.16 (m, 9H, CH=), 7.23 (d, 1H, CH=, $^3J_{H\text{-}H}$ =8.4 Hz), 7.34 (d, 1H, CH=, $^3J_{H\text{-}H}$ =8.4 Hz), 7.70 (d, 2H, CH=, $^3J_{H\text{-}H}$ =8.0 Hz), 8.11 (s, 1H, CH=), 8.13 (s, 1H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ=-0.5 (CH_3, $SiMe_3$), -0.3 (d, CH_3, $SiMe_3$, $J_{C\text{-}P}$ =4.6 Hz), 26.8 (CH_3), 26.9 (CH_3), 36.5 (CH_2-S), 63.9 (CH_2-O), 75.9 (*C*HCH_2S), 79.6 (*C*HCH_2O), 109.2 (CMe_2), 122.3-152.6 (aromatic carbons). MS HR-ESI [found 735.2154, $C_{39}H_{45}O_5PSSi_2$ $(M\text{-}Na)^+$ requires 735.2156].

L1g. Yield: 289.7 mg (41%); SiO_2-flash chromatography (toluene/hexane/NEt_3 = 5:5:0.1). ^{31}P NMR (161.9 MHz, C_6D_6): δ=132.1 (s). ^{1}H NMR (400 MHz, C_6D_6): δ=0.51 (s, 9H, CH_3,

$SiMe_3$), 0.57 (s, 9H, CH_3, $SiMe_3$), 1.22 (s, 3H, CH_3), 1.27 (s, 3H, CH_3), 2.73 (dd, 1H, CH_2-S, $^2J_{H-H}$ =13.6 Hz, $^3J_{H-H}$ =6.0 Hz), 2.92 (dd, 1H, CH_2-S, $^2J_{H-H}$ =13.6 Hz, $^2J_{H-H}$ =4.8 Hz), 3.57-3.62 (m, 1H, CH_2-O), 3.77-3.81 (m, 2H, C*H*CH_2S, C*H*CH_2O), 4.10-4.14 (m, 1H, CH_2-O), 6.84-7.16 (m, 9H, CH=), 7.23 (d, 1H, CH=, $^3J_{H-H}$ =8.4 Hz), 7.35 (d, 1H, CH=, $^3J_{H-H}$ =8.4 Hz), 7.69 (t, 2H, CH=, $^3J_{H-H}$ =6.8 Hz), 8.10 (s, 1H, CH=), 8.14 (s, 1H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ=-0.4 (CH_3, $SiMe_3$), -0.2 (d, CH_3, $SiMe_3$, J_{C-P} =5.4 Hz), 26.7 (CH_3), 26.9 (CH_3), 36.5 (CH_2-S), 64.4 (d, CH_2-O, $^2J_{C-P}$ = 5.1 Hz), 75.5 (*C*HCH_2S), 79.5 (d, *C*HCH_2O, $^3J_{C-P}$ =3.1 Hz), 109.3 (CMe_2), 122.2-152.9 (aromatic carbons). MS HR-ESI [found 735.2155, $C_{39}H_{45}O_5PSSi_2$ $(M-Na)^+$ requires 735.2156].

L2a. Yield: 322 mg (51%); SiO_2-flash chromatography (toluene/hexane/NEt_3 = 5:5:0.1). ^{31}P NMR (400 MHz, C_6D_6) δ: 135.4 (s). ^{1}H NMR (C_6D_6), δ: 1.23 (s, 9H, CH_3, ^{t}Bu), 1.24 (s, 9H, CH_3, ^{t}Bu), 1.28 (s, 3H, CH_3), 1.28 (s, 3H, CH_3), 1.53 (s, 9H, CH_3, ^{t}Bu), 1.55 (s, 9H, CH_3, ^{t}Bu), 1.79 (s, 3H, CH_3), 2.36 (dd, 1H, $^2J_{H-H}$= 14 Hz, $^3J_{H-H}$= 6 Hz, CH_2-S), 2.46 (dd, 1H, $^2J_{H-H}$= 13.6 Hz, $^3J_{H-H}$= 5.2 Hz, CH_2-S), 3.78-3.83 (m, 1H, C*H*CH_2O), 3.93-3.98 (m, 1H, C*H*CH_2S), 4.00-4.02 (m, 2H, CH_2-O), 6.95-7.54 (m, 4H, CH-Ar).^{13}C NMR (C_6D_6), δ: 16.1 (CH_3), 26.9 (CH_3), 27.0 (CH_3), 30.9 (2CH_3, ^{t}Bu), 31.1 (CH_3, ^{t}Bu), 31.2 (CH_3, ^{t}Bu), 34.3 (2C, ^{t}Bu), 35.3 (2C, ^{t}Bu), 36.5 (CH_2-S), 64.4 (CH_2-O), 77.5 (*C*HCH_2S), 79.5 (d, *C*HCH_2O, J_{C-P}= 3. Hz), 109.0 (CMe_2), 124.1 (CH-Ar), 125.2 (C-Ar), 126.6 (CH-Ar), 128.1 (CH-Ar), 128.9 (CH-Ar),133.1 (C-Ar), 133.2 (C-Ar), 140.0 (C-Ar), 140.1 (C-Ar), 146.4 (C-Ar), 146.5 (C-Ar), 146.6 (C-Ar). MS HR-ESI [found 653.3399, $C_{36}H_{55}O_5PS$ $(M-Na)^+$ requires 653.3400].

L3a. Yield: 376 mg (56%); SiO_2-flash chromatography (toluene/hexane/NEt_3 = 5:5:0.1). ^{31}P NMR (400 MHz, C_6D_6) δ: 135.0 (s). ^{1}H NMR (C_6D_6), δ: 1.09 (s, 9H, CH_3, ^{t}Bu), 1.23 (s, 9H, CH_3, ^{t}Bu), 1.24 (s, 9H, CH_3, ^{t}Bu),1.28 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 1.54 (s, 3H, CH_3, ^{t}Bu), 1.56 (s, 9H, CH_3, ^{t}Bu), 2.57 (dd, 1H, $^2J_{H-H}$= 12.8 Hz, $^3J_{H-H}$= 7.2 Hz, CH_2-S), 2.71 (dd, 1H, $^2J_{H-H}$= 12.8 Hz, $^3J_{H-H}$= 5.2 Hz, CH_2-S), 3.83-3.87 (m, 1H, C*H*CH_2O), 3.94-4.00 (m, 1H, C*H*CH_2S), 4.01-4.08 (m, 2H, CH_2-O), 6.95-7.53 (m, 4H, CH=). ^{13}C NMR (C_6D_6), δ: 26.9 (CH_3), 27.2 (CH_3), 30.5 (CH_3, ^{t}Bu), 30.9 (CH_3, ^{t}Bu), 31.2 (CH_3, ^{t}Bu), 31.4 (CH_2-S), 34.3 (C, ^{t}Bu), 35.3 (C, ^{t}Bu), 41.6 (C, ^{t}Bu), 64.6 (CH_2-O), 77.2 (*C*HCH_2S), 80.0 (d, *C*HCH_2O, J_{C-P}= 3.9 Hz), 109.0 (CMe_2), 124.0 (CH=), 125.2 (C), 126.6 (CH=), 128.1 (CH=),128.9 (CH=), 133.1 (C), 140.0 (C), 146.3 (C), 146.7 (C). MS HR-ESI [found 695.3870, $C_{39}H_{61}O_5PS$ $(M-Na)^+$ requires 695.3870].

L2f. Yield: 462 mg (71%); SiO_2-flash chromatography (toluene/hexane/NEt_3 = 5:5:0.1). ^{31}P NMR (161.9 MHz, C_6D_6): δ=134.0 (s). ^{1}H NMR (400 MHz, C_6D_6): δ=0.52 (s, 9H, CH_3, $SiMe_3$), 0.54 (s, 9H, CH_3, $SiMe_3$), 1.31 (s, 6H, CH_3), 1.66 (s, 3H, CH_3), 2.29 (dd, 1H, CH_2-S, $^2J_{H-H}$ =14.0 Hz, $^3J_{H-H}$ =5.6 Hz), 2.40 (dd, 1H, CH_2-S, $^2J_{H-H}$ =14.0 Hz, $^2J_{H-H}$ =5.6 Hz), 3.43-3.48 (m, 1H, CH_2-O), 3.67-3.48 (m, 1H, C*H*CH_2O), 3.86-3.91 (m, 1H, C*H*CH_2S), 4.25-4.31 (m, 1H, CH_2-O), 6.85-6.90 (m, 2H, CH=), 6.99-7.15 (m, 2H, CH=), 7.25 (d, 1H, CH=, $^3J_{H-H}$ =8.0 Hz), 7.35 (d, 1H, CH=, $^3J_{H-H}$ =8.0 Hz), 7.69 (d, 2H, CH=, $^3J_{H-H}$ =8.0 Hz), 8.10 (s, 1H, CH=), 8.13 (s, 1H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ=0.1 (CH_3, $SiMe_3$), 0.2 (d, CH_3, $SiMe_3$, J_{C-P} =4.5 Hz), 16.4 (CH_3), 27.3 (CH_3), 27.5 (CH_3), 36.9 (CH_2-S), 64.7 (d, CH_2-O, $^2J_{C-P}$ =3.8 Hz), 77.5 (*C*HCH_2S), 80.1 (d, *C*HCH_2O, $^3J_{C-P}$ =3.0 Hz), 109.5 (CMe_2), 122.9-153.3 (aromatic carbons). MS HR-ESI [found 673.1998, $C_{34}H_{43}O_5PSSi_2$ $(M-Na)^+$ requires 673.2000].

L2g. Yield: 436 mg (68%).; SiO_2-flash chromatography (toluene/hexane/NEt_3 = 5:5:0.1). ^{31}P NMR (161.9 MHz, C_6D_6): δ=132.9 (s). ^1H NMR (400 MHz, C_6D_6): δ=0.52 (s, 9H, CH_3, $SiMe_3$), 0.57 (s, 9H, CH_3, $SiMe_3$), 1.28 (s, 6H, CH_3), 1.74 (s, 3H, CH_3), 2.23 (dd, 1H, CH_2-S, $^2J_{H-H}$ =14.0 Hz, $^3J_{H-H}$ =5.6 Hz), 2.34 (dd, 1H, CH_2-S, $^2J_{H-H}$ =14.0 Hz, $^2J_{H-H}$ =5.6 Hz), 3.48-3.54 (m, 1H, CH_2-O), 3.67-3.72 (m, 1H, C*H*CH_2O) 3.73-3.78 (m, 1H, C*H*CH_2S), 4.07-4.13 (m, 1H, CH_2-O), 6.85-6.91 (m, 2H, CH=), 6.99-7.15 (m, 2H, CH=), 7.26 (d, 1H, CH=, $^3J_{H-H}$ =8.8 Hz), 7.37 (d, 1H, CH=, $^3J_{H-H}$ =8.4 Hz), 7.69 (d, 2H, CH=, $^3J_{H-H}$ =8.0 Hz), 8.10 (s, 1H, CH=), 8.15 (s, 1H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ=-0.3 (CH_3, $SiMe_3$), -0.1 (d, CH_3, $SiMe_3$, J_{C-P} =4.6 Hz), 16.1 (CH_3), 26.8 (CH_3), 27.0 (CH_3), 36.3 (CH_2-S), 64.3 (d, CH_2-O, $^2J_{C-P}$ =4.5 Hz), 76.7 (*C*HCH_2S), 79.3 (d, *C*HCH_2O, $^3J_{C-P}$ =3.8 Hz), 109.1 (CMe_2), 122.4-153.0 (aromatic carbons). MS HR-ESI [found 673.1999, $C_{34}H_{43}O_5PSSi_2$ $(M-Na)^+$ requires 673.2000].

L3d. Yield: 321 mg (52%); SiO_2-flash chromatography (toluene/hexane/NEt_3 = 5:5:0.1). ^{31}P NMR (400 MHz, C_6D_6) δ: 128.4 (s). ^1H NMR (C_6D_6), δ: 1.09 (s, 9H, CH_3, ^{t}Bu), 1.30 (s, 6H, CH_3), 1.54 (s, 9H, CH_3, ^{t}Bu), 1.56 (s, 9H, CH_3, ^{t}Bu), 1.64 (s, 3H, CH_3), 1.75 (s, 3H, CH_3), 2.02 (s, 3H, CH_3), 2.06 (s, 3H, CH_3), 2.56 (dd, 1H, $^2J_{H-H}$= 12.8 Hz, $^3J_{H-H}$= 6.8 Hz, CH_2-S), 2.69 (dd, 1H, $^2J_{H-H}$= 13.2 Hz, $^3J_{H-H}$= 6 Hz, CH_2-S), 3.58-3.64 (m, 1H, CH_2-O), 3.78-3.82 (m, 1H, C*H*CH_2O), 3.97-4.02 (m, 1H, C*H*CH_2S), 4.26-4.32 (m, 1H, CH_2-O), 6.95-7.18 (m, 2H, CH=). ^{13}C NMR (C_6D_6), δ: 16.1 (CH_3), 16.3 (CH_3), 20.0 (CH_3), 26.9 (CH_3), 27.1 (CH_3), 30.5 (CH_3, ^{t}Bu), 31.0 (CH_3, ^{t}Bu), 31.2 (CH_3, ^{t}Bu), 31.3 (CH_2-S), 34.5 (C, ^{t}Bu), 34.6 (C, ^{t}Bu), 41.6 (C, ^{t}Bu), 64.3 (CH_2-O), 77.5 (*C*HCH_2S), 80.0 (d, *C*HCH_2O, J_{C-P}= 3.1 Hz), 109.0 (CMe_2), 128.2 (CH=), 128.9 (CH=), 131.1 (C), 131.4 (C), 131.7 (C), 132.2 (C), 134.3 (C), 134.9 (C), 137.4 (C), 138.1 (C), 145.7(C), 145.8 (C). MS HR-ESI [found 639.3244, $C_{35}H_{53}O_5PS$ $(M-Na)^+$ requires 639.3244].

L3e. Yield: 388 mg (63%); SiO_2-flash chromatography (toluene/hexane/NEt_3 = 5:5:0.1). ^{31}P NMR (400 MHz, C_6D_6) δ: 125.8 (s). ^1H NMR (C_6D_6), δ: 1.10 (s, 9H, CH_3, ^{t}Bu), 1.25 (s, 3H, CH_3), 1.27 (s, 3H, CH_3), 1.53 (s, 9H, CH_3, ^{t}Bu), 1.55 (s, 9H, CH_3, ^{t}Bu), 1.62 (s, 3H, CH_3), 1.72 (s, 3H, CH_3), 2.00 (s, 3H, CH_3), 2.06 (s, 3H, CH_3), 2.55 (dd, 1H, $^2J_{H-H}$= 12.8 Hz, $^3J_{H-H}$= 6.4 Hz, CH_2-S), 2.70 (dd, 1H, $^2J_{H-H}$= 12.8 Hz, $^3J_{H-H}$= 5.2 Hz, CH_2-S), 3.57-3.62 (m, 1H, CH_2-O), 3.81-3.86 (m, 1H, C*H*CH_2O), 3.93-3.98 (m, 1H, C*H*CH_2S), 4.19-4.28 (m, 1H, CH_2-O), 6.94-7.18 (m, 2H, CH-Ar). ^{13}C NMR (C_6D_6), δ: 16.1 (CH_3), 16.3 (CH_3), 20.0 (CH_3), 26.7 (CH_3), 27.1 (CH_3), 30.5 (CH_3, ^{t}Bu), 30.9 (CH_3, ^{t}Bu), 31.2 (CH_3, ^{t}Bu), 31.3 (CH_3, ^{t}Bu), 31.4 (CH_2-S), 34.5 (C, ^{t}Bu), 34.6 (C, ^{t}Bu), 41.5 (C, ^{t}Bu), 64.4 (CH_2-O), 77.1 (*C*HCH_2S), 79.8 (d, *C*HCH_2O, J_{C-P}= 3.9 Hz), 109.0 (CMe_2), 128.2 (CH=), 128.9 (CH=), 131.0 (C), 131.4 (C), 131.7 (C), 132.3 (C), 134.3 (C), 134.9 (C), 137.4 (C), 138.1 (C), 145.7(C), 146.1 (C). MS HR-ESI [found 639.3243, $C_{35}H_{53}O_5PS$ $(M-Na)^+$ requires 639.3244].

L4a. Yield: 462 mg (64%); SiO_2-flash chromatography (toluene/hexane/NEt_3 = 5:5:0.1). ^{31}P NMR (400 MHz, C_6D_6) δ: 134.9 (s). ^1H NMR (C_6D_6), δ: 1.31 (s, 9H, CH_3, ^{t}Bu), 1.31 (s, 9H, CH_3, ^{t}Bu), 1.32 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 1.60 (s, 9H, CH_3, ^{t}Bu), 1.61 (s, 9H, CH_3, ^{t}Bu), 2.15 (s, 3H, CH_3), 2.52 (s, 3H, CH_3), 2.73-2.76 (m, 2H, CH_2-S), 3.89-3.92 (m, 1H, C*H*CH_2O), 3.98-4.03 (m, 1H, C*H*CH_2S), 4.05 (m, 2H, CH_2-O), 6.95-7.63 (m, 7H, CH=).^{13}C NMR (C_6D_6), δ: 21.8 (CH_3-Ar), 22.6 (CH_3-Ar), 27.5 (CH_3), 27.8 (CH_3), 31.6 (CH_3, ^{t}Bu), 31.9 (CH_3, ^{t}Bu), 35.0 (C,

^{t}Bu), 36.0 (C, ^{t}Bu), 38.8 (CH_2-S), 65.0 (CH_2-O), 77.9 (*C*HCH_2S), 80.2 (d, *C*HCH_2O, $J_{C\text{-}P}$= 3.8 Hz), 110.0 (CMe_2), 124.8 (CH=), 126.0 (CH=), 127.4 (CH=), 128.1 (CH=), 128.3 (CH=), 128.6 (CH=), 129.6 (CH=), 133.9 (C), 134.2 (C), 138.1(C), 140.9 (C), 143.6 (C), 147.2 (C), 147.3 (C). MS HR-ESI [found 743.3870, $C_{43}H_{61}O_5PS$ $(M\text{-}Na)^+$ requires 743.3870].

L4d. Yield: 315 mg (47%); SiO_2-flash chromatography (toluene/hexane/NEt_3 = 5:5:0.1). ^{31}P NMR (400 MHz, C_6D_6) δ: 125.4 (s). ^{1}H NMR (C_6D_6), δ: 1.24 (s, 3H, CH_3), 1.26 (s, 3H, CH_3), 1.51 (s, 9H, CH_3, ^{t}Bu), 1.54 (s, 9H, CH_3, ^{t}Bu), 1.64 (s, 3H, CH_3), 1.72 (s, 3H, CH_3), 2.44 (s, 6H, CH_3), 2.62 (m, 2H, CH_2-S), 3.48-3.53(m, 1H, CH_2-O), 3.76-3.81 (m, 1H, C*H*CH_2O), 3.88-3.93 (m, 1H, C*H*CH_2S), 4.13-4.19 (m, 1H, CH_2-O), 6.86-7.18 (m, 5H, CH=). ^{13}C NMR (C_6D_6), δ: 16.1 (CH_3), 16.3 (CH_3), 20.0 (CH_3), 21.8 (CH_3), 26.7 (CH_3), 27.0 (CH_3), 30.9 (CH_3, ^{t}Bu), 31.2 (CH_3, ^{t}Bu), 34.5 (C, ^{t}Bu), 38.0 (CH_2-S), 64.1 (CH_2-O), 77.2 (*C*HCH_2S), 79.5 (d, *C*HCH_2O, $J_{C\text{-}P}$= 3 Hz), 109.2 (CMe_2), 127.8 (CH=), 128.0 (CH=), 128.1 (CH=), 128.2 (CH=), 128.9 (C), 131.1 (C), 131.5 (C), 131.6 (C), 131.7 (C), 132.3 (C), 133.6 (C), 134.4 (C), 134.9 (C), 136.9(C), 138.1 (C), 142.8 (C), 145.8 (C). MS HR-ESI [found 687.3243, $C_{39}H_{53}O_5PS$ $(M\text{-}Na)^+$ requires 687.3244].

L4e. Yield: 297 mg (45%); SiO_2-flash chromatography (toluene/hexane/NEt_3 = 5:5:0.1). ^{31}P NMR (400 MHz, C_6D_6) δ: 128.0 (s). ^{1}H NMR (C_6D_6), δ: 1.16 (s, 3H, CH_3), 1.19 (s, 3H, CH_3), 1.46 (s, 18H, CH_3, ^{t}Bu), 1.57 (s, 3H, CH_3), 1.68 (s, 3H, CH_3), 1.96 (s, 3H, CH_3), 2.00 (s, 3H, CH_3), 2.42 (s, 6H, CH_3), 2.61 (m, 2H, CH_2-S), 3.41-3.46 (m, 1H, CH_2-O), 3.70-3.75 (m, 1H, C*H*CH_2O), 3.84-3.89 (m, 1H, C*H*CH_2S), 4.06-4.12 (m, 1H, CH_2-O), 6.84-7.11 (m, 5H, CH=). ^{13}C NMR (C_6D_6), δ: 16.1 (CH_3), 16.3 (CH_3), 20.0 (CH_3), 21.9 (CH_3), 26.6 (CH_3), 27.1 (CH_3), 30.9 (CH_3, ^{t}Bu), 31.2 (CH_3, ^{t}Bu), 34.5 (C, ^{t}Bu), 34.6 (C, ^{t}Bu), 38.1 (CH_2-S), 64.0 (CH_2-O), 77.0 (*C*HCH_2S), 79.4 (d, *C*HCH_2O, $J_{C\text{-}P}$= 3.8 Hz), 109.2 (CMe_2), 128.0 (CH=), 128.1 (CH=), 128.2 (CH=), 128.9 (CH=), 131.0 (C), 131.5 (C), 131.6 (C), 132.4 (C), 133.6 (C), 134.4 (C), 135.0 (C), 136.9 (C), 137.0 (C), 138.0 (C), 142.8 (C), 145.6 (C), 146.0 (C). MS HR-ESI [found 687.3244, $C_{39}H_{53}O_5PS$ $(M\text{-}Na)^+$ requires 687.3244].

L5d. Yield: 381 mg (62%); SiO_2-flash chromatography (toluene/hexane/NEt_3 = 5:5:0.1). ^{31}P NMR (400 MHz, C_6D_6) δ: 128.6 (s). ^{1}H NMR (C_6D_6), δ: 1.37 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 1.47 (m, 6H, CH_2, Ad), 1.61 (s, 9H, CH_3, ^{t}Bu), 1.63 (s, 9H, CH_3, ^{t}Bu), 1.69 (s, 3H, CH_3), 1.76 (m, 6H, CH_2, Ad), 1.80 (m, 6H, CH, Ad, CH_3), 2.06 (s, 3H, CH_3), 2.10 (s, 3H, CH_3), 2.60 (dd, 1H, $^2J_{H\text{-}H}$= 12.8 Hz, $^3J_{H\text{-}H}$= 6.8 Hz, CH_2-S), 2.81 (dd, 1H, $^2J_{H\text{-}H}$= 13.2 Hz, $^3J_{H\text{-}H}$= 5.6 Hz, CH_2-S), 3.67-3.72 (m, 1H, CH_2-O), 3.86-3.90 (m, 1H, C*H*CH_2O), 4.05-4.10 (m, 1H, C*H*CH_2S), 4.39-4.45 (m, 1H, CH_2-O), 6.99-7.25 (m, 2H, CH=). ^{13}C NMR (C_6D_6), δ: 16.9 (CH_3), 17.1 (CH_3), 20.7 (CH_3), 20.8 (CH_3), 27.7 (CH_3), 27.9 (CH_3), 29.5 (CH_2-S), 30.3 (CH, Ad), 31.8 (CH_3, ^{t}Bu), 31.9 (CH_3, ^{t}Bu), 35.3 (C, ^{t}Bu), 35.4 (C, ^{t}Bu), 36.7 (CH_2, Ad), 44.0 (CH_2, Ad), 44.6 (C, Ad), 65.1 (CH_2-O), 78.2 (*C*HCH_2S), 81.0 (d, *C*HCH_2O, $J_{C\text{-}P}$= 3.1 Hz), 109.7 (CMe_2), 129.6 (CH=), 131.9 (C), 132.2 (C), 132.5 (C), 132.9 (C), 135.1 (C), 135.6 (C), 137.7 (C), 138.2 (C), 138.9 (C), 146.6 (C). MS HR-ESI [found 717.3711, $C_{41}H_{59}O_5PS$ $(M\text{-}Na)^+$ requires 717.3713].

L5e. Yield: 331 mg (54%); SiO_2-flash chromatography (toluene/hexane/NEt_3 = 5:5:0.1). ^{31}P NMR (400 MHz, C_6D_6) δ: 125.8 (s). ^{1}H NMR (C_6D_6), δ: 1.32 (s, 3H, CH_3), 1.39 (s, 3H, CH_3), 1.51 (m, 6H, CH_2, Ad),1.61 (s, 9H, CH_3, ^{t}Bu), 1.63 (s, 9H, CH_3, ^{t}Bu), 1.68 (s, 3H, CH_3), 1.78 (s,

3H, CH_3),1.79 (m, 6H, CH_2, Ad), 1.82 (m, 3H, CH, Ad), 2.05 (s, 3H, CH_3), 2.12 (s, 3H, CH_3), 2.61 (dd, 1H, $^2J_{H-H}$= 13.2 Hz, $^3J_{H-H}$= 7.2 Hz, CH_2-S), 2.83 (dd, 1H, $^2J_{H-H}$= 12.4 Hz, $^3J_{H-H}$= 4.8 Hz, CH_2-S), 3.72-3.76 (m, 1H, CH_2-O), 3.93-4.02 (m, 2H, C*H*CH_2O, C*H*CH_2S), 4.30-4.35 (m, 1H, CH_2-O), 6.99-7.27 (m, 2H, CH=). ^{13}C NMR (C_6D_6), δ: 16.1 (CH_3), 16.4 (CH_3), 20.0 (CH_3), 20.1 (CH_3), 26.8 (CH_3), 27.2 (CH_3), 28.8 (CH_2-S), 29.6 (CH, Ad), 30.9 (CH_3, ^{t}Bu), 31.3 (CH_3, ^{t}Bu), 34.6 (C, ^{t}Bu), 34.7 (C, ^{t}Bu), 36.0 (CH_2, Ad), 43.3 (CH_2, Ad), 43.9 (C, Ad), 64.7 (CH_2-O), 77.3 (*C*HCH_2S), 80.2 (d, *C*HCH_2O, J_{C-P}= 4 Hz), 109.0 (CMe_2), 128.1 (CH=), 128.9 (CH=), 131.1 (C), 131.4 (C), 131.7 (C), 132.9 (C), 134.4 (C), 134.9 (C), 136.9 (C), 138.1 (C), 145.8 (C), 146.6 (C). MS HR-ESI [found 717.3712, $C_{41}H_{59}O_5PS$ $(M-Na)^+$ requires 717.3713].

L6d. Yield: 344 mg (56%); SiO_2-flash chromatography (toluene/hexane/NEt_3 = 5:5:0.1). ^{31}P NMR (400 MHz, C_6D_6) δ: 128.6 (s). ^{1}H NMR (C_6D_6), δ: 1.30 (s, 3H, CH_3), 1.31 (s, 3H, CH_3), 1.52 (s, 9H, CH_3, ^{t}Bu), 1.58 (s, 9H, CH_3, ^{t}Bu), 1.67 (s, 3H, CH_3), 1.75 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 2.06 (s, 3H, CH_3), 2.89 (dd, 1H, $^2J_{H-H}$= 8.8 Hz, $^3J_{H-H}$= 6 Hz, CH_2-S), 3.05 (dd, 1H, $^2J_{H-H}$= 13.2 Hz, $^3J_{H-H}$= 6 Hz, CH_2-S), 3.56-3.62 (m, 1H, CH_2-O), 3.89-3.93 (m, 1H, C*H*CH_2O), 4.06-4.10 (m, 1H, C*H*CH_2S), 4.23-4.30 (m, 1H, CH_2-O), 6.99-8.54 (m, 9H, CH=). ^{13}C NMR (C_6D_6), δ: 16.8 (CH_3), 17.0 (CH_3), 20.7 (CH_3), 27.6 (CH_3), 27.8 (CH_3), 31.6 (CH_3, ^{t}Bu), 31.9 (CH_3, ^{t}Bu), 35.2 (CH_2-S), 37.8 (C, ^{t}Bu), 65.0 (CH_2-O), 77.0 (*C*HCH_2S), 80.7 (d, *C*HCH_2O, J_{C-P}= 2.3 Hz), 110.0 (CMe_2), 125.8 (CH=), 126.0 (CH=), 126.2 CH=), 126.8 (CH=), 127.0 (CH=), 127.9 (CH=), 128.8 (CH=), 129.2 (CH=), 129.6 (CH=), 131.8 (C), 132.2 (C), 132.4 (C), 133.0 (C), 133.7 (C), 134.2 (C), 134.8 (C), 135.2 (C), 135.7 (C), 137.7 (C), 138.1 (C), 138.8 (C), 146.4 (C). MS HR-ESI [found 709.3085, $C_{41}H_{51}O_5PS$ $(M-Na)^+$ requires 709.3087].

L6e. Yield: 331 mg (54%); SiO_2-flash chromatography (toluene/hexane/NEt_3 = 5:5:0.1). ^{31}P NMR (400 MHz, C_6D_6) δ: 126.2 (s). ^{1}H NMR (C_6D_6), δ: 1.25 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 1.55 (s, 9H, CH_3, ^{t}Bu), 1.56 (s, 9H, CH_3, ^{t}Bu), 1.66 (s, 3H, CH_3), 1.76 (s, 3H, CH_3), 2.02 (s, 3H, CH_3), 2.04 (s, 3H, CH_3), 2.94 (dd, 1H, $^2J_{H-H}$= 12.8 Hz, $^3J_{H-H}$= 5.6 Hz, CH_2-S), 3.05 (dd, 1H, $^2J_{H-H}$= 12.8 Hz, $^3J_{H-H}$= 6 Hz, CH_2-S), 3.62-3.67 (m, 1H, CH_2-O), 3.92-3.96 (m, 1H, C*H*CH_2O), 4.03-4.08 (m, 1H, C*H*CH_2S), 4.21-4.27 (m, 1H, CH_2-O), 7.00-8.58 (m, 9H, CH=). ^{13}C NMR (C_6D_6), δ: 16.8 (CH_3), 17.1 (CH_3), 20.7 (CH_3), 27.5 (CH_3), 27.8 (CH_3), 31.6 (CH_3, ^{t}Bu), 31.9 (CH_3, ^{t}Bu), 35.2 (C, ^{t}Bu), 35.3 (C, ^{t}Bu), 37.8 (CH_2-S), 65.1 (CH_2-O), 77.1 (*C*HCH_2S), 80.4 (d, *C*HCH_2O, J_{C-P}= 3.8 Hz), 110.1 (CMe_2), 125.8 (CH=), 126.0 (CH=), 126.2 (CH=), 126.8 (CH=), 127.0 (CH=), 127.9 (CH=), 128.9 (CH=), 129.2 (CH=), 129.6 (CH=),131.8 (C), 132.3 (C), 133.1 (C), 133.7 (C), 134.4 (C), 134.8 (C), 135.2 (C), 135.7 (C), 137.7 (C), 138.2 (C), 138.8 (C), 146.4 (C), 146.7 (C). MS HR-ESI [found 709.3086, $C_{41}H_{51}O_5PS$ $(M-Na)^+$ requires 709.3087].

L7d. Yield: 270 mg (60%); SiO_2-flash chromatography (toluene/hexane/NEt_3 = 5:5:0.1). ^{31}P NMR (400 MHz, C_6D_6) δ: 126.2 (s). ^{1}H NMR (C_6D_6), δ: 1.25 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 1.55 (s, 9H, CH_3, ^{t}Bu), 1.56 (s, 9H, CH_3, ^{t}Bu), 1.66 (s, 3H, CH_3), 1.76 (s, 3H, CH_3), 2.02 (s, 3H, CH_3), 2.04 (s, 3H, CH_3), 2.94 (dd, 1H, $^2J_{H-H}$= 12.8 Hz, $^3J_{H-H}$= 5.6 Hz, CH_2-S), 3.05 (dd, 1H, $^2J_{H-H}$= 12.8 Hz, $^3J_{H-H}$= 6 Hz, CH_2-S), 3.62-3.67 (m, 1H, CH_2-O), 3.92-3.96 (m, 1H, C*H*CH_2O), 4.03-4.08 (m, 1H, C*H*CH_2S), 4.21-4.27 (m, 1H, CH_2-O), 7.00-8.58 (m, 9H, CH=). ^{13}C NMR (C_6D_6), δ: 16.8 (CH_3), 17.1 (CH_3), 20.7 (CH_3), 27.5 (CH_3), 27.8 (CH_3), 31.6 (CH_3, ^{t}Bu), 31.9 (CH_3, ^{t}Bu), 35.2 (C,

^{t}Bu), 35.3 (C, ^{t}Bu), 37.8 (CH_2-S), 65.1 (CH_2-O), 77.1 (*C*HCH$_2$S), 80.4 (d, *C*HCH$_2$O, $J_{C\text{-}P}$= 3.8 Hz), 110.1 (CMe_2), 125.8 (CH=), 126.0 (CH=), 126.2 (CH=), 126.8 (CH=), 127.0 (CH=), 127.9 (CH=), 128.9 (CH=), 129.2 (CH=), 129.6 (CH=),131.8 (C), 132.3 (C), 133.1 (C), 133.7 (C), 134.4 (C), 134.8 (C), 135.2 (C), 135.7 (C-Ar), 137.7 (C), 138.2 (C), 138.8 (C), 146.4 (C), 146.7 (C). MS HR-ESI [found 709.3085, $C_{41}H_{51}O_5PS$ (M-Na)$^+$ requires 709.3087].

L7e. Yield: 234 mg (52%); SiO_2-flash chromatography (toluene/hexane/NEt_3 = 5:5:0.1). ^{31}P NMR (400 MHz, C_6D_6) δ: 126.4 (s). ^{1}H NMR (C_6D_6), δ: 1.25 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 1.56 (s, 9H, CH_3, ^{t}Bu), 1.57 (s, 9H, CH_3, ^{t}Bu), 1.66 (s, 3H, CH_3), 1.75 (s, 3H, CH_3), 2.02 (s, 3H, CH_3), 2.04 (s, 3H, CH_3), 3.00 (dd, 1H, $^2J_{H\text{-}H}$= 13.6 Hz, $^3J_{H\text{-}H}$= 5.6 Hz, CH_2-S), 3.11 (dd, 1H, $^2J_{H\text{-}H}$= 13.6 Hz, $^3J_{H\text{-}H}$= 5.2 Hz, CH_2-S), 3.63-3.68 (m, 1H, CH_2-O), 3.94-3.99 (m, 1H, C*H*CH$_2$O), 4.04-4.09 (m, 1H, C*H*CH$_2$S), 4.22-4.28 (m, 1H, CH_2-O), 6.99-7.74 (m, 9H, CH=). ^{13}C NMR (C_6D_6), δ: 16.1 (CH_3), 16.3 (CH_3), 19.9 (CH_3), 20.0 (CH_3), 26.7 (CH_3), 27.0 (CH_3), 30.9(CH_3, ^{t}Bu), 31.2 (CH_3, ^{t}Bu), 34.5 (C, ^{t}Bu), 34.6 (C, ^{t}Bu), 36.4 (CH_2-S), 64.4 (CH_2-O), 76.4 (*C*HCH$_2$S), 79.6 (d, *C*HCH$_2$O, $J_{C\text{-}P}$= 3.8 Hz), 109.4 (CMe_2), 125.2 (CH=), 125.4 (CH=), 126.3 (CH=), 126.7 (CH=), 127.1 (CH=), 127.2 (CH=), 128.2 (CH=), 128.4 (CH=), 128.9 (CH=),131.0 (C), 131.6 (C), 131.7 (C), 131.8 (C), 132.4 (C), 134.0 (C), 134.1 (C),134.4 (C), 135.0 (C), 137.0 (C), 137.4 (C), 138.1 (C), 145.7 (C). MS HR-ESI [found 709.3083, $C_{41}H_{51}O_5PS$ (M-Na)$^+$ requires 709.3087].

L8a. Yield: 312 mg (55%); Al_2O_3-flash chromatography (toluene/hexane/NEt_3 = 6:4:0.1). ^{31}P NMR (400 MHz, C_6D_6) δ: 150.4 (s). ^{1}H NMR (C_6D_6), δ: 1.15 (s, 3H, CH_3), 1.22 (s, 9H, CH_3, ^{t}Bu), 1.23 (s, 9H, CH_3, ^{t}Bu), 1.27 (s, 3H, CH_3), 1.50 (s, 3H, CH_3), 1.53 (s, 9H, CH_3, ^{t}Bu), 1.56 (s, 9H, CH_3, ^{t}Bu), 1.65 (s, 3H, CH_3), 2.57 (dd, 1H, $^2J_{H\text{-}H}$= 14.8 Hz, $^3J_{H\text{-}H}$= 7.6 Hz, CH_2-S), 3.07 (dd, 1H, $^2J_{H\text{-}H}$= 14.8 Hz, $^3J_{H\text{-}H}$= 2.4 Hz, CH_2-S), 3.88-3.91 (m, 1H, C*H*CMe$_2$O), 4.22-4.28 (m, 1H, C*H*CH$_2$S), 6.71-7.57 (m, 9H, CH=). ^{13}C NMR (C_6D_6), δ: 24.0 (CH_3), 26.7 (CH_3), 27.2 (CH_3), 28.1 (CH_3), 30.9 (CH_3, ^{t}Bu), 31.1 (CH_3, ^{t}Bu), 31.2 (CH_3, ^{t}Bu), 34.3 (C, ^{t}Bu), 35.1 (C, ^{t}Bu), 35.2 (C, ^{t}Bu), 36.0 (CH_2-S), 76.4 (*C*HCH$_2$S), 79.9 (*C*Me$_2$O), 84.5 (d, *C*HCMe$_2$O, $J_{C\text{-}P}$= 1 Hz), 109.0 (CMe_2), 123.8 (CH=),124.1 (CH=), 124.7 (CH=), 127.0 (CH=), 128.0 (CH=), 128.1 (CH=), 128.4 (CH=), 128.7 (CH=), 128.9 (CH=), 130.3 (C), 135.3 (C), 137.2 (C), 139.9 (C), 146.4 (C). MS HR-ESI [found 743.3868, $C_{43}H_{61}O_5PS$ (M-Na)$^+$ requires 743.3870].

L8d. Yield: 360 mg (62%); Al_2O_3-flash chromatography (toluene/hexane/NEt_3 = 6:4:0.1). ^{31}P NMR (400 MHz, C_6D_6) δ: 142.4 (s). ^{1}H NMR (C_6D_6), δ: 1.21 (s, 3H, CH_3), 1.29 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 1.57 (s, 9H, CH_3, ^{t}Bu), 1.59 (s, 9H, CH_3, ^{t}Bu), 1.68 (s, 3H, CH_3), 1.75 (s, 3H, CH_3), 1.76 (s, 3H, CH_3), 1.84 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 2.07 (s, 3H, CH_3), 2.62 (dd, 1H, $^2J_{H\text{-}H}$= 14.8 Hz, $^3J_{H\text{-}H}$= 6.8 Hz, CH_2-S), 2.93 (dd, 1H, $^2J_{H\text{-}H}$= 14.8 Hz, $^3J_{H\text{-}H}$= 2.8 Hz, CH_2-S), 4.06 (d, 1H, $^3J_{H\text{-}H}$= 4 Hz, C*H*CMe$_2$O), 4.20-4.25 (m, 1H, C*H*CH$_2$S), 6.87-7.33 (m, 7H, CH=). ^{13}C NMR (C_6D_6), δ: 16.1 (CH_3), 16.5 (CH_3), 20.0 (CH_3), 23.6 (CH_3), 26.8 (CH_3), 27.1 (CH_3), 27.9 (CH_3), 30.9 (CH_3, ^{t}Bu), 31.6 (CH_3, ^{t}Bu), 34.3 (C, ^{t}Bu), 34.6 (C, ^{t}Bu), 36.4 (CH_2-S), 76.5 (*C*HCH$_2$S), 79.9 (d, *C*Me$_2$O, $J_{C\text{-}P}$= 11.4 Hz), 84.4 (*C*HCMe$_2$O), 108.8 (CMe_2), 124.9 (CH=),125.9 (CH=), 128.0 (CH=), 128.1 (CH=), 128.4 (CH=), 128.5 (CH=), 128.9 (CH=), 131.1 (C), 131.8 (C), 131.7 (C), 132.2(C), 132.3 (C), 134.7 (C), 135.1 (C), 137.3 (C),137.6 (C), 138.0 (C). MS HR-ESI [found 687.3243, $C_{39}H_{53}O_5PS$ (M-Na)$^+$ requires 687.3244].

L8e. Yield: 323 mg (57%); Al_2O_3-flash chromatography (toluene/hexane/NEt_3 = 6:4:0.1). ^{31}P NMR (400 MHz, C_6D_6) δ: 143.4 (s). ^1H NMR (C_6D_6), δ: 1.08 (s, 3H, CH_3), 1.31 (s, 3H, CH_3), 1.51 (s, 9H, CH_3, ^{t}Bu), 1.54 (s, 3H, CH_3), 1.57 (s, 3H, CH_3), 1.64 (s, 3H, CH_3), 1.65 (s, 9H, CH_3, ^{t}Bu), 1.69 (s, 3H, CH_3), 2.04 (s, 3H, CH_3), 2.14 (s, 3H, CH_3), 2.41 (dd, 1H, $^2J_{H-H}$= 14.8 Hz, $^3J_{H-H}$= 9.6 Hz, CH_2-S), 2.94 (dd, 1H, $^2J_{H-H}$= 14.8 Hz, $^3J_{H-H}$= 1.6 Hz, CH_2-S), 3.76 (d, 1H, $^3J_{H-H}$= 8.8 Hz, C*H*CMe_2O), 4.16-4.21 (m, 1H, C*H*CH_2S), 6.74-7.23 (m, 7H, CH=). ^{13}C NMR (C_6D_6), δ: 16.2 (CH_3), 16.4 (CH_3), 20.0 (CH_3), 20.1 (CH_3), 23.8 (CH_3), 26.4 (CH_3), 27.2 (CH_3), 28.5 (CH_3), 31.1 (CH_3, ^{t}Bu), 31.7 (CH_3, ^{t}Bu), 34.3 (C, ^{t}Bu), 34.4 (C, ^{t}Bu), 34.6 (CH_2-S), 75.0 (*C*HCH_2S), 79.5 (d, *C*Me_2O, J_{C-P}= 9.9 Hz), 84.3 (*C*HCMe_2O), 108.4 (CMe_2), 124.1 (CH=),125.3 (CH=), 126.8 (CH=), 128.1 (CH=), 128.7 (CH=), 128.9 (CH=), 131.0 (C), 132.4 (C), 134.7 (C), 135.3 (C), 136.5 (C), 137.2 (C), 137.3 (C), 137.4 (C), 144.5 (C), 145.9 (C). MS HR-ESI [found 687.3244, $C_{39}H_{53}O_5PS$ $(M-Na)^+$ requires 687.3244].

L9a. Yield: 524 mg (68%); Al_2O_3-flash chromatography (toluene/hexane/NEt_3 = 6:4:0.1). ^{31}P NMR (161.9 MHz, C_6D_6): δ=150.4 (s). ^1H NMR (400 MHz, C_6D_6): δ=1.19 (s, 3H, CH_3), 1.22 (s, 9H, CH_3, ^{t}Bu), 1.24 (s, 9H, CH_3, ^{t}Bu), 1.31 (s, 3H, CH_3), 1.53 (s, 3H, CH_3), 1.58 (s, 18H, CH_3, ^{t}Bu), 1.71 (s, 3H, CH_3), 2.69 (dd, 1H, CH_2-S, $^2J_{H-H}$ =14.6 Hz, $^3J_{H-H}$ =7.7 Hz), 3.21 (dd, 1H, CH_2-S, $^2J_{H-H}$ =14.5 Hz, $^3J_{H-H}$ =2.6 Hz), 3.97 (d, 1H, C*H*CMe_2O, $^3J_{H-H}$ =7.9 Hz), 4.33 (m, 1H, C*H*CH_2S), 7.00-7.02 (m, 2H, CH=), 7.10-7.12 (m, 2H, CH=), 7.24-7.37 (m, 3H, CH=), 7.45-7.47 (m, 1H, CH=), 7.62 (m, 1H, CH=), 7.68 (s, 1H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 24.0 (CH_3), 26.8 (CH_3), 27.2 (CH_3), 28.2 (CH_3), 30.9 (CH_3, ^{t}Bu), 31.1 (CH_3, ^{t}Bu), 31.2 (CH_3, ^{t}Bu), 31.3 (CH_3, ^{t}Bu), 34.3 (C, ^{t}Bu), 35.2 (C, ^{t}Bu), 36.3 (CH_2-S), 76.5 (*C*HCH_2S), 79.9 (CMe_2O), 84.7 (*C*HCMe_2O), 109.0 (CMe_2), 124.0-146.5 (aromatic carbons). MS HR-ESI [found 793.4025, $C_{47}H_{63}O_5PS$ $(M-Na)^+$ requires 793.4026].

L9f. Yield: 406 mg (59%); Al_2O_3-flash chromatography (toluene/hexane/NEt_3 = 6:4:0.1). ^{31}P NMR (161.9 MHz, C_6D_6): δ=154.3 (s). ^1H NMR (400 MHz, C_6D_6): δ=0.56 (s, 9H, CH_3, $SiMe_3$), 0.57 (s, 9H, CH_3, $SiMe_3$), 1.17 (s, 3H, CH_3), 1.23 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 1.77 (d, 3H, CH_3, $^4J_{H-H}$ =2.4 Hz), 2.48 (dd, 1H, CH_2-S, $^2J_{H-H}$ =14.0 Hz, $^3J_{H-H}$ =7.2 Hz), 2.63 (dd, 1H, CH_2-S, $^2J_{H-H}$ =14.4 Hz, $^3J_{H-H}$ =3.2 Hz), 3.97 (d, 1H, C*H*CMe_2O, $^3J_{H-H}$ =8.0 Hz), 4.20-4.24 (m, 1H, C*H*CH_2S), 6.78-6.85 (m, 2H, CH=), 6.98-7.26 (m, 6H, CH=), 7.34 (d, 1H, CH=, $^3J_{H-H}$ =7.6 Hz), 7.41 (d, 1H, CH=, $^3J_{H-H}$ =8.8 Hz), 7.47-7.70 (m, 4H, CH=), 7.69 (d, 1H, CH=, $^3J_{H-H}$ =8.0 Hz), 8.11 (s, 1H, CH=), 8.12 (s, 1H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ=0.3 (d, CH_3, $SiMe_3$, J_{C-P} =4.6 Hz), 0.9 (CH_3, $SiMe_3$), 24.6 (CH_3), 27.5 (CH_3), 27.7 (CH_3), 28.9 (d, CH_3, $^3J_{C-P}$ =18.4 Hz), 37.7 (CH_2-S), 77.3 (*C*HCH_2S), 80.9 (d, CMe_2-O, $^2J_{C-P}$ =3.8 Hz), 85.1 (*C*HCMe_2O), 109.6 (CMe_2), 125.3-153.1 (aromatic carbons). MS HR-ESI [found 813.2625, $C_{45}H_{51}O_5PSSi_2$ $(M-Na)^+$ requires 813.2626].

L9g. Yield: 498 mg (63%); Al_2O_3-flash chromatography (toluene/hexane/NEt_3 = 6:4:0.1). ^{31}P NMR (161.9 MHz, C_6D_6): δ=155.4 (s). ^1H NMR (400 MHz, C_6D_6): δ=0.52 (s, 9H, CH_3, $SiMe_3$), 0.61 (s, 9H, CH_3, $SiMe_3$), 1.04 (s, 3H, CH_3), 1.32 (s, 3H, CH_3), 1.59 (s, 3H, CH_3), 1.80 (s, 3H, CH_3), 2.51 (dd, 1H, CH_2-S, $^2J_{H-H}$ =14.4 Hz, $^3J_{H-H}$ =8.4 Hz), 2.96 (d, 1H, CH_2-S, $^2J_{H-H}$ =14.8 Hz), 3.95 (d, 1H, C*H*CMe_2O, $^3J_{H-H}$ =8.0 Hz), 4.15 (pt, 1H, C*H*CH_2S, $^3J_{H-H}$ =8.0 Hz), 6.43 (pt, 1H, CH=, $^3J_{H-H}$ =7.2 Hz), 6.78-6.87 (m, 2H, CH=), 6.99-7.36 (m, 8H, CH=), 7.37 (m, 1H, CH=), 7.48 (m,

1H, CH=), 7.61 (d, 1H, CH=, $^{3}J_{H-H}$ =8.4 Hz), 7.69 (d, 1H, CH=, $^{3}J_{H-H}$ =8.4 Hz), 8.17 (s, 1H, CH=), 8.19 (s, 1H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ=0.3 (d, CH_3, $SiMe_3$, J_{C-P} =5.3 Hz), 1.0 (CH_3, $SiMe_3$), 25.0 (d, CH_3, $^{3}J_{C-P}$ =7.6 Hz), 27.2 (CH_3), 27.9 (CH_3), 29.1 (d, CH_3, $^{3}J_{C-P}$ =11.5 Hz), 35.8 (CH_2-S), 75.6 (*C*HCH_2S), 80.8 (d, CMe_2-O, $^{2}J_{C-P}$ =7.6 Hz), 84.8 (*C*$HCMe_2$O), 109.3 (CMe_2), 123.3-153.0 (aromatic carbons). MS HR-ESI [found 813.2626, $C_{45}H_{51}O_5PSSi_2$ $(M-Na)^+$ requires 813.2626].

L10f. Yield: 457 mg (57%); SiO_2-flash chromatography (toluene/hexane/NEt_3 = 5:5:0.1). ^{31}P NMR (161.9 MHz, C_6D_6): δ=135.6 (s). ^{1}H NMR (400 MHz, C_6D_6): δ=0.55 (s, 18H, CH_3, $SiMe_3$), 1.07 (b, 3H, CH_3), 1.17 (b, 3H, CH_3), 1.44 (s, 3H, CH_3), 3.22 (b, 1H, CH_2-O), 4.14 (b, 1H, CH_2-O), 4.18-4.22 (m, 1H, C*H*CH_2O), 4.43 (d, 1H, $CHCMe_2$S, $^{3}J_{H-H}$ =7.6 Hz), 6.84-6.89 (m, 4H, CH=), 6.97-7.13 (m, 5H, CH=), 7.22-7.26 (m, 3H, CH=), 7.38 (d, 1H, CH=, $^{3}J_{H-H}$ =8.0 Hz), 7.38 (d, 1H, CH=, $^{3}J_{H-H}$ =8.0 Hz), 7.47 (d, 2H, CH=, $^{3}J_{H-H}$ =8.4 Hz), 7.64 (d, 1H, CH=, $^{3}J_{H-H}$ =8.0 Hz), 7.71 (d, 1H, CH=, $^{3}J_{H-H}$ =8.4 Hz), 8.08 (s, 1H, CH=), 8.13 (s, 1H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ=0.5 (CH_3, $SiMe_3$), 0.6 (d, CH_3, $SiMe_3$, J_{C-P} =4.6 Hz), 13.2 (CH_3), 27.1 (CH_3), 28.5 (CH_3), 60.9 (CH_2-O), 67.3 (CMe_2-S), 79.2 (d, *C*HCH_2O, $^{3}J_{C-P}$ =3.1 Hz), 80.8 (b, *C*$HCMe_2$S), 110.2 (CMe_2), 123.3-153.6 (aromatic carbons). MS HR-ESI [found 825.2624, $C_{46}H_{51}O_5PSSi_2$ $(M-Na)^+$ requires 825.2626].

L10g. Yield: 538 mg (67%); SiO_2-flash chromatography (toluene/hexane/NEt_3 = 5:5:0.1). ^{31}P NMR (161.9 MHz, C_6D_6): δ=133.5 (s). ^{1}H NMR (400 MHz, C_6D_6): δ=0.57 (s, 9H, CH_3, $SiMe_3$), 0.61 (s, 9H, CH_3, $SiMe_3$), 0.96 (b, 3H, CH_3), 1.28 (b, 3H, CH_3), 1.35 (s, 3H, CH_3), 3.58 (b, 1H, CH_2-O), 4.09 (b, 1H, CH_2-O), 4.27-4.31 (m, 1H, C*H*CH_2O), 4.36 (d, 1H, $CHCMe_2$S, $^{3}J_{H-H}$ =8.0 Hz), 6.84-6.90 (m, 3H, CH=), 6.95-7.14 (m, 7H, CH=), 7.25 (d, 1H, CH=, $^{3}J_{H-H}$ =8.8 Hz), 7.31 (d, 2H, CH=, $^{3}J_{H-H}$ =7.6 Hz), 7.38 (d, 1H, CH=, $^{3}J_{H-H}$ =8.0 Hz), 7.52 (d, 2H, CH=, $^{3}J_{H-H}$ =7.6 Hz), 7.62 (d, 1H, CH=, $^{3}J_{H-H}$ =7.6 Hz), 7.69 (d, 1H, CH=, $^{3}J_{H-H}$ =8.4 Hz), 8.11 (s, 2H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ=0.4 (CH_3, $SiMe_3$), 0.5 (d, CH_3, $SiMe_3$, J_{C-P} =4.6 Hz), 13.2 (CH_3), 27.1 (CH_3), 28.2 (CH_3), 60.9 (d, CH_2-O, $^{2}J_{C-P}$ =26.2 Hz), 67.3 (CMe_2-S), 78.5 (*C*HCH_2O), 79.3 (b, *C*$HCMe_2$S), 110.4 (CMe_2), 125.3-153.8 (aromatic carbons).). MS HR-ESI [found 825.2625, $C_{46}H_{51}O_5PSSi_2$ $(M-Na)^+$ requires 825.2626].

L11a. Yield: 415.1 mg (58%); SiO_2-flash chromatography (toluene/hexane/NEt_3 = 8:2:0.1). ^{31}P NMR (161.9 MHz, C_6D_6): δ=145.3 (s). ^{1}H NMR (400 MHz, C_6D_6): δ=1.26 (s, 9H, CH_3, ^{t}Bu), 1.27 (s, 9H, CH_3, ^{t}Bu), 1.28 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 1.33 (s, 3H, CH_3), 1.55 (s, 9H, CH_3, ^{t}Bu), 1.58 (s, 9H, CH_3, ^{t}Bu), 2.83 (dd, 1H, CH_2-S, $^{2}J_{H-H}$ =14.2 Hz, $^{3}J_{H-H}$ =5.6 Hz), 3.08 (dd, 1H, CH_2-S, $^{2}J_{H-H}$ =14.4 Hz, $^{3}J_{H-H}$ =4.4 Hz), 3.94 (pt, 1H, C*H*CHO, $^{3}J_{H-H}$ =7.3 Hz), 4.35-4.39 (m, 1H, C*H*CH_2S), 4.57-4.62 (m, 1H, CH-O), 6.86-7.15 (m, 3H, CH=), 7.28-7.33 (m, 4H, CH=), 7.57 (d, 1H, CH=, $^{4}J_{H-H}$ =2.4 Hz), 7.60 (d, 1H, CH=, $^{4}J_{H-H}$ =2.8 Hz). ^{13}C NMR (100.6 MHz, C_6D_6): δ=19.2 (d, CH_3, $^{3}J_{C-P}$ =3.0 Hz), 26.9 (CH_3), 27.1 (CH_3), 31.1 (d, CH_3, ^{t}Bu, J_{C-P} =3.1 Hz), 31.2 (CH_3, ^{t}Bu), 31.3 (CH_3, ^{t}Bu), 34.3 (C, ^{t}Bu), 34.4 (C, ^{t}Bu), 35.3 (C, ^{t}Bu), 35.4 (C, ^{t}Bu), 36.5 (CH_2-S), 73.0 (d, CH-O, $^{2}J_{C-P}$ =6.1 Hz), 78.4 (*C*HCH_2S), 82.6 (d, *C*HCHO, $^{3}J_{C-P}$ = 3.8 Hz), 109.4 (CMe_2), 124.0-146.7 (aromatic carbons). MS HR-ESI [found 729.3712, $C_{42}H_{59}O_5PS$ $(M-Na)^+$ requires 729.3719].

L11f. Yield: 429 mg (59%); SiO_2-flash chromatography (toluene/hexane/NEt_3 = 8:2:0.1). ^{31}P NMR (161.9 MHz, C_6D_6): δ=147.4 (s). ^{1}H NMR (400 MHz, C_6D_6): δ=0.52 (s, 9H, CH_3, $SiMe_3$), 0.56 (s, 9H, CH_3, $SiMe_3$), 1.22 (s, 3H, CH_3), 1.32 (s, 3H, CH_3), 1.49 (d, 3H, CH_3, $^{3}J_{H-H}$ =6.4 Hz), 2.33 (dd, 1H, CH_2-S, $^{2}J_{H-H}$ =13.6 Hz, $^{2}J_{H-H}$ =4.3 Hz), 2.40 (dd, 1H, CH_2-S, $^{2}J_{H-H}$ =14.0 Hz, $^{2}J_{H-H}$ =3.6 Hz), 3.83 (pt, 1H, C*H*CHO, $^{3}J_{H-H}$ =7.6 Hz), 4.08 (m, 1H, C*H*CH_2S), 4.49 (m, 1H, CH-O), 6.84-7.16 (m, 9H, CH=), 7.28 (d, 1H, CH=, $^{3}J_{H-H}$ =8.8 Hz), 7.33 (d, 1H, CH=, $^{3}J_{H-H}$ =8.4 Hz), 7.69 (dd, 2H, CH=, $^{3}J_{H-H}$ =10.8 Hz, $^{3}J_{H-H}$ =8.4 Hz), 8.11 (s, 1H, CH=), 8.16 (s, 1H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ=-0.9 (d, CH_3, $SiMe_3$, J_{C-P} =4.6 Hz), 0.7 (CH_3, $SiMe_3$), 18.3 (CH_3), 26.0 (CH_3), 26.2 (CH_3), 37.4 (CH_2-S), 72.1 (d, CH-O, $^{2}J_{C-P}$ = 4.6 Hz), 77.4 (*C*HCH_2S), 81.2 (d, *C*HCHO, $^{3}J_{C-P}$ =2.7 Hz), 111.2 (CMe_2), 124.0-136.4 (aromatic carbons). MS HR-ESI [found 749.2313, $C_{40}H_{47}O_5PSSi_2$ $(M-Na)^+$ requires 749.2318].

L11g. Yield: 480 mg (66%); SiO_2-flash chromatography (toluene/hexane/NEt_3 = 8:2:0.1). ^{31}P NMR (161.9 MHz, C_6D_6): δ=140.9 (s). ^{1}H NMR (400 MHz, C_6D_6): δ=0.50 (s, 9H, CH_3, $SiMe_3$), 0.54 (s, 9H, CH_3, $SiMe_3$), 0.78 (d, 3H, CH_3, $^{3}J_{H-H}$ =6.8 Hz), 1.32 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 3.00 (d, 2H, CH_2-S, $^{3}J_{H-H}$ =5.6 Hz), 3.93 (dd, 1H, C*H*CHO, $^{3}J_{H-H}$ =5.6 Hz, $^{3}J_{H-H}$ =1.1 Hz), 4.20 (m, 1H, C*H*CH_2S), 4.66 (m, 1H, CH-O), 6.83-7.22 (m, 10H, CH=), 7.34 (d, 1H, CH=, $^{3}J_{H-H}$ =8.8 Hz), 7.69 (dd, 2H, CH=, $^{3}J_{H-H}$ =6.4 Hz, $^{4}J_{H-H}$ =3.6 Hz), 8.10 (s, 1H, CH=), 8.13 (s, 1H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ=0.1 (d, CH_3, $SiMe_3$, J_{C-P} =4.0 Hz), 0.1 (CH_3, $SiMe_3$), 17.8 (CH_3), 26.9 (CH_3), 27.1 (CH_3), 37.5 (CH_2-S), 72.4 (d, CH-O, $^{2}J_{C-P}$ = 6.9 Hz), 77.1 (*C*HCH_2S), 82.9 (d, *C*HCHO, $^{3}J_{C-P}$ =4.6 Hz), 109.3 (CMe_2), 122.5-137.3 (aromatic carbons). MS HR-ESI [found 749.2314, , $C_{40}H_{47}O_5PSSi_2$ $(M-Na)^+$ requires 749.2318].

L12a. Yield: 137.0 mg (36%); SiO_2-flash chromatography (toluene/hexane/NEt_3 = 8:2:0.1). ^{31}P NMR (161.9 MHz, C_6D_6): δ=145.2 (s). ^{1}H NMR (400 MHz, C_6D_6): δ=1.24 (s, 9H, CH_3, ^{t}Bu), 1.26 (s, 9H, CH_3, ^{t}Bu), 1.28 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 1.32 (s, 3H, CH_3), 1.53 (s, 9H, CH_3, ^{t}Bu), 1.57 (s, 9H, CH_3, ^{t}Bu), 2.89 (dd, 1H, CH_2-S, $^{2}J_{H-H}$ =14.4 Hz, $^{3}J_{H-H}$ =5.6 Hz), 3.17 (dd, 1H, CH_2-S, $^{2}J_{H-H}$ =14.4 Hz, $^{3}J_{H-H}$ =4.4 Hz), 3.97 (pt, 1H, C*H*CHO, $^{3}J_{H-H}$ =6.8 Hz), 4.38-4.43 (m, 1H, C*H*CH_2S), 4.58-4.64 (m, 1H, CH-O), 7.15-7.19 (m, 3H, CH=), 7.30-7.52 (m, 5H, CH=), 7.57 (d, 1H, CH=, $^{4}J_{H-H}$ = 2.4 Hz), 7.60 (d, 1H, CH=, $^{4}J_{H-H}$ = 2.4 Hz), 7.80 (m, 1H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ=19.3 (b, CH_3), 26.9 (CH_3), 27.1 (CH_3), 31.0 (d, CH_3, ^{t}Bu, $^{3}J_{C-P}$ =3.0 Hz), 31.1 (CH_3, ^{t}Bu), 31.2 (CH_3, ^{t}Bu), 34.3 (C, ^{t}Bu), 34.4 (C, ^{t}Bu), 35.3 (C, ^{t}Bu), 35.4 (C, ^{t}Bu), 36.5 (CH_2-S), 72.9 (d, CH-O, $^{2}J_{C-P}$ =4.6 Hz), 78.4 (*C*HCH_2S), 82.7 (d, *C*HCHO, $^{3}J_{C-P}$ = 3.8 Hz), 109.5 (CMe_2), 124.0-146.7 (aromatic carbons). MS HR-ESI [found 779.3875, $C_{46}H_{61}O_5PS$ $(M-Na)^+$ requires 779.3875].

L12f. Yield: 198.9 mg (51%); SiO_2-flash chromatography (toluene/hexane/NEt_3 = 8:2:0.1). ^{31}P NMR (161.9 MHz, C_6D_6): δ=147.4 (s). ^{1}H NMR (400 MHz, C_6D_6): δ=0.51 (s, 9H, CH_3, $SiMe_3$), 0.55 (s, 9H, CH_3, $SiMe_3$), 1.20 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 1.49 (d, 3H, CH_3, $^{3}J_{H-H}$ =6.4 Hz), 2.40 (dd, 1H, CH_2-S, $^{2}J_{H-H}$ =14.0 Hz, $^{3}J_{H-H}$ =5.6 Hz), 2.49 (dd, 1H, CH_2-S, $^{2}J_{H-H}$ =14.0 Hz, $^{3}J_{H-H}$ =4.0 Hz), 3.86 (pt, 1H, C*H*CHO, $^{3}J_{H-H}$ =7.2 Hz), 4.10-4.15 (m, 1H, C*H*CH_2S), 4.48-4.53 (m, 1H, CH-O), 6.78-6.87 (m, 2H, CH=), 6.99-7.20 (m, 5H, CH=), 7.26 (d, 1H, CH=, $^{3}J_{H-H}$ =8.8 Hz), 7.34 (m, 2H, CH=), 7.48 (dd, 2H, CH=, $^{3}J_{H-H}$ =8.8 Hz, $^{3}J_{H-H}$ =8.0 Hz), 7.52 (d, 1H, CH=, $^{4}J_{H-H}$

=1.2 Hz), 7.59 (d, 1H, CH=, $^{3}J_{H-H}$ =7.3 Hz), 7.70 (d, 1H, CH=, $^{3}J_{H-H}$ =8.4 Hz), 8.12 (s, 1H, CH=), 8.15 (s, 1H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ=0.0 (CH_3, $SiMe_3$), 0.3 (CH_3, $SiMe_3$), 19.2 (CH_3), 26.8 (CH_3), 27.1 (CH_3), 35.7 (CH_2-S), 73.0 (d, CH-O, $^{2}J_{C-P}$ = 3.6 Hz), 78.3 (*C*HCH$_2$S), 82.2 (*C*HCHO), 109.5 (CMe_2), 124.9-152.0 (aromatic carbons). MS HR-ESI [found 799.2460, $C_{44}H_{49}O_5PSSi_2$ (M-Na)$^+$ requires 799.2475].

L12g. Yield: 396.0 mg (51%); SiO_2-flash chromatography (toluene/hexane/NEt_3 = 8:2:0.1). ^{31}P NMR (161.9 MHz, C_6D_6): δ=141.0 (s). ^{1}H NMR (400 MHz, C_6D_6): δ=0.48 (s, 9H, CH_3, $SiMe_3$), 0.53 (s, 9H, CH_3, $SiMe_3$), 0.80 (d, 3H, CH_3, $^{3}J_{H-H}$ =6.0 Hz), 1.34 (s, 3H, CH_3), 1.37 (s, 3H, CH_3), 3.11 (d, 2H, CH_2-S, $^{3}J_{H-H}$ =5.6 Hz), 3.97 (dd, 1H, C*H*CHO, $^{3}J_{H-H}$ =7.2 Hz, $^{3}J_{H-H}$ =5.6 Hz), 4.26-4.31 (m, 1H, C*H*CH$_2$S), 4.66-4.71 (m, 1H, CH-O), 6.81-6.87 (m, 2H, CH=), 6.99-7.23 (m, 5H, CH=), 7.31-7.53 (m, 5H, CH=), 7.67-7.70 (m, 3H, CH=), 8.10 (s, 1H, CH=), 8.12 (s, 1H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ=0.8 (d, CH_3, $SiMe_3$, J_{C-P} =4.7 Hz), 0.9 (CH_3, $SiMe_3$), 18.8 (CH_3), 28.1 (CH_3), 28.3 (CH_3), 38.6 (CH_2-S), 73.6 (d, CH-O, $^{2}J_{C-P}$ = 6.5 Hz), 78.3 (*C*HCH$_2$S), 84.1 (d, *C*HCHO, $^{3}J_{C-P}$ =3.8 Hz), 110.5 (CMe_2), 123.6-153.2 (aromatic carbons). MS HR-ESI [found 799.2473, $C_{44}H_{49}O_5PSSi_2$ (M-Na)$^+$ requires 799.2475].

L13a. Yield: 374.6 mg (44%); SiO_2-flash chromatography (toluene/hexane/NEt_3 = 8:2:0.1). ^{31}P NMR (161.9 MHz, C_6D_6): δ=147.1 (s). ^{1}H NMR (400 MHz, C_6D_6): δ=0.06 (s, 3H, CH_3, OTBDMS), 0.09 (s, 3H, CH_3, OTBDMS), 0.97 (s, 9H, CH_3, ^{t}Bu, OTBDMS), 1.24 (s, 9H, CH_3, ^{t}Bu), 1.28 (s, 9H, CH_3, ^{t}Bu), 1.29 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 1.55 (s, 9H, CH_3, ^{t}Bu), 1.61 (s, 9H, CH_3, ^{t}Bu), 2.65 (dd, 1H, CH_2-S, $^{2}J_{H-H}$ =14.4 Hz, $^{3}J_{H-H}$ =4.4 Hz), 3.10 (dd, 1H, CH_2-S, $^{2}J_{H-H}$ =14.8 Hz, $^{3}J_{H-H}$ =2.4 Hz), 3.77-3.81 (m, 1H, CH_2-OTBDMS), 4.11-4.17 (m, 2H, C*H*CHO, CH_2-OTBDMS), 4.55-4.63 (m, 2H, C*H*CH$_2$S, CH-O), 6.85-6.92 (m, 3H, CH=), 7.26 (d, 1H, CH=, $^{4}J_{H-H}$ =2.4 Hz), 7.35 (m, 3H, CH=), 7.58 (d, 1H, CH=, $^{4}J_{H-H}$ =2.4 Hz), 7.61 (d, 1H, CH=, $^{4}J_{H-H}$ =2.4 Hz). ^{13}C NMR (100.6 MHz, C_6D_6): δ=-5.6 (CH_3, OTBDMS), 18.1 (C, tBu, OTDMS), 25.8 (CH_3, ^{t}Bu, OTBDMS), 26.8 (CH_3), 26.9 (CH_3), 31.1 (CH_3, ^{t}Bu), 31.2 (CH_3, ^{t}Bu), 31.3 (CH_3, ^{t}Bu), 31.4 (CH_3, ^{t}Bu), 34.4 (C, ^{t}Bu), 35.3 (C, ^{t}Bu), 35.4 (CH_2-S), 35.5 (C, ^{t}Bu), 64.8 (CH_2-OTBDMS), 77.8 (CH-O, *C*HCHO), 78.9 (*C*HCH$_2$S), 109.5 (CMe_2), 123.9-146.6 (aromatic carbons). MS HR-ESI [found 879.4215, $C_{50}H_{69}O_6PSSi$ (M-Na)$^+$ requires 879.4214].

L13f. Yield: 535 mg (61%); SiO_2-flash chromatography (toluene/hexane/NEt_3 = 8:2:0.1). ^{31}P NMR (161.9 MHz, C_6D_6): δ=150.0 (s). ^{1}H NMR (400 MHz, C_6D_6): δ=0.11 (s, 3H, CH_3, OTBDMS), 0.14 (s, 3H, CH_3, OTBDMS), 0.53 (s, 9H, CH_3, $SiMe_3$), 0.58 (s, 9H, CH_3, $SiMe_3$), 1.04 (s, 9H, CH_3, ^{t}Bu, OTBDMS), 1.25 (s, 3H, CH_3), 1.29 (s, 3H, CH_3), 2.09 (dd, 1H, CH_2-S, $^{2}J_{H-H}$ =14.0 Hz, $^{3}J_{H-H}$ =4.4 Hz), 2.37 (dd, 1H, CH_2-S, $^{2}J_{H-H}$ =14.4 Hz, $^{3}J_{H-H}$ =4.0 Hz), 3.87-3.95 (m, 2H, CH_2-OTBDMS, C*H*CHO), 4.20-4.23 (m, 1H, CH_2-OTBDMS), 4.40-4.44 (m, 1H, C*H*CH$_2$S), 4.50-4.57 (CH-O), 6.82-6.94 (m, 5H, CH=), 7.00-7.16 (m, 4H, CH=), 7.30 (t, 2H, CH=, $^{3}J_{H-H}$ =8.4 Hz), 7.67-7.72 (m, 2H, CH=), 8.10 (s, 1H, CH=), 8.17 (s, 1H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ=-4.9 (CH_3, OTBDMS), -4.8 (CH_3, OTBDMS), 0.78 (d, CH_3, $SiMe_3$, J_{C-P} =4.6 Hz), 0.9 (CH_3, $SiMe_3$), 18.9 (C, ^{t}Bu, OTBDMS), 26.5 (CH_3, ^{t}Bu, OTBDMS), 27.6 (CH_3), 35.8 (CH_2-S), 65.8 (CH_2-OTBDMS), 78.4 (*C*HCHO), 78.6 (CH-O), 79.5 (*C*HCH$_2$S), 110.4 (CMe_2), 122.7-152.1 (aromatic carbons). MS HR-ESI [found 899.2812, $C_{48}H_{57}O_6PSSi_3$ (M-Na)$^+$ requires 899.2813].

L14a. Yield: 562 mg (62%); SiO_2-flash chromatography (toluene/hexane/NEt_3 = 8:2:0.1). ^{31}P NMR (161.9 MHz, C_6D_6): δ=146.5 (s). ^{1}H NMR (400 MHz, C_6D_6): δ=0.07 (s, 3H, CH_3, OTBDMS), 0.10 (s, 3H, CH_3, OTBDMS), 0.98 (s, 9H, CH_3, ^{t}Bu, OTBDMS), 1.22 (s, 9H, CH_3, ^{t}Bu), 1.29 (s, 15H, CH_3, CH_3 ^{t}Bu), 1.55 (s, 9H, CH_3, ^{t}Bu), 1.64 (s, 9H, CH_3, ^{t}Bu), 2.70 (dd, 1H, CH_2-S, $^2J_{H-H}$ =14.4 Hz, $^3J_{H-H}$ =4.4 Hz), 3.19 (dd, 1H, CH_2-S, $^2J_{H-H}$ =14.4 Hz, $^3J_{H-H}$ =3.2 Hz), 3.81 (dd, 1H, CH_2-OTBDMS, $^2J_{H-H}$ =11.6 Hz, $^3J_{H-H}$ =7.2 Hz), 4.12 (dd, 1H, CH_2-OTBDMS, $^2J_{H-H}$ =10.8 Hz), 4.19 (dd, 1H, C*H*CHO, $^2J_{H-H}$ =7.2 Hz, $^3J_{H-H}$ =4.0 Hz), 4.58-4.65 (m, 2H, C*H*CH_2S, CH-O), 7.00-7.22 (m, 2H, CH=), 7.31 (d, 1H, CH=, $^4J_{H-H}$ =2.4 Hz), 7.34 (d, 1H, CH=, $^4J_{H-H}$ =2.4 Hz), 7.38 (d, 1H, CH=, $^3J_{H-H}$ =8.8 Hz), 7.46 (d, 2H, $^3J_{H-H}$ =8.4 Hz), 7.52 (d, 1H, CH=, $^3J_{H-H}$ =8.0 Hz), 7.58 (d, 1H, CH=, $^4J_{H-H}$ =2.4 Hz), 7.64 (d, 1H, CH=, $^4J_{H-H}$ =2.4 Hz), 7.86 (s, 1H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ=-5.6 (CH_3, OTBDMS), 18.1 (C, ^{t}Bu, OTBDMS), 25.8 (CH_3, ^{t}Bu, OTBDMS), 26.7 (CH_3), 26.8 (CH_3), 31.1 (CH_3, ^{t}Bu), 31.3 (CH_3, ^{t}Bu), 31.4 (CH_3, ^{t}Bu), 34.3 (C, ^{t}Bu), 34.4 (C, ^{t}Bu), 35.3 (C, ^{t}Bu), 35.5 (CH_2-S), 64.8 (CH_2-OTBDMS), 77.6 (CH-O), 78.0 (*C*HCHO), 78.9 (*C*HCH_2S), 109.6 (CMe_2), 124.0-146.7 (aromatic carbons). MS HR-ESI [found 929.4368, $C_{54}H_{71}O_6PSSi$ $(M\text{-}Na)^+$ requires 929.4370].

L14g. Yield: 535 mg (58%); SiO_2-flash chromatography (toluene/hexane/NEt_3 = 8:2:0.1). ^{31}P NMR (161.9 MHz, C_6D_6): δ=143.6 (s). ^{1}H NMR (400 MHz, C_6D_6): δ=-0.38 (s, 3H, CH_3, OTBDMS), -0.33 (s, 3H, CH_3, OTBDMS), 0.45 (s, 9H, CH_3, $SiMe_3$), 0.55 (s, 9H, CH_3, $SiMe_3$), 0.75 (s, 9H, CH_3, ^{t}Bu, OTBDMS), 1.43 (s, 3H, CH_3), 1.52 (s, 3H, CH_3), 3.10 (dd, 1H, CH_2-OTBDMS, $^2J_{H-H}$ =10.4 Hz, $^3J_{H-H}$ =5.2 Hz), 3.24 (dd, 1H, CH_2-S, $^2J_{H-H}$ =13.6 Hz, $^3J_{H-H}$ =6.4 Hz), 3.38 (dd, 1H, CH_2-S, $^2J_{H-H}$ =13.6 Hz, $^3J_{H-H}$ =3.6 Hz), 3.51 (dd, 1H, CH_2-OTBDMS, $^2J_{H-H}$ =10.8 Hz, $^3J_{H-H}$ =8.0 Hz), 4.48 (dd, 1H, C*H*CHO, $^3J_{H-H}$ =7.2 Hz, $^3J_{H-H}$ =4.0 Hz), 4.69-4.74 (m, 1H, C*H*CH_2S), 4.83-4.90 (m, 1H, CH-O), 6.83-6.88 (m, 2H, CH=), 7.02-7.23 (m, 3H, CH=), 7.32 (d, 1H, CH=, $^3J_{H-H}$ =8.4 Hz), 7.45 (s, 2H, CH=), 7.50-7.53 (m, 2H, CH=), 7.69 (t, 2H, CH=, $^3J_{H-H}$ =7.2 Hz), 7.82 (s, 1H, CH=), 8.08 (s, 1H, CH=), 8.10 (s, 1H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ=-5.5 (CH_3, OTBDMS), -5.2 (CH_3, OTBDMS), 0.55 (d, CH_3, $SiMe_3$, J_{C-P} =4.6 Hz), 0.7 (CH_3, $SiMe_3$), 18.5 (C, ^{t}Bu, OTBDMS), 26.3 (CH_3, ^{t}Bu, OTBDMS), 28.1 (CH_3), 38.4 (CH_2-S), 63.2 (CH_2-OTBDMS), 75.3 (d, CH-O, $^2J_{C-P}$ =7.3 Hz), 76.9 (*C*HCH_2S), 80.4 (d, *C*HCHO, $^3J_{C-P}$ =3.4 Hz), 110.4 (CMe_2), 125.5-152.7 (aromatic carbons). MS HR-ESI [found 949.2968, $C_{52}H_{59}O_6PSSi_3$ $(M\text{-}Na)^+$ requires 949.2970].

L15g. Yield: 623 mg (63%); SiO_2-flash chromatography (toluene/hexane/NEt_3 = 8:2:0.1). ^{31}P NMR (161.9 MHz, C_6D_6): δ=145.2 (s). ^{1}H NMR (400 MHz, C_6D_6): δ=0.42 (s, 9H, CH_3, $SiMe_3$), 0.52 (s, 9H, CH_3, $SiMe_3$), 0.93 (s, 9H, CH_3, ^{t}Bu, OTBDPS), 1.41 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 3.23 (dd, 1H, CH_2-S, $^2J_{H-H}$ =13.6 Hz, $^3J_{H-H}$ =6.8 Hz), 3.34 (d, 1H, CH_2-S, $^2J_{H-H}$ =11.2 Hz), 3.52 (dd, 1H, CH_2-OTBDPS, $^2J_{H-H}$ =11.2 Hz, $^3J_{H-H}$ =6.0 Hz), 3.79 (dd, 1H, CH_2-OTBDPS, $^2J_{H-H}$ =11.2 Hz, $^3J_{H-H}$ =8.4 Hz), 4.48 (pt, 1H, C*H*CHO, $^3J_{H-H}$ =5.2 Hz), 4.69-4.73 (m, 1H, C*H*CH_2S), 4.86-4.94 (m, 1H, CH-O), 6.77-6.86 (m, 2H, CH=), 7.00-7.22 (m, 12H, CH=), 7.38-7.53 (m, 8H, CH=), 7.56 (d, 1H, CH=, $^3J_{H-H}$ =8.0 Hz), 7.69 (d, 1H, CH=, $^3J_{H-H}$ =8.0 Hz), 7.78 (s, 1H, CH=), 7.92 (s, 1H, CH=), 8.10 (s, 1H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ=0.6 (d, CH_3, $SiMe_3$, J_{C-P} =3.8 Hz), 0.7 (CH_3, $SiMe_3$), 19.7 (C, ^{t}Bu, OTBDPS), 27.2 (CH_3, ^{t}Bu, OTBDPS), 28.0 (CH_3), 28.1 (CH_3),

38.6 (CH_2-S), 64.5 (CH_2-OTBDPS), 76.1 (d, CH-O, $^2J_{C-P}$ =4.5 Hz), 77.5 (*C*HCH$_2$S), 80.3 (d, *C*HCHO, $^3J_{C-P}$ =3.2 Hz), 110.5 (CMe_2), 123.2-152.5 (aromatic carbons). MS HR-ESI [found 1011.3127, $C_{57}H_{61}O_6PSSi_3$ $(M-Na)^+$ requires 1011.3126].

L16g. Yield: 636 mg (67%); SiO_2-flash chromatography (toluene/hexane/NEt_3 = 8:2:0.1). ^{31}P NMR (161.9 MHz, C_6D_6): δ=142.2 (s). ^1H NMR (400 MHz, C_6D_6): δ=0.40 (s, 9H, CH_3, $SiMe_3$), 0.42-0.45 (m, 3H, CH, TIPS), 0.57 (s, 9H, CH_3, $SiMe_3$), 0.74 (d, 9H, CH_3, $^3J_{H-H}$ =8.4 Hz), 0.81 (d, 9H, CH_3, $^3J_{H-H}$ =7.6 Hz), 1.48 (s, 3H, CH_3), 1.63 (s, 3H, CH_3), 2.85 (dd, 1H, CH_2-OTIPS, $^2J_{H-H}$ =10.4 Hz, $^3J_{H-H}$ =6.4 Hz), 3.33 (dd, 1H, CH_2-S, $^2J_{H-H}$ =14.0 Hz, $^3J_{H-H}$ =6.8 Hz), 3.46-3.53 (m, 2H, CH_2-OTIPS, CH_2-S), 4.55 (dd, 1H, C*H*CHO, $^3J_{H-H}$ =8.0 Hz, $^3J_{H-H}$ =3.2 Hz), 4.82-4.86 (m, 1H, C*H*CH$_2$S), 5.03-5.08 (m, 1H, CH-O), 6.84-6.90 (m, 2H, CH=), 7.00-7.30 (m, 7H, CH=), 7.48-7.56 (m, 3H, CH=), 7.66 (t, 2H, CH=, $^3J_{H-H}$ =8.8 Hz), 7.88 (s, 1H, CH=), 8.05 (s, 1H, CH=), 8.07 (s, 1H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ=0.4 (d, CH_3, $SiMe_3$, J_{C-P} =4.6 Hz), 0.6 (CH_3, $SiMe_3$), 11.9 (CH, OTIPS), 18.2 (s, CH_3, OTIPS), 18.4 (s, CH_3, OTIPS), 28.2 (CH_3), 38.7 (CH_2-S), 63.3 (CH_2-OTIPS), 74.1 (d, CH-O, $^2J_{C-P}$ =10.7 Hz), 76.0 (*C*HCH$_2$S), 80.5 (d, *C*HCHO, $^3J_{C-P}$ =3.7 Hz), 110.5 (CMe_2), 123.7-152.5 (aromatic carbons). MS HR-ESI [found 971.3750, $C_{53}H_{69}O_6PSSi_3$ $(M-Na)^+$ requires 971.3752].

L17g. Yield: 538 mg (58%); SiO_2-flash chromatography (toluene/hexane/NEt_3 = 8:2:0.1). ^{31}P NMR (161.9 MHz, C_6D_6): δ=145.3 (s). ^1H NMR (400 MHz, C_6D_6): δ=0.40 (s, 9H, CH_3, $SiMe_3$), 0.57 (s, 9H, CH_3, $SiMe_3$), 1.45 (s, 3H, CH_3), 1.51 (s, 3H, CH_3), 2.97 (dd, 1H, CH_2-OTr, $^2J_{H-H}$ =10.4 Hz, $^3J_{H-H}$ =6.0 Hz), 3.06-3.11 (d, 1H, CH_2-OTr), 3.21 (dd, 1H, CH_2-S, $^2J_{H-H}$ =13.2 Hz, $^3J_{H-H}$ =6.8 Hz), 3.36 (dd, 1H, CH_2-S, $^2J_{H-H}$ =13.6 Hz, $^3J_{H-H}$ =3.6 Hz), 4.57 (dd, 1H, C*H*CHO, $^3J_{H-H}$ =7.6 Hz, $^3J_{H-H}$ =3.6 Hz), 4.67-4.71 (m, 1H, C*H*CH$_2$S), 4.91-4.98 (m, 1H, CH-O), 6.82-6.93 (m, 12H, CH=), 7.00-7.18 (m, 11H, CH=), 7.38-7.47 (m, 3H, CH=), 7.54 (d, 1H, CH=, $^3J_{H-H}$ =6.8 Hz), 7.59 (d, 1H, CH=, $^3J_{H-H}$ =8.4 Hz), 7.71 (d, 1H, CH=, $^3J_{H-H}$ =8.0 Hz), 7.78 (s, 1H, CH=), 7.95 (s, 1H, CH=), 8.12 (s, 1H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ=-0.1 (d, CH_3, $SiMe_3$, J_{C-P} =4.5 Hz), 0.1 (CH_3, $SiMe_3$), 27.4 (CH_3), 37.6 (CH_2-S), 63.7 (CH_2-OTr), 73.2 (d, CH-O, $^2J_{C-P}$ =5.7 Hz), 75.7 (*C*HCH$_2$S), 80.0 (d, *C*HCHO, $^3J_{C-P}$ =4.0 Hz), 87.4 (C, Tr), 109.7 (CMe_2), 122.6-151.8 (aromatic carbons). MS HR-ESI [found 1057.3512, $C_{63}H_{63}O_6PSSi_2$ $(M-Na)^+$ requires 1057.3514

L18a. Yield: 329.2 mg (46%); SiO_2-flash chromatography (toluene/hexane/NEt_3 = 8:2:0.1). ^{31}P NMR (161.9 MHz, C_6D_6): δ=148.5 (s). ^1H NMR (400 MHz, C_6D_6): δ=1.10 (d, 3H, CH_3, $^3J_{H-H}$ =6.0 Hz), 1.26 (s, 21H, CH_3, CH_3 ^{t}Bu), 1.35 (s, 3H, CH_3), 1.57 (s, 18H, CH_3, ^{t}Bu), 2.89 (dd, 1H, CH_2-S, $^2J_{H-H}$ =14.4 Hz, $^3J_{H-H}$ =6.8 Hz), 3.10 (dd, 1H, CH_2-S, $^2J_{H-H}$ =13.6 Hz, $^3J_{H-H}$ =4.0 Hz), 3.95 (dd, 1H, C*H*CHO, $^3J_{H-H}$ =4.4 Hz, $^3J_{H-H}$ =7.3 Hz), 4.18-4.22 (m, 1H, C*H*CH$_2$S), 4.51-4.54 (m, 1H, CH-O), 6.86-7.14 (m, 3H, CH=), 7.25-7.31 (m, 4H, CH=), 7.58 (d, 2H, CH=, $^4J_{H-H}$ =2.4 Hz). ^{13}C NMR (100.6 MHz, C_6D_6): δ=17.9 (d, CH_3, $^3J_{C-P}$ =3.1 Hz), 26.9 (CH_3), 27.3 (CH_3), 31.2 (CH_3, ^{t}Bu), 34.3 (C, ^{t}Bu), 35.3 (C, ^{t}Bu), 36.8 (CH_2-S), 71.0 (d, CH-O, $^2J_{C-P}$ =1.7 Hz), 75.5 (*C*HCH$_2$S), 82.1 (d, *C*HCHO, $^3J_{C-P}$ =3.1 Hz), 109.4 (CMe_2), 123.9-146.4 (aromatic carbons). MS HR-ESI [found 729.3718, $C_{42}H_{59}O_5PS$ $(M-Na)^+$ requires 729.3717].

L18f. Yield: 237.1 mg (32%); SiO_2-flash chromatography (toluene/hexane/NEt_3 = 8:2:0.1). ^{31}P NMR (161.9 MHz, C_6D_6): δ=143.6 (s). ^1H NMR (400 MHz, C_6D_6): δ=0.53 (s, 9H,

CH_3, $SiMe_3$), 0.54 (s, 9H, CH_3, $SiMe_3$), 0.78 (d, 3H, CH_3, $^3J_{H-H}$ =6.4 Hz), 1.31 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 2.96 (dd, 1H, CH_2-S, $^2J_{H-H}$ =13.6 Hz, $^3J_{H-H}$ =6.4 Hz), 3.10 (dd, 1H, CH_2-S, $^2J_{H-H}$ =13.6 Hz, $^3J_{H-H}$ =4.0 Hz), 3.97 (dd, 1H, C*H*CHO, $^3J_{H-H}$ =4.8 Hz, $^3J_{H-H}$ =7.2 Hz), 4.13 (m, 1H, C*H*CH_2S), 4.55 (m, 1H, CH-O), 6.83-7.15 (m, 7H, CH=), 7.23-7.34 (m, 4H, CH=), 7.68-7.71 (m, 2H, CH=), 8.10 (s, 1H, C=H), 8.14 (s, 1H, C=H). ^{13}C NMR (100.6 MHz, C_6D_6): δ=-0.1 (d, CH_3, $SiMe_3$, J_{C-P} =4.5 Hz), 0.1 (CH_3, $SiMe_3$), 17.6 (CH_3), 27.0 (CH_3), 27.2 (CH_3), 37.3 (CH_2-S), 71.6 (CH-O), 75.8 (*C*HCH_2S), 82.2 (d, *C*HCHO, $^3J_{C-P}$ =4.6 Hz), 109.5 (CMe_2), 122.5-152.3 (aromatic carbons). MS HR-ESI [found 749.2316, $C_{40}H_{47}O_5PSSi_2$ $(M-Na)^+$ requires 749.2318].

L18g. Yield: 289.0 mg (39%); SiO_2-flash chromatography (toluene/hexane/NEt_3 = 8:2:0.1). ^{31}P NMR (161.9 MHz, C_6D_6): δ=151.4 (s). ^{1}H NMR (400 MHz, C_6D_6): δ=0.51 (s, 9H, CH_3, $SiMe_3$), 0.53 (s, 9H, CH_3, $SiMe_3$), 1.15 (s, 3H, CH_3), 1.25 (m, 6H, CH_3), 2.53 (dd, 1H, CH_2-S, $^2J_{H-H}$ =14.0 Hz, $^3J_{H-H}$ =6.0 Hz), 2.69 (dd, 1H, CH_2-S, $^2J_{H-H}$ =13.6 Hz, $^3J_{H-H}$ =2.6 Hz), 3.95-4.00 (m, 2H, C*H*CHO, C*H*CH_2S), 4.50-4.55 (m, 1H, CH-O), 6.85-6.86 (m, 3H, CH=), 6.92-6.96 (m, 2H, CH=), 6.98-7.00 (m, 1H, CH=), 7.09-7.15 (m, 5H, CH=), 7.24 (d, 1H, C=H, $^3J_{H-H}$ =8.4 Hz), 7.31 (d, 1H, C=H, $^3J_{H-H}$ =8.4 Hz), 7.69 (d, 1H, C=H, $^3J_{H-H}$ =8.4 Hz), 8.10 (d, 1H, C=H, $^3J_{H-H}$ =8.4 Hz). ^{13}C NMR (100.6 MHz, C_6D_6): δ=-0.1 (d, CH_3, $SiMe_3$, J_{C-P} =4.6 Hz), 0.2 (CH_3, $SiMe_3$), 17.6 (CH_3), 26.8 (CH_3), 27.1 (CH_3), 36.3 (CH_2-S), 70.1 (d, CH-O, $^2J_{C-P}$ =10.0 Hz), 75.1 (*C*HCH_2S), 81.0 (*C*HCHO), 109.1 (CMe_2), 122.5-152.1 (aromatic carbons). MS HR-ESI [found 749.2317, $C_{40}H_{47}O_5PSSi_2$ $(M-Na)^+$ requires 749.2318].

L19a. Yield: 322.0 mg (45%); SiO_2-flash chromatography (toluene/hexane/NEt_3 = 8:2:0.1). ^{31}P NMR (161.9 MHz, C_6D_6): δ=135.3 (s). ^{1}H NMR (400 MHz, C_6D_6): δ=1.25 (s, 21H, CH_3, CH_3 ^{t}Bu), 1.31 (s, 3H, CH_3), 1.42 (s, 3H), 1.56 (s, 9H, CH_3, ^{t}Bu), 1.59 (s, 9H, CH_3, ^{t}Bu), 3.28-3.31 (m, 1H, CH-S), 3.94-3.97 (dd, 1H, C*H*CHS, $^2J_{H-H}$ =7.6 Hz, $^3J_{H-H}$ =3.6 Hz), 4.02 (b, 1H, CH_2-O), 4.16 (b, 1H, CH_2-O), 4.33-4.38 (m, 1H, C*H*CH_2O), 6.90-6.95 (m, 3H, CH=), 7.29-7.34 (m, 4H, CH=), 7.58 (s, 2H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ=18.0 (CH_3), 26.9 (CH_3), 27.1 (CH_3), 30.9 (CH_3, ^{t}Bu), 31.2 (CH_3, ^{t}Bu), 34.3 (C, ^{t}Bu), 35.3 (C, ^{t}Bu), 45.1 (CH-S), 65.6 (CH_2-O), 77.3 (*C*HCH_2O), 80.5 (*C*HCHS), 109.4 (CMe_2), 124.2-146.5 (aromatic carbons). MS HR-ESI [found 729.3719, $C_{42}H_{59}O_5PS$ $(M-Na)^+$ requires 729.3719].

L19f. Yield: 259.4 mg (35%); SiO_2-flash chromatography (toluene/hexane/NEt_3 = 8:2:0.1). ^{31}P NMR (161.9 MHz, C_6D_6): δ=132.0 (s). ^{1}H NMR (400 MHz, C_6D_6): δ=0.51 (s, 9H, CH_3, $SiMe_3$), 0.58 (s, 9H, CH_3, $SiMe_3$), 1.23 (d, 3H, CH_3, $^3J_{H-H}$ =6.8 Hz), 1.24 (s, 3H, CH_3), 1.38 (s, 3H), 3.18-3.24 (m, 1H, CH-S), 3.68-3.73 (m, 1H, CH_2-O), 3.82 (dd, 1H, C*H*CHS, $^3J_{H-H}$ =3.6 Hz, $^3J_{H-H}$ =7.6 Hz), 4.16-4.25 (m, 2H, C*H*CH_2O, CH_2-O), 6.85-6.94 (m, 5H, CH=), 7.00-7.20 (m, 4H), 7.25 (d, 1H, CH=, $^3J_{H-H}$ =8.8 Hz), 7.36 (d, 1H, CH=, $^3J_{H-H}$ =8.4 Hz), 7.66 (d, 1H, CH=, $^3J_{H-H}$ = 8.0 Hz), 7.69 (d, 1H, CH=, $^3J_{H-H}$ =8.4 Hz), 8.11 (s, 1H, CH=), 8.15 (s, 1H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ=-0.3 (CH_3, $SiMe_3$), -0.1 (d, CH_3, $SiMe_3$, J_{C-P} =5.3 Hz), 17.3 (CH_3), 26.9 (CH_3), 27.0 (CH_3), 44.8 (CH-S), 65.4 (d, CH_2-O, $^2J_{C-P}$ =5.4 Hz), 77.8 (d, *C*HCH_2O, $^3J_{C-P}$ =3.8 Hz), 79.6 (*C*HCHS), 109.3 (CMe_2), 122.4-154.0 (aromatic carbons). MS HR-ESI [found 749.2315, $C_{40}H_{47}O_5PSSi_2$ $(M-Na)^+$ requires 749.2318].

L19g. Yield: 274.2 mg (37%); SiO_2-flash chromatography (toluene/hexane/NEt_3 = 8:2:0.1). ^{31}P NMR (161.9 MHz, C_6D_6): δ=134.4 (s). ^1H NMR (400 MHz, C_6D_6): δ=0.52 (s, 9H, CH_3, $SiMe_3$), 0.54 (s, 9H, CH_3, $SiMe_3$), 1.15 (d, 3H, CH_3, $^3J_{H-H}$ =7.2 Hz), 1.27 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 3.15-3.18 (m, 1H, CH-S), 3.51-3.57 (m, 1H, CH_2-O), 3.82 (dd, 1H, C*H*CHS, $^3J_{H-H}$ =7.6 Hz, $^3J_{H-H}$ =3.2 Hz), 4.26-4.31 (m, 2H, C*H*CH_2O, CH_2-O), 6.84-6.89 (m, 5H, CH=), 7.11 (1, 2H, CH=, $^3J_{H-H}$ =8.0 Hz), 7.16 (s, 1H, CH=), 7.23-7.28 (m, 3H, CH=), 7.34 (d, 1H, CH=, $^3J_{H-H}$ =8.4 Hz), 7.69 (pt, 2H, CH=, $^3J_{H-H}$ = 8.4 Hz), 8.11 (s, 2H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ=-0.4 (CH_3, $SiMe_3$), -0.2 (d, CH_3, $SiMe_3$, J_{C-P} =4.6 Hz), 18.2 (CH_3), 26.9 (CH_3), 27.0 (CH_3), 45.4 (CH-S), 65.5 (CH_2-O), 77.6 (*C*HCH_2O), 80.5 (*C*HCHS), 109.5 (CMe_2), 122.4-152.8 (aromatic carbons). MS HR-ESI [found 749.2317, $C_{40}H_{47}O_5PSSi_2$ $(M-Na)^+$ requires 749.2318].

L20a. Yield: 503 mg (68%); SiO_2-flash chromatography (toluene/hexane/NEt_3 = 5:5:0.1). ^{31}P NMR (161.9 MHz, C_6D_6): δ=136.0 (s). ^1H NMR (400 MHz, C_6D_6): δ=1.26 (s, 9H, CH_3), 1.27 (s, 9H, CH_3), 1.28 (s, 3H, CH_3), 1.33 (s, 3H, CH_3), 1.56 (s, 9H, CH_3), 1.58 (S, 9H, CH_3), 2.86 (dd, 1H, CH_2-Se, $^2J_{H-H}$= 12.6 Hz, $^3J_{H-H}$ =6.0 Hz), 2.97 (dd, 1H, CH_2-Se, $^2J_{H-H}$ =12.6 Hz, $^3J_{H-H}$ =5.6 Hz), 3.86-4.14 (m, 4H, C*H*CH_2Se, C*H*CH_2O, CH_2-O), 6.89-6.96 (m, 3H, CH=), 7.33 (d, 2H, CH=, $^3J_{H-H}$ =2.4 Hz), 7.36-7.44 (m, 2H, CH=), 7.58 (d, 2H, CH=, $^4J_{H-H}$ =2.4 Hz). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 28.0 (CH_3), 28.1 (CH_3), 31.1 (CH_2-Se), 31.9 (CH_3, ^{t}Bu), 32.2 (CH_3, ^{t}Bu), 35.3 (C, ^{t}Bu), 36.3 (C, ^{t}Bu), 65.6 (CH_2-O), 78.1 (*C*HCH_2Se), 81.0 (d, *C*HCH_2O, $^3J_{C-P}$ =3.0 Hz), 110.3 (CMe_2), 125.1-147.5 (aromatic carbons). MS HR-ESI [found 763.3000, $C_{41}H_{57}O_5PSe$ $(M-Na)^+$ requires 763.3001].

L20f. Yield: 448 mg (59%); SiO_2-flash chromatography (toluene/hexane/NEt_3 = 5:5:0.1). ^{31}P NMR (161.9 MHz, C_6D_6): δ=133.9 (s). ^1H NMR (400 MHz, C_6D_6): δ=0.51 (s, 9H, CH_3, $SiMe_3$), 0.55 (s, 9H, CH_3, $SiMe_3$), 1.27 (s, 3H, CH_3), 1.32 (s, 3H, CH_3), 2.79 (dd, 1H, CH_2-Se, $^2J_{H-H}$ =12.5 Hz, $^3J_{H-H}$ =6.1 Hz), 2.88 (dd, 1H, CH_2-Se, $^2J_{H-H}$ =12.5 Hz, $^3J_{H-H}$ =5.5 Hz), 3.41 (m, 1H, CH_2-O), 3.75 (m, C*H*CH_2O), 3.99 (m, 1H, C*H*CH_2Se), 4.31 (m, 1H, CH_2-O), 6.84-6.93 (m, 5H, CH=), 7.09-7.17 (m, 2H, CH=), 7.25 (d, 1H, CH=, $^3J_{H-H}$ =8.6 Hz), 7.27-7.33 (m, 2H, CH=), 7.35 (d, 1H, $^3J_{H-H}$ =8.5 Hz, CH=), 7.70 (d, 2H, CH=, $^3J_{H-H}$ =8.2 Hz), 8.11 (s, 1H, CH=), 8.13 (s, 1H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ=0.6 (CH_3, $SiMe_3$), 0.8 (d, CH_3, $SiMe_3$, J_{C-P} =4.8 Hz), 27.9 (CH_3), 28.1 (CH_3), 31.2 (CH_2-Se), 65.1 (CH_2-O), 77.6 (*C*HCH_2Se), 81.0 (*C*HCH_2O), 110.15 (CMe_2), 123.5-153.8 (aromatic carbons). MS HR-ESI [found 783.1601, $C_{39}H_{45}O_5PSeSi_2$ $(M-Na)^+$ requires 783.1601].

L20g. Yield: 471 mg (62%); SiO_2-flash chromatography (toluene/hexane/NEt_3 = 5:5:0.1). ^{31}P NMR (161.9 MHz, C_6D_6): δ=132.4 (s). ^1H NMR (400 MHz, C_6D_6): δ=0.51 (s, 9H, CH_3, $SiMe_3$), 0.56 (s, 9H, CH_3, $SiMe_3$), 1.24 (s, 3H, CH_3), 1.29 (s, 3H, CH_3), 2.73 (dd, 1H, CH_2-Se, $^2J_{H-H}$ =12.5 Hz, $^3J_{H-H}$ =6.3 Hz), 2.87 (dd, 1H, CH_2-Se, $^2J_{H-H}$ =12.5 Hz, $^3J_{H-H}$ =5.4 Hz), 3.57 (m, 1H, CH_2-O), 3.75 (m, 1H, C*H*CH_2O), 3.86 (m, 1H, C*H*CH_2Se), 4.12 (m, 1H, CH_2-O), 6.83-6.93 (m, 5H, CH=), 7.08-7.19 (m, 2H, CH=), 7.24 (d, 1H, $^3J_{H-H}$ =8.4 Hz, CH=), 7.28-7.34 (m, 2H, CH=), 7.37 (d, 1H, $^3J_{H-H}$ =8.4 Hz, CH=), 7.64-7.73 (m, 2H, CH=), 8.1 (s, 1H, CH=), 8.2 (s, 1H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ=0.6 (CH_3, $SiMe_3$), 0.8 (d, CH_3, $SiMe_3$, J_{C-P} =4.7 Hz), 27.7 (CH_3), 28.1 (CH_3), 31.0 (CH_2-Se), 65.5 (d, CH_2-O, $^2J_{H-H}$ =5.4 Hz), 77.2 (*C*HCH_2Se), 80.9 (d, *C*HCH_2O, $^3J_{H-H}$

=3.8 Hz), 110.3 (CMe_2), 123.4-153.9 (aromatic carbons). MS HR-ESI [found 783.1598, $C_{39}H_{45}O_5PSeSi_2$ $(M-Na)^+$ requires 783.1601].

L21f. Yield: 510 mg (63%); SiO_2-flash chromatography (toluene/hexane/NEt_3 = 5:5:0.1). ^{31}P NMR (161.9 MHz, C_6D_6): δ=133.8 (s). ^1H NMR (400 MHz, C_6D_6): δ=0.49 (s, 9H, CH_3, $SiMe_3$), 0.53 (s, 9H, CH_3, $SiMe_3$), 1.27 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 2.90 (dd, 1H, CH_2-Se, $^2J_{H-H}$ =12.6 Hz, $^3J_{H-H}$ =5.8 Hz), 2.97 (dd, 1H, CH_2-Se, $^2J_{H-H}$ =12.8 Hz, $^3J_{H-H}$ =6.0 Hz), 3.47 (m, 1H, CH_2-O), 3.81 (m, 1H, C*H*CH_2O), 4.07 (m, 1H, C*H*CH_2Se), 4.33 (m, 1H, CH_2-O), 6.87 (m, 2H, CH=), 7.06-7.14 (m, 2H, CH=), 7.18-7.23 (m, 2H, CH=), 7.26 (d, 1H, CH=, $^3J_{H-H}$ =8.5 Hz), 7.33-7.44 (m, 3H, CH=), 7.45-7.50 (m, 1H, CH=), 7.51-7.56 (m, 1H, CH=), 7.64-7.74 (m, 2H, CH=), 7.84-7.88 (m, 1H, CH=), 8.11 (s, 1H, CH=), 8.12 (s, 1H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ=0.5 (CH_3, $SiMe_3$), 0.7 (d, CH_3, $SiMe_3$, J_{C-P} =4.8 Hz), 27.8 (CH_3), 28.0 (CH_3), 31.2 (CH_2-Se), 65.1 (d, CH_2-O, $^2J_{C-P}$ =3.7 Hz), 77.8 (*C*HCH_2Se), 81.0 (d, *C*HCH_2O, $^3J_{C-P}$ =2.7 Hz), 110.3 (CMe_2), 123.4-153.8 (aromatic carbons). MS HR-ESI [found 833.1754, $C_{43}H_{47}O_5PSeSi_2$ $(M-Na)^+$ requires 833.1757].

L21g. 429 mg (53%); SiO_2-flash chromatography (toluene/hexane/NEt_3 = 5:5:0.1). ^{31}P NMR (161.9 MHz, C_6D_6): δ=133.0 (s). ^1H NMR (400 MHz, C_6D_6) δ=0.50 (s, 9H, CH_3, $SiMe_3$), 0.55 (s, 9H, CH_3, $SiMe_3$), 1.25 (s, 3H, CH_3), 1.31 (s, 3H, CH_3), 2.84 (dd, 1H, , CH_2-Se, $^2J_{H-H}$ =12.5 Hz, $^3J_{H-H}$ =6.0 Hz), 2.95 (dd, 1H, CH_2-Se, $^2J_{H-H}$ =12.5 Hz, $^3J_{H-H}$ =5.6 Hz), 3.59 (m, 1H, CH_2-O), 3.80 (m, 1H, C*H*CH_2O), 3.95 (m, 1H, C*H*CH_2Se), 4.14 (m, 1H, CH_2-O), 6.87 (m, 2H, CH=), 7.05-7.16 (m, 2H, CH=), 7.18-7.22 (m, 2H, CH=), 7.25 (d, 1H, CH=, $^3J_{H-H}$ =8.5 Hz), 7.34-7.43 (m, 3H, CH=), 7.44-7.50 (m, 1H, CH=), 7.50-7.56 (m, 1H, CH=), 7.62 (d, 1H, CH=, $^3J_{H-H}$ =8.2 Hz), 7.69 (d, 1H, CH=, $^3J_{H-H}$ =8.2 Hz), 7.86 (s, 1H, CH=), 8.10 (s, 1H, CH=), 8.13 (s, 1H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ=0.7 (CH_3, SiMe3), 0.8 (d, CH_3, $SiMe_3$, J_{C-P} =4.8 Hz), 27.8 (CH_3), 28.1 (CH_3), 31.0 (CH_2-Se), 65.4 (d, CH_2-O, $^2J_{C-P}$ =5.2 Hz), 77.3 (*C*HCH_2Se), 80.9 (d, $^3J_{C-P}$ =3.6 Hz, *C*HCH_2O), 110.3 (CMe_2), 123.3-153.9 (aromatic carbons). MS HR-ESI [found 833.1753, $C_{43}H_{47}O_5PSeSi_2$ $(M-Na)^+$ requires 833.1757].

L22f. 410 mg (49%); Al_2O_3-flash chromatography (toluene/hexane/NEt_3 = 6:4:0.1). ^{31}P NMR (161.9 MHz, C_6D_6): δ=153.8 (s). ^1H NMR (400 MHz, C_6D_6) δ=0.54 (s, 9H, CH_3, $SiMe_3$), 0.57 (s, 9H, CH_3, $SiMe_3$), 1.17 (s, 3H, CH_3), 1.25 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 1.76 (s, 3H, CH), 2.44 (dd, CH_2-Se, 1H, $^2J_{H-H}$ =13.4 Hz, $^3J_{H-H}$ =6.8 Hz), 2.55 (dd, 1H, CH_2-Se, $^2J_{H-H}$ =13.3 Hz, $^3J_{H-H}$ =2.8 Hz), 3.95 (d, 1H, $CHCMe_2O$, $^3J_{H-H}$ =7.5 Hz), 4.20-4.24 (m, 1H, C*H*CH_2Se), 6.84 (m, 3H, CH=), 7.00-7.25 (m, 5H, CH=), 7.36-7.43 (m, 4H, CH=), 7.50 (t, 2H, , CH=, $^3J_{H-H}$ =9.0 Hz), 7.63 (d, 1H, CH=, $^3J_{H-H}$ =8.1 Hz), 7.70 (d, 1H, CH=, $^3J_{H-H}$ =8.1 Hz), 8.12 (s, 1H, CH=), 8.14 (s, 1H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ=0.6 (CH_3, $SiMe_3$), 0.7 (CH_3, $SiMe_3$), 25.2 (CH_3), 27.9 (CH_3), 28.1 (CH_3), 29.2 (d, CH_3, $^3J_{C-P}$ =18.5 Hz), 32.4 (CH_2-Se), 77.9 (*C*HCH_2Se), 81.2 (d, CMe_2O, $^3J_{C-P}$ =3.4 Hz), 86.2 (*C*HCMe_2O), 109.7 (CMe_2), 123.7-153.3 (aromatic carbons). MS HR-ESI [found 861.2068, $C_{45}H_{51}O_5PSeSi_2$ $(M-Na)^+$ requires 861.2070].

L22g. 452 mg (54%); Al_2O_3-flash chromatography (toluene/hexane/NEt_3 = 6:4:0.1). ^{31}P NMR (161.9 MHz, C_6D_6): δ=154.9 (s). ^1H NMR (400 MHz, C_6D_6): δ=0.53 (s, 9H, CH_3, $SiMe_3$), 0.58 (s, 9H, CH_3, $SiMe_3$), 1.04 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 1.56 (s, 3H, CH_3), 1.75 (s, 3H,

CH), 2.52 (dd, 1H, CH_2-Se, $^2J_{H-H}$ =13.6 Hz, $^3J_{H-H}$ =8.2 Hz), 2.87 (dd, 1H, CH_2-Se, $^2J_{H-H}$ =13.6 Hz, $^3J_{H-H}$ =2.4 Hz), 3.91 (d, 1H, $CHCMe_2O$, $^3J_{H-H}$ =8.1 Hz), 4.09-4.14 (m, 1H, C*H*CH_2Se), 6.55-6.59 (m, 1H, CH=), 6.77-6.85 (m, 1H, CH=), 6.95 (t, CH=, 1H, $^3J_{H-H}$ =7.5 Hz), 7.00-7.05 (m, 1H, CH=), 7.05-7.28 (m, 8H, CH=), 7.41-7.47 (m, 2H, CH=), 7.69 (t, 2H, CH=, $^3J_{H-H}$ =7.4 Hz), 8.15 (s, 1H, CH=), 8.21 (s, 1H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ=0.0 (d, CH_3, J_{C-P} =4.9 Hz), 0.8 (CH_3, $SiMe_3$), 24.9 (d, CH_3, $^3J_{C-P}$ =8.7 Hz), 26.9 (CH_3), 27.6 (CH_3), 28.8 (d, CH_3, $^3J_{C-P}$ =8.7 Hz), 30.0 (CH_2-Se), 76.3 (*C*HCH_2Se), 80.5 (d, CMe_2O, $^3J_{C-P}$ =7.3 Hz), 85.3 (*C*$HCMe_2O$), 108.9 (CMe_2), 124.9-152.7 (aromatic carbons). MS HR-ESI [found 833.1756, $C_{43}H_{47}O_5PSeSi_2$ $(M-Na)^+$ requires 833.1757].

L23f. Yield: 420 mg (51%); SiO_2-flash chromatography (toluene/hexane/NEt_3 = 8:2:0.1). ^{31}P NMR (161.9 MHz, C_6D_6): δ=147.5 (s). ^{1}H NMR (400 MHz, C_6D_6): δ=0.50 (s, 9H, CH_3, $SiMe_3$), 0.53 (s, 9H, CH_3, $SiMe_3$), 1.21 (s, 3H, CH_3), 1.32 (s, 3H, CH_3), 1.47 (d, 3H, CH_3, $^3J_{H-H}$ =6.0 Hz), 2.38 (dd, 1H, CH_2-Se, $^2J_{H-H}$ =13.2 Hz, $^3J_{H-H}$ =5.6 Hz), 2.43 (dd, 1H, CH_2-Se, $^2J_{H-H}$ =12.8 Hz, $^3J_{H-H}$ =3.6 Hz), 3.80 (dd, 1H, C*H*CHO, $^3J_{H-H}$ =7.6 Hz, $^3J_{H-H}$ =6.8 Hz), 4.12-4.17 (m, 1H, C*H*CH_2Se), 4.46-4.55 (m, 1H, CH-O), 6.80-6.88 (m, 2H, CH=), 7.02-7.06 (m, 1H, CH=), 7.10-7.21 (m, 3H, CH=), 7.27 (d, 1H, CH=, $^3J_{H-H}$ =8.4 Hz), 7.33 (s, 2H, CH=), 7.35 (d, 1H, CH=, $^3J_{H-H}$ =8.8 Hz), 7.45-7.52 (m, 2H, CH=), 7.63 (d, 1H, CH=, $^3J_{H-H}$ =8.4 Hz), 7.69 (d, 1H, CH=, $^3J_{H-H}$ =9.2 Hz), 7.77 (s, 1H, CH=), 8.11 (s, 1H, CH=), 8.14 (s, 1H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ=0.0 (d, CH_3, $SiMe_3$, J_{C-P} =2.2 Hz), 0.1 (CH_3, $SiMe_3$), 19.2 (CH_3), 26.9 (CH_3), 27.2 (CH_3), 29.9 (CH_2-Se), 72.9 (d, CH-O, $^2J_{C-P}$ =4.6 Hz), 78.6 (*C*HCH_2Se), 83.0 (d, *C*HCHO, $^3J_{C-P}$ =2.2 Hz), 109.3 (CMe_2), 122.6-152.0 (aromatic carbons). MS HR-ESI [found 847.1913, $C_{44}H_{49}O_5PSeSi_2$ $(M-Na)^+$ requires 847.1914].

L23g. Yield: 519 mg (63%); SiO_2-flash chromatography (toluene/hexane/NEt_3 = 8:2:0.1). ^{31}P NMR (161.9 MHz, C_6D_6): δ=140.7 (s). ^{1}H NMR (400 MHz, C_6D_6): δ=0.48 (s, 9H, CH_3, $SiMe_3$), 0.53 (s, 9H, CH_3, $SiMe_3$), 0.81 (d, 3H, CH_3, $^3J_{H-H}$ =6.4 Hz), 1.33 (s, 3H, CH_3), 1.39 (s, 3H, CH_3), 3.05 (dd, 1H, CH_2-Se, $^2J_{H-H}$ =12.8 Hz, $^3J_{H-H}$ =6.0 Hz), 3.12 (dd, 1H, CH_2-Se, $^2J_{H-H}$ =12.8 Hz, $^3J_{H-H}$ =4.8 Hz), 3.96 (dd, 1H, C*H*CHO, $^3J_{H-H}$ =7.2 Hz, $^3J_{H-H}$ =5.2 Hz), 4.29-4.33 (m, 1H, C*H*CH_2Se), 4.66-4.71 (m, 1H, CH-O), 6.80-6.87 (m, 2H, CH=), 7.05-7.24 (m, 5H, CH=), 7.34-7.52 (m, 5H, CH=), 7.67-7.70 (m, 2H, CH=), 7.88 (s, 1H, CH=), 8.10 (s, 1H, CH=), 8.12 (s, 1H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ=-0.1 (d, CH_3, $SiMe_3$, J_{C-P} =4.6 Hz), 0.0 (CH_3, $SiMe_3$), 17.9 (d, CH_3, $^3J_{C-P}$ =3.0 Hz), 27.1 (CH_3), 27.4 (CH_3), 31.5 (CH_2-Se), 72.8 (d, CH-O, $^2J_{C-P}$ = 6.8 Hz), 77.8 (*C*HCH_2Se), 83.6 (d, *C*HCHO, $^3J_{C-P}$ =3.8 Hz), 109.4 (CMe_2), 122.6-152.3 (aromatic carbons). MS HR-ESI [found 833.1753, $C_{43}H_{47}O_5PSeSi_2$ $(M-Na)^+$ requires 833.1757].

3.2.4.3. Typical procedure for the preparation of hydroxyl-thioether compounds 6-8

To a cooled (-15 °C) suspension of the desired thiolate sodium salt (10.2 mmol) in THF (20 mL), a solution of the corresponding tosylate (3.2 mmol) in THF (10 mmol) was added. The reaction mixture was stirred at room temperature for minimum 48 h and quenched with water. The THF was removed under reduced pressure. The aqueous phase was

extracted with CH_2Cl_2 (3 x 25 mL), dried with $MgSO_4$ and the solvent was evaporated. The crude was purified by flash chromatography (AcOEt/EP = 1/2) to produce the desired alcohol-thioethers as white solids.

((4*S*,5*R*)-2,2-Dimethyl-5-((methylthio)methyl)-1,3-dioxolan-4-yl)methanol (6). Yield: 0.43 g (66%). ^{1}H NMR ($CDCl_3$), δ: 1.40 (s, 3H, CH_3), 1.41 (s, 3H, CH_3), 2.12 (s, 1H, OH), 2.16 (s, 3H, CH_3-S), 2.67 (dd, 1H, $^2J_{H-H}$= 13.6 Hz, $^3J_{H-H}$= 6.4 Hz, CH_2-S), 2.78 (dd, 1H, $^2J_{H-H}$= 14 Hz, $^3J_{H-H}$= 6 Hz, CH_2-S), 3.69 (dd, 1H, $^2J_{H-H}$= 11.6 Hz, $^3J_{H-H}$= 4 Hz, CH_2-O), 3.85 (dd, 1H, $^2J_{H-H}$= 15.2 Hz, $^3J_{H-H}$= 4.8 Hz, CH_2-O), 3.90 (dd, 1H, $^2J_{H-H}$= 8 Hz, $^3J_{H-H}$= 3.6 Hz, C*H*CH_2O), 4.08 (dd, 1H, $^2J_{H-H}$= 13.6 Hz, $^3J_{H-H}$= 6 Hz, C*H*CH_2S). ^{13}C NMR ($CDCl_3$), δ: 16.6 (CH_3-S), 27.2(CH_3), 27.3 (CH_3), 36.7 (CH_2-S), 62.4 (CH_2-O), 76.2 (*C*HCH_2S), 81.3 (*C*HCH_2S), 109.4 (CMe_2).

((4*S*,5*R*)-5-((*tert*-Butylthio)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanol (7). Yield: 0.47 g (63%). ^{1}H NMR ($CDCl_3$), δ: 1.31 (s, 9H, CH_3, ^{t}Bu),1.28 (s, 3H, CH_3), 1.39 (s, 3H, CH_3), 1.41 (s, 3H, CH_3, ^{t}Bu), 2.05 (b, 1H, OH), 2.69 (dd, 1H, $^2J_{H-H}$= 12.4 Hz, $^3J_{H-H}$= 7.2 Hz, CH_2-S), 2.87 (dd, 1H, $^2J_{H-H}$= 12.4 Hz, $^3J_{H-H}$= 5.2 Hz, CH_2-S), 3.67-3.87 (m, 2H, CH_2-O), 3.88-3.89 (m, 1H, C*H*CH_2O), 4.01 (dd, 1H, $^2J_{H-H}$= 7.2 Hz, $^3J_{H-H}$= 2 Hz, C*H*CH_2S). ^{13}C NMR ($CDCl_3$), δ: 27.2 (CH_3), 27.3 (CH_3), 31.0 (CH_3, ^{t}Bu), 31.3 (CH_2-S), 42.7 (C, ^{t}Bu), 62.7(CH_2-O), 76.7 (*C*HCH_2S), 81.8 (*C*HCH_2O), 109.3 (CMe_2).

((4*S*,5*R*)-5-(((2,6-Dimethylphenyl)thio)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanol (8). Yield: 0.57 g (53%). ^{1}H NMR ($CDCl_3$), δ: 1.40 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 1.86 (s, 1H, OH), 2.53 (s, 6H, CH_3), 2.84 (dd, 1H, $^2J_{H-H}$= 12 Hz, $^3J_{H-H}$= 8 Hz, CH_2-S), 2.89 (dd, 1H, $^2J_{H-H}$= 12 Hz, $^3J_{H-H}$= 4 Hz, CH_2-S), 3.66 (dd, 1H, $^2J_{H-H}$= 12 Hz, $^3J_{H-H}$= 4 Hz, CH_2-O), 3.83 (dd, 1H, $^2J_{H-H}$= 12 Hz, $^3J_{H-H}$= 4 Hz, CH_2-O), 3.89-3.93 (m, 1H, C*H*CH_2O), 3.97-4.02 (m, 1H, C*H*CH_2S), 7.08-7.11 (m, 3H, CH=).^{13}C NMR ($CDCl_3$), δ: 22.3 (CH_3-Ar), 27.3 (CH_3), 27.4 (CH_3), 38.3 (CH_2-S), 62.4 (CH_2-O), 76.2 (*C*HCH_2S), 81.3 (*C*HCH_2O), 109.5 (CMe_2), 128.4 (CH=), 128.6 (CH=), 133.4 (C), 143.1 (C).

3.2.4.4. Typical procedure for the preparation of hydroxyl-selenoether compounds 9-10[23]

Powdered $NaBH_4$ (98.4 mg, 2.6 mmol) was added in portions to a solution of the corresponding $(Se\text{-}Ar)_2$[24] (2 mmol) in THF (2 mL) at 0 °C. The reaction mixture was stirred for 10 min at room temperature. 1-Deoxy-2,3-O-isopropylidene-1-tosyl-D-arabinitol (1 mmol) in THF (5 mL) was added, and the reaction mixture was stirred overnight. The reaction was quenched with water and extracted with dichloromethane for three times. The extract was dried over anhydrous magnesium sulfate and concentrated. The residue was purified by SiO_2-column chromatography (PE/EtOAc = 1/10) to produce the desired selenide compound as colorless oil.

((4*S*,5*R*)-5-((phenylselanyl)methyl)-1,3-dioxolan-4-yl)methanol (9). Yield: 608 mg (70%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.40 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 1.96 (b, 1H, OH), 3.08 (dd, 1H, CH_2-Se, $^2J_{H-H}$ =12.4 Hz, $^3J_{H-H}$= 6.4 Hz), 3.19 (dd, 1H, CH_2-Se, $^2J_{H-H}$ =12.4 Hz, $^3J_{H-H}$ =4.8 Hz), 3.68 (dd, 1H, CH_2-O, $^2J_{H-H}$ =12.0 Hz, $^3J_{H-H}$= 4.8 Hz), 3.85 (dd, 1H, CH_2-O, $^2J_{H-H}$ =12.4

Hz, $^3J_{H-H}$ =3.6 Hz), 3.94 (m, 1H, C*H*CH_2O), 4.12 (m, 1H, C*H*CH_2Se), 7.24-7.28 (m, 3H, CH=), 7.51-7.53 (m, 2H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 27.2 (CH_3), 27.3 (CH_3), 30.1 (CH_2-Se), 62.5 (CH_2), 76.0 (*C*HCH_2Se), 81.6 (*C*HCH_2O), 109.3 (CMe_2), 127.2 (CH=), 129.2 (CH=), 129.6 (C), 132.7 (CH=).

((4*S*,5*R*)-5-((naphthalene-2-ylselanyl)methyl)-1,3-dioxolan-4-yl)methanol (10). Yield: 730 mg (62%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.41 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 2.35 (b, 1H, OH), 3.18 (dd, 1H, CH_2-Se, $^2J_{H-H}$ =12.6 Hz, $^3J_{H-H}$ =6.5 Hz), 3.29 (dd, 1H, CH_2-Se, $^{,2}J_{H-H}$ =12.6 Hz, $^3J_{H-H}$ =5.6 Hz), 3.70 (dd, 1H, CH_2-O, $^2J_{H-H}$ =11.9 Hz, $^3J_{H-H}$ =4.6 Hz), 3.86 (dd, 1H, CH_2-O, $^3J_{H-H}$ =11.9 Hz, $^2J_{H-H}$ =3.3 Hz), 3.98 (m, 1H, C*H*CH_2O), 4.14 (m, 1H, C*H*CH_2Se), 7.44-7.50 (m, 2H, CH=), 7.57-7.60 (m, 1H, CH=), 7.73 (d, 1H, CH=, $^3J_{H-H}$ =8.3 Hz), 7.5-7.82 (m, 2H, CH=), 8.01 (s, 1H, CH=). ^{13}C NMR ($CDCl_3$), δ: 27.9 (CH_3), 28.0 (CH_3), 30.8 (CH_2-Se), 63.3 (CH_2-O), 76.8 (*C*HCH_2Se), 82.3 (*C*HCH_2O), 110.1 (CMe_2), 126.9-134.6 (aromatic carbons).

3.2.4.5. Typical procedure for the preparation of hydroxyl-thioether compounds 12-14

The already monosilane-protected compound **3** (890 mg, 3.2 mmol) was azeotropically dried with toluene (3 x 2 mL) and then dissolved in CH_2Cl_2 (20 mL) to which pyridine (0.56 mL, 6.8 mmol) was added. The alcohol solution was cooled to -15 °C and Tf_2O (0.78 mL, 4.5 mmol) was added slowly over 2 min. The reaction mixture was stirred at -15 °C for 2 h and quenched with water. The aqueous phase was extracted with diethyl ether (3 x 50 mL), dried with $MgSO_4$ and the solvents were removed at room temperature. To the crude product, petroleum ether (25 mL) was added and the insoluble impurities were removed by filtration. Evaporation of the solvent provided the desired monotriflate **11** in 93% yield (1.22 g), which was used without further purification in the next step.

To a suspension of NaH (385 mg, 9.6 mmol) in THF (5 mL) a solution of the desired thiol (0.94 g, 5.6 mmol) in THF (15 mL) was added. After 2 min, the suspension was cooled to -78 °C and a solution of **11** (1.22 g, 3.0 mmol) in THF (20 mL) was added. After 90 min, water (25 mL) was added and the THF was evaporated. The solution was extracted with CH_2Cl_2 (3 x 50 mL), dried with $MgSO_4$ and the solvents were evaporated. The crude was purified by flash chromatography (AcOEt/EP = 1/19) to produce the desired compounds as white solids.

((4*S*,5*R*)-5-((Adamantan-1-ylthio)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanol (*tert*-butyl) dimethylsilane. Yield: 830 mg (66%). ^{1}H NMR ($CDCl_3$), δ: 0.06 (s, 6H, CH_3-Si), 0.89 (s, 9H, CH_3, Si^{t}Bu),1.37 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 1.65 (m, 6H, CH_2, Ad), 1.85 (m, 6H, CH_2, Ad), 2.02 (m, 3H, CH, Ad), 2.77 (d, 1H, $^2J_{H-H}$= 6.4 Hz, CH_2-S), 3.77-3.83 (m, 3H, CH_2-O, C*H*CH_2O), 4.03 (m, 1H, C*H*CH_2S).

***tert*-Butyl(((4*S*,5*R*)-2,2-dimethyl-5-((naphthalen-1-ylthio)methyl)-1,3-dioxolan-4-yl)methoxy)dimethylsilane**. Yield: 830 mg (67%). ^{1}H NMR ($CDCl_3$), δ: 0.01 (s, 6H, CH_3-Si), 0.84 (s, 9H, CH_3, Si^{t}Bu),1.49 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 3.25 (dd, 1H, $^2J_{H-H}$= 12 Hz, $^3J_{H-H}$= 8 Hz, CH_2-S), 3.31 (dd, 1H, $^2J_{H-H}$= 12 Hz, $^3J_{H-H}$= 4 Hz, CH_2-S), 3.74 (dd, 1H, $^2J_{H-H}$= 8 Hz, $^3J_{H-H}$= 4 Hz,

CH_2-O), 3.83 (dd, 1H, $^2J_{H-H}$= 8 Hz, $^3J_{H-H}$= 4 Hz, CH_2-O), 3.92-3.96 (m, 1H, C*H*CH_2O), 4.17-4.22 (m, 1H, C*H*CH_2S), 7.41-8.47 (m, 7H, CH=).

***tert*-Butyl(((4*S*,5*R*)-2,2-dimethyl-5-((naphthalen-2-ylthio)methyl)-1,3-dioxolan-4-yl)methoxy)dimethylsilane**. Yield: 780 mg (63%).^{1}H NMR ($CDCl_3$), δ: 0.01 (s, 6H, CH_3-Si), 0.84 (s, 9H, CH_3, Si^{t}Bu),1.39 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 3.27 (dd, 1H, $^2J_{H-H}$= 13.6 Hz, $^3J_{H-H}$= 6.8 Hz, CH_2-S), 3.34 (dd, 1H, $^2J_{H-H}$= 13.2 Hz, $^3J_{H-H}$= 4.8 Hz, CH_2-S), 3.74 (dd, 1H, $^2J_{H-H}$= 10.8 Hz, $^3J_{H-H}$= 6 Hz, CH_2-O), 3.83 (dd, 1H, $^2J_{H-H}$= 10.8 Hz, $^3J_{H-H}$= 4.4 Hz, CH_2-O), 3.91-3.95 (m, 1H, C*H*CH_2O), 4.15-4.20 (m, 1H, C*H*CH_2S), 7.40-7.78 (m, 7H, CH=).^{13}C NMR ($CDCl_3$), δ: -5.2 (CH_3-Si), 18.5 (C-Si), 26.0 (CH_3, Si^{t}Bu), 27.2 (CH_3), 27.5 (CH_3), 37.0 (CH_2-S), 63.9 (CH_2-O), 77.2 (*C*HCH_2S), 80.8 (*C*HCH_2O), 109.6 (CMe_2), 125.9 (CH=), 126.7 (CH=), 127.1 (CH=), 127.2 (CH=), 127.5 (CH=), 127.9 (CH=), 128.6 (C).

The desired monosilane-protected thioether compound (1.27 mmol) was dissolved in THF (5 mL) to which TBAF (3.8 mL of 1M in THF, 3.8 mmol) was added slowly. The reaction mixture was stirred at room temperature for 90 min and quenched with diethyl ether (25 mL). The organic phase was washed with HCl 1M, brine and water, dried with $MgSO_4$ and evaporated. The crude was purified by flash chromatography (AcOEt/EP = 1/3) to produce the desired thioether-alcohols as white solids.

((4*S*,5*R*)-5-((Adamantan-1-ylthio)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanol (12). Yield: 241 mg (63%). ^{1}H NMR ($CDCl_3$), δ: 1.34 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 1.60-1.62 (m, 6H, CH_2, Ad), 1.78-1.79 (m, 6H, CH_2, Ad), 1.97 (m, 3H, CH, Ad), 2.51 (m, 1H, OH), 2.60 (dd, 1H, $^2J_{H-H}$= 12.8 Hz, $^3J_{H-H}$= 7.6 Hz, CH_2-S), 2.81 (dd, 1H, $^2J_{H-H}$= 12.8 Hz, $^3J_{H-H}$= 5.6 Hz, CH_2-S), 3.62-3.69 (m, 1H, CH_2-O), 3.77-3.83 (m, 2H, CH_2-O, C*H*CH_2O), 3.89-3.94 (m, 1H, C*H*CH_2S). ^{13}C NMR ($CDCl_3$), δ: 27.0 (CH_3), 27.1 (CH_3), 28.5 (CH_2-S), 29.5 (CH, Ad), 36.1 (CH_2, Ad), 43.3 (CH_2, Ad), 53.4 (C, Ad), 62.6 (CH_2-O), 76.8 (*C*HCH_2S), 81.7 (*C*HCH_2O), 109.0 (CMe_2).

((4*S*,5*R*)-2,2-dimethyl-5-((naphthalen-1-ylthio)methyl)-1,3-dioxolan-4-yl)methanol (13). Yield: 255 mg (66%). ^{1}H NMR ($CDCl_3$), δ: 1.40 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 2.84 (b, 1H, OH), 3.13 (dd, 1H, $^2J_{H-H}$= 13.2 Hz, $^3J_{H-H}$= 5.6 Hz, CH_2-S), 3.27 (dd, 1H, $^2J_{H-H}$= 13.2 Hz, $^3J_{H-H}$= 5.6 Hz, CH_2-S), 3.64 (m, 1H, CH_2-O), 3.80 (m, 1H, CH_2-O), 3.95-3.99 (m, 1H, C*H*CH_2O), 4.10 (m, 1H, C*H*CH_2S), 7.34-8.41 (m, 7H, CH=).^{13}C NMR ($CDCl_3$), δ: 27.1 (CH_3), 27.2 (CH_3), 37.1 (CH_2-S), 62.5 (CH_2-O), 75.7 (*C*HCH_2S), 81.3 (*C*HCH_2O), 109.5 (CMe_2), 124.9 (CH=), 125.6 (CH=), 126.3 (CH=), 126.6 (CH=), 127.6 (CH=), 128.4 (CH=), 128.6 (CH=), 132.7 (C), 133.9 (C).

((4*S*,5*R*)-2,2-dimethyl-5-((naphthalen-2-ylthio)methyl)-1,3-dioxolan-4-yl)methanol (14). Yield: 201 mg (52%). ^{1}H NMR ($CDCl_3$), δ: 1.41 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 2.04 (s, 1H, OH), 3.11 (dd, 1H, $^2J_{H-H}$= 16 Hz, $^3J_{H-H}$= 8 Hz, CH_2-S), 3.32 (dd, 1H, $^2J_{H-H}$= 12 Hz, $^3J_{H-H}$= 4 Hz, CH_2-S), 3.65 (dd, 1H, $^2J_{H-H}$= 8 Hz, $^3J_{H-H}$= 4 Hz, CH_2-O), 3.81 (dd, 1H, $^2J_{H-H}$= 12 Hz, $^3J_{H-H}$= 4 Hz, CH_2-O), 3.92-3.96 (m, 1H, C*H*CH_2O), 4.02-4.09 (m, 1H, C*H*CH_2S), 7.43-7.81 (m, 7H, CH=).^{13}C NMR ($CDCl_3$), δ: 27.1 (CH_3), 27.2 (CH_3), 36.5 (CH_2-S), 62.5 (CH_2-O), 75.5 (*C*HCH_2S), 81.2 (*C*HCH_2O), 109.5 (CMe_2), 125.8 (CH=), 126.6 (CH=), 127.1 (CH=), 127.2 (CH=), 127.7 (CH=), 128.6 (CH=), 131.8 (C), 132.8 (C), 133.7 (C).

3.2.4.6. Preparation of compounds 15 and 16

(4*R*,5*S*)-Ethyl-5-(hydroxymethyl)-2,2-dimethyl-1,3-dioxolane-4-carboxylate. To a stirred solution of compound **1** (10 g, 40.6 mmol) in ethanol (40 mL), with cooling (ice-bath), was added, portionwise, $NaBH_4$ (922 mg, 24.4 mmol) over a **1** hour period. The resulting mixture was then stirred at room temperature for a further 30 min. After, the ethanol was removed under reduced pressure. To the crude product was added water and extracted in ethyl acetate (3 x 25 mL), dried with $MgSO_4$ and dried in the rotavapor. The crude was purified by flash chromatography on silica (Et_2O/EP = 1/1) afforded diester **1**. Further elution (Et_2O/EP = 3/1) afforded the desired monoester. Yield: 2.7 g (33%). ^{1}H NMR ($CDCl_3$), δ: 1.27 (m, 3H, CH_3, Et), 1.39 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 2.40 (b, 1H, OH), 3.69-3.72 (m, 1H, CH_2-O), 3.89-3.92 (m, 1H, CH_2-O), 4.17-4.24 (m, 3H, C*H*CH_2O, CH_2, Et), 4.38-4.42 (m, 1H, C*H*COOEt). ^{13}C NMR ($CDCl_3$), δ: 14.1 (CH_3, Et), 25.5 (CH_3), 26.7 (CH_3), 61.5 (CH_2, Et), 61.8 (CH_2-O), 74.8 (*C*HCOOEt), 79.2 (*C*HCH_2O), 111.3 (CMe_2), 170.8 (C=O). Further elution with ethyl acetate (100%) afforded diol **3**.

(4*R*,5*S*)-Ethyl-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-2,2-dimethyl-1,3-dioxolane-4-carboxylate (15). The already prepared monoester (1.8 g, 8.8 mmol), tert-butyldimethylsilyl chloride (1.59 g, 10.6 mmol) and imidazole (1.5 g, 22 mmol) were stirred together in dry DMF (4.5 mL) at room temperature for 1 h. The crude product was extracted in Et_2O (3 x 25 mL), dried with $MgSO_4$ and dried in the rotavapor. The crude was purified by flash chromatography (Et_2O/EP = 1/10) to produce **15** as an oil. Yield: 2.1 g (75%). ^{1}H NMR ($CDCl_3$), δ: 0.00 (s, 6H, CH_3-Si), 0.82 (s, 9H, CH_3, Si^{t}Bu), 1.21 (m, 3H, CH_3, Et), 1.36 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 3.71 (dd, 1H, $^2J_{H\text{-}H}$= 8 Hz, $^3J_{H\text{-}H}$= 4 Hz, CH_2-O), 3.8 (dd, 1H, $^2J_{H\text{-}H}$= 12 Hz, $^3J_{H\text{-}H}$= 4 Hz, CH_2-O), 4.11-4.18 (m, 3H, C*H*CH_2O, CH_2, Et), 4.38 (d, 1H, $^2J_{H\text{-}H}$= 4 Hz, CHCOOEt). ^{13}C NMR ($CDCl_3$), δ: -5.4 (CH_3-Si), -5.3 (CH_3-Si), 14.1 (CH_3, Et), 18.3 (C-Si), 25.8 (CH_3, Si^{t}Bu), 25.9 (CH_3), 26.8 (CH_3), 61.2 (CH_2, Et), 62.6 (CH_2-O), 75.2 (*C*HCOOEt), 79.7 (*C*HCH_2O), 111.2 (CMe_2), 170.9 (C=O).

2-((4*R*,5*S*)-5-(((*tert*-Butyldimethylsilyl)oxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)propan-2-ol (16). To a solution of compound **15** (2.1 g, 6.5 mmol) in dry stirred THF (16.5 mL) under nitrogen, at -60 ^{o}C was added methyllithium (as a complex with LiBr, 11 mL of 1.5 mol dm^{-3}, solution in diethyl ether, 16.2 mmol) dropwise. The resulting mixture was stirred at -60 ^{o}C for 0.5 h, then was warmed to room temperature and quenched with water. The crude product was extracted in Et_2O (3 x 25 mL), dried with $MgSO_4$ and dried in the rotavapor. The crude was purified by flash chromatography (Et_2O/EP = 1/4) to produce **16** as an oil. Yield: 1.1 g (52%). ^{1}H NMR ($CDCl_3$), δ: 0.06 (s, 6H, CH_3-Si), 0.88 (s, 9H, CH_3, Si^{t}Bu), 1.19 (s, 3H, CH_3), 1.22 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 1.39 (s, 3H, CH_3), 2.82 (b, 1H, OH), 3.70-3.79 (m, 3H, CH_2, C*H*-CH_2), 3.93-3.97 (m, 1H, C*H*-CMe_2). ^{13}C NMR ($CDCl_3$), δ: -5.5 (CH_3-Si), -5.4 (CH_3-Si), 18.3 (C-Si), 25.8 (CH_3, Si^{t}Bu), 25.9 (CH_3), 26.1(CH_3), 27.0 (CH_3), 27.1 (CH_3), 64.3 (CH_2), 69.5 (CMe_2), 77.3 (*C*H-CH_2), 84.7(*C*H-CMe_2), 108.5 (CMe_2).

3.2.4.7. General procedure for the preparation of thioether-hydroxy compounds 17 and 18 and selenoether-hydroxy compounds 19-20

2-((4*R*,5*S*)-5-(Hydroxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)propan-2-ol. Compound **16** (500 mg, 1.6 mmol) was dissolved in THF (5 mL) to which TBAF (5 mL, 5 mmol) was added slowly. The reaction mixture was stirred at room temperature for 90 min. The THF was removed under reduced pressure. The crude product was purified by flash chromatography (AcOEt/EP = 2/1) to produce the deprotected alcohol as a white solid. Yield: 265 mg (85%). ^{1}H NMR ($CDCl_3$), δ: 1.21 (s, 3H, CH_3), 1.28 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 2.08 (b, 2H, 2OH), 3.65-3.84 (m, 3H, CH_2, C*H*-CH_2), 4.07-4.11 (m, 1H, C*H*-CMe_2).^{13}C NMR ($CDCl_3$), δ: 25.7 (CH_3), 26.3 (CH_3), 27.1 (CH_3), 27.2 (CH_3), 63.4 (CH_2), 69.8 (C-O), 77.4 (*C*H-CH_2), 83.5 (*C*H-CMe_2), 108.8 (CMe_2).

((4*S*,5*R*)-5-(2-Hydroxypropan-2-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl 4-methylbenzenesulfonate. To a solution of the previously synthesized diol (100 mg, 0.52 mmol) in anhydrous pyridine (0.3 mL) at 0 °C, a solution of tosylchloride (100.2 mg, 0.52 mmol) in dichloromethane (2 mL) was added dropwise. The reaction mixture was stirred overnight at room temperature and quenched with water. The crude product was extracted in CH_2Cl_2 (3 x 20 ml), then washed with $CuSO_4$ and water, finally dried with $MgSO_4$ and dried in the rotavapor. The crude was purified by flash chromatography (AcOEt/EP = 1/1) to produce the tosylated product as white solid. Yield: 148 mg (82%). ^{1}H NMR ($CDCl_3$), δ: 1.12 (s, 3H, CH_3), 1.23 (s, 3H, CH_3), 1.32 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 1.95 (b, 1H, OH), 2.45 (s, 3H, CH_3, OTs), 3.74 (d, 1H, $^{2}J_{H\text{-}H}$= 7.6 Hz, C*H*-CMe_2), 4.08 (dd, 1H, $^{2}J_{H\text{-}H}$= 10.8 Hz, $^{3}J_{H\text{-}H}$= 4.8 Hz, CH_2), 4.13-4.16 (m, 1H, C*H*-CH_2), 4.23 (dd, 1H, $^{2}J_{H\text{-}H}$= 10.8 Hz, $^{3}J_{H\text{-}H}$= 2.8 Hz, CH_2), 7.33-7.81 (m, 4H, CH=). ^{13}C NMR ($CDCl_3$), δ: 21.6 (CH_3, OTs), 25.1 (CH_3), 26.7 (CH_3), 27.1 (CH_3), 69.6 (C-O), 70.1 (CH_2), 74.7 (*C*H-CH_2), 82.4 (*C*HCMe_2), 109.7(CMe_2), 128.0 (CH=), 129.8 (CH=), 132.7 (C), 145.0 (C).

Treatment of the previously synthesized tosylated compound as previously described for compounds **5**-**10** and **9**-**10** afforded the desired thioether-hydroxy acompounds **17**-**18** and selenoether-hydroxy compounds **19**.

2-((4*R*,5*R*)-2,2-Dimethyl-5-((phenylthio)methyl)-1,3-dioxolan-4-yl)propan-2-ol (17). Yield: 770 mg (70%). ^{1}H NMR ($CDCl_3$), δ: 1.15 (s, 3H, CH_3), 1.24 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 2.01 (b, 1H, OH), 3.13 (dd, 1H, $^{2}J_{H\text{-}H}$= 12 Hz, $^{3}J_{H\text{-}H}$= 8 Hz, CH_2-S), 3.3 (dd, 1H, $^{2}J_{H\text{-}H}$ = 16 Hz, $^{3}J_{H\text{-}H}$ = 4 Hz, CH_2-S), 3.76 (d, 1H, $^{2}J_{H\text{-}H}$ = 8 Hz, C*H*CMe_2O), 4.18-4.23 (m, 1H, C*H*CH_2S), 7.17-7.41 (m, 5H, CH=). ^{13}C NMR ($CDCl_3$), δ: 25.2 (CH_3), 27.0 (CH_3), 27.1 (CH_3), 27.3 (CH_3), 38.8 (CH_2-S), 69.8 (*C*Me_2OH), 75.7 (*C*HCH_2S), 85.9 (*C*HCMe_2O), 109.2 (CMe_2), 126.3 (CH=), 128.9 (CH=), 129.6 (CH=), 146.4 (C).

2-((4*R*,5*R*)-2,2-dimethyl-5-((napthalen-2-ylthiol)methyl)-1,3-dioxolan-4-yl)propan-2-ol (18). Yield: 1.2 g (77%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.18 (s, 3H, CH_3), 1.25 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 2.01 (s, 1H, OH), 3.23 (dd, 1H, CH_2-S, $^{2}J_{H\text{-}H}$ =13.2 Hz, $^{3}J_{H\text{-}H}$ =6.8 Hz), 3.41 (dd, 1H, CH_2-S, $^{2}J_{H\text{-}H}$ =13.6 Hz, $^{3}J_{H\text{-}H}$ =3.2 Hz), 3.80 (d, 1H, CHCMe_2O, $^{2}J_{H\text{-}H}$ =8.0

Hz), 4.25-4.29 (m, 1H, C*H*CH_2S), 7.41-7.49 (m, 3H, CH=), 7.73-7.83 (m, 4H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 25.4 (CH_3), 27.0 (CH_3), 27.2 (CH_3), 27.4 (CH_3), 38.6 (CH_2-S), 69.9 (CMe_2O), 75.8 (*C*HCH_2S), 86.0 (*C*$HCMe_2O$), 109.3 (CMe_2), 125.8 (CH=), 126.6 (CH=), 127.0 (CH=), 127.1 (CH=), 127.7 (CH=), 128.0 (CH=), 131.8 (C=), 133.7 (C=).

2-((4*R*,5*R*)-2,2-dimethyl-5-((naphthalen-2-ylselanyl)methyl)-1,3-dioxolan-4-yl)propan-2-ol (19). Yield: 186 mg (49%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.13 (s, 3H, CH_3), 1.23 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 2.07 (s, 1H, OH), 3.19 (dd, 1H, $^2J_{H\text{-}H}$ =12.7 Hz, $^3J_{H\text{-}H}$ =7.2 Hz, CH_2-Se), 3.38 (dd, 1H, $^2J_{H\text{-}H}$ =16.0 Hz, $^3J_{H\text{-}H}$ =4.0 Hz, CH_2-Se), 3.77 (d, 1H, $^3J_{H\text{-}H}$ =8.0 Hz, $CHCMe_2O$), 4.28-4.22 (m, 1H, C*H*CH_2Se), 7.44-7.49 (m, 2H, CH=), 7.60-7.62 (m, 1H, CH=), 7.71-7.82 (m, 3H, CH=), 8.02-8.05 (m, 1H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 25.6 (CH_3), 27.4 (CH_3), 27.5 (CH_3), 27.8 (CH_3), 32.8 (CH_2-Se), 70.1 (CMe_2O), 76.5 (*C*HCH_2Se), 86.8 (*C*$HCMe_2O$), 109.4 (CMe_2), 126.0 (CH=), 126.8 (CH=), 127.5 (CH=), 128.0 (CH=), 128.2 (C), 128.8 (CH=), 130.5 (CH=), 131.7 (CH=), 132.5 (C), 134.2 (C).

3.2.4.8. Preparation of compound 20

(5-(((*tert*-butyldimethylsilyl)oxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)diphenylmethanol. To a solution of compound **15** (3.7 g, 11.6 mmol) in dry stirred THF (30 mL) under nitrogen, at 0 °C a Et_2O solution of phenylmagnesium bromide (3M, 11.6 mL, 34.8 mmol) was added dropwise. The resulting mixture was stirred overnight at room temperature and quenched with water. The crude product was extracted in Et_2O (3 x 25 mL), dried with $MgSO_4$ and dried in the rotavapor. Then, PE was added and product precipitate. Finally, the crude was purified by flash chromatography (EtOAc/PE = 10/3) to produce the desired compound as an oil. Yield: 4.2 g (85%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.12 (s, 3H, CH_3, OTBDMS), 0.17 (s, 3H, CH_3, OTBDMS), 1.09 (s, 9H, CH_3, ^{t}Bu, OTBDMS), 1.60 (s, 3H, CH_3), 1.71 (s, 3H, CH_3), 2.51 (dd, 1H, CH_2-O, $^2J_{H\text{-}H}$ =11.2 Hz, $^3J_{H\text{-}H}$ =2.8 Hz), 3.51 (dd, 1H, CH_2-O, $^2J_{H\text{-}H}$ =11.6 Hz, $^3J_{H\text{-}H}$ =2.4 Hz), 3.65 (s, 1H, OH), 4.20 (m, 1H, C*H*CH_2O), 5.30 (d, 1H, $CHCPh_2O$, $^3J_{H\text{-}H}$ =8.4 Hz), 7.35-7.51 (m, 4H, CH=), 7.56-7.61 (m, 3H, CH=), 7.74-7.80 (m, 3H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=-5.6 (CH_3, OTBDMS), -5.4 (CH_3, OTBDMS), 18.3 (C, ^{t}Bu, OTBDMS), 25.9 (CH_3, ^{t}Bu, OTBDMS), 27.2 (CH_3), 62.2 (CH_2-O), 76.3 (CPh_2O), 77.8 (*C*HCH_2O), 78.2 (*C*$HCPh_2O$), 109.0 (CMe_2), 125.9 (CH=), 127.1 (CH=), 127.2 (CH=), 127.3 (CH=), 128.1 (CH=), 128.7 (CH=), 142.6 (C=), 146.1 (C=).

(5-(((*tert*-Butyldimethylsilyl)oxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)diphenylmethanethiol (20). To a solution of **15** (5.9 g, 13.8 mmol), in toluene (50 mL), Lawesson's reagent (4.5 g, 11.1 mmol) was added. The reaction mixture was stirred for 3h at 60 °C. Then, solvent was evaporated and the crude product was purified by SiO_2-chromathography (EtOAc/PE = 1/20 → 1/3) to yield thiol **20** as a white solid. Yield: 1.3g (40%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=-0.06 (s, 3H, CH_3, OTBDMS), 0.00 (s, 3H, CH_3, OTBDMS), 0.90 (s, 9H, CH_3, ^{t}Bu, OTBDMS), 1.55 (s, 3H, CH_3), 1.60 (s, 3H, CH_3), 2.74 (s, 1H, SH), 2.18 (dd, 1H, CH_2-O, $^2J_{H\text{-}H}$ =10.0 Hz), 3.31 (dd, 1H, CH_2-O, $^2J_{H\text{-}H}$ =11.2 Hz, $^3J_{H\text{-}H}$ =1.2 Hz), 4.12 (m, 1H, C*H*CH_2O), 5.11 (d, 1H, $CHCPh_2S$, $^3J_{H\text{-}H}$ =7.6 Hz), 7.21-7.25 (m, 1H, CH=), 7.28-7.38 (m, 7H,

CH=), 7.58 (d, 2H, CH=, $^{3}J_{H-H}$ =6.0 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=-5.5 (CH_3, OTBDMS), -5.3 (CH_3, OTBDMS), 18.4 (C, ^{t}Bu, OTBDMS), 26.0 (CH_3, ^{t}Bu, OTBDMS), 27.6 (CH_3), 27.7 (CH_3), 60.4 (CPh_2S), 62.5 (CH_2-O), 78.6 (*C*HCPh_2S), 80.2 (*C*HCH_2O), 109.4 (CMe_2), 126.6 (CH=), 127.7 (CH=), 127.9 (CH=), 128.2 (CH=), 128.3 (CH=), 128.7 (CH=), 142.7 (C=), 148.8 (C=).

3.2.4.9. Preparation of hydroxyl-thioether compound 21

***tert*-Butyl((2,2-dimethyl-5-((methylthio)diphenylmethyl)-1,3-dioxolan-4-yl)methoxy)dimethylsilane**. To a cooled solution (0°C) of thiol **20** (1.1 g, 2.5 mmol) in MeOH (20 mL), triethylamine (0.42 mL, 3.0 mmol) and iodomethane (0.18 mL, 2.7 mmol) were slowly added. The reaction mixture was stirred overnight at room temperature. The reaction was quenched by adding an aqueous solution of $NaHCO_3$ (10%) and the product was extracted with Et_2O (x3). The organic phase was washed with brine, dried with anhydrous $MgSO_4$ and evaporated to dryness. The crude residue was purified by flash SiO_2-chromatography (PE/EtOAc = 1/20) and the pure product was afforded as white solid. Yield: 941.8 mg (83%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=-0.05 (s, 3H, CH_3, OTBDMS), 0.00 (s, 3H, CH_3, OTBDMS), 0.87 (s, 9H, CH_3, ^{t}Bu, OTBDMS), 1.29 (b, 3H, CH_3), 1.49 (s, 3H, CH_3), 1.80 (s, 3H, CH_3), 2.69 (b, 1H, CH_2-O), 3.46 (d, 1H, CH_2-O, $^{2}J_{H-H}$ =11.2 Hz), 4.03 (m, 1H, C*H*CH_2O), 5.08 (d, 1H, $CHCPh_2S$, $^{3}J_{H-H}$ =7.6 Hz), 7.22-7.38 (m, 8H, CH=), 7.51 (d, 2H, CH=, $^{3}J_{H-H}$ =7.2 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=-5.5 (CH_3, OTBDMS), -5.3 (CH_3, OTBDMS), 13.8 (CH_3), 18.4 (C, ^{t}Bu, OTBDMS), 26.0 (CH_3, ^{t}Bu, OTBDMS), 26.9 (CH_3), 27.5 (CH_3), 61.0 (CPh_2S), 63.1 (CH_2-O), 79.0 (*C*HCPh_2S), 80.1 (*C*HCH_2O), 108.9 (CMe_2), 126.7 (CH=), 126.9 (CH=), 127.5 (CH=), 127.8 (CH=), 129.1 (CH=), 130.4 (CH=), 143.2 (C=), 143.3 (C=).

(2,2-Dimethyl-5-((methylthio)diphenylmethyl)-1,3-dioxolan-4-yl)methanol (21). Treatment of silylated compound (682.1 mg, 2.1 mmol) in THF (50 mL) with a THF solution of TBAF (1 M, 3.1 mL, 3.1 mmol) provided the desired deprotected compound. The reaction mixture was concentrated under vacuum and purified by SiO_2-column chromatography (PE/EtOAc = 1/3) yielding pure thioether-hydroxy compound **21** as a white solid. Yield: 411 mg (91%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.27 (b, 3H, CH_3), 1.48 (s, 3H, CH_3), 1.78 (s, 3H, CH_3), 1.84 (t, 1H, OH, $^{3}J_{H-H}$ =4.0 Hz), 2.77 (b, 1H, CH_2-O), 3.17 (b, 1H, CH_2-O), 4.08-4.12 (m, 1H, C*H*CH_2O), 4.85 (d, 1H, $CHCPh_2S$, $^{3}J_{H-H}$ =8.0 Hz), 7.21-7.34 (m, 8H, CH=), 7.48 (d, 2H, CH=, $^{3}J_{H-H}$ =8.0 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=13.8 (CH_3), 26.7 (CH_3), 27.7 (CH_3), 60.7 (CPh_2S), 62.8 (CH_2-O), 79.5 (*C*HCH_2O), 80.2 (*C*HCPh_2S), 109.1 (CMe_2), 126.8 (CH=), 127.2 (CH=), 127.6 (CH=), 128.0 (CH=), 128.9 (CH=), 130.3 (CH=), 142.9 (C=).

3.2.4.10. Preparation of acetal-thioether compounds 22-23

A suspension of NaH (3.1 mg, 77.4 mmol), washed three times in hexane, in THF (25 mL) was cooled to -15 °C, and the corresponding thiol (37.5 mmol) in THF (8 mL), at -15 °C was added. After 10 min a solution of 1-deoxy-2,3-O-isopropylidene-1-tosyl-D-arabinitol (16.3 mmol) in THF (25 ml) was added at -15 °C. The reaction was stirred for 72h at room temperature. The reaction was quenched with water and extracted with dichloromethane

for three times. The extract was dried over anhydrous $MgSO_4$ and concentrated. The residue was purified by SiO_2-column chromatography (PE/EtOAc = 1/6) to produce the corresponding thioether-derived compound as colorless oil.

1-Deoxy-2,3:4,5-di-*O*-isopropylidene-1-phenylthio-D-arabinitol (22). Yield: 3.6 g (84%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.35 (s, 3H, CH_3), 1.37 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 3.09 (dd, 1H, CH_2-S, $^2J_{H-H}$ =13.6 Hz, $^3J_{H-H}$ =6.8 Hz), 3.46 (dd, 1H, CH_2-S, $^2J_{H-H}$ =13.6 Hz, $^3J_{H-H}$ =3.2 Hz), 3.78 (pt, 1H, C*H*CHO, $^3J_{H-H}$ =7.3 Hz), 3.95 (dd, 1H, CH_2-O, $^2J_{H-H}$ =8.4 Hz, $^3J_{H-H}$ =4.8 Hz), 4.04-4.08 (m, 1H, CH-O), 4.13 (dd, 1H, CH_2-O, $^2J_{H-H}$ =8.0 Hz, $^3J_{H-H}$ =6.0 Hz), 4.16-4.19 (m, 1H, C*H*CH_2S), 7.15-7.19 (m, 1H, CH=), 7.25-7.29 (m, 2H, CH=), 7.39-7.41 (m, 2H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 25.5 (CH_3), 26.9 (CH_3), 27.3 (CH_3), 27.4 (CH_3), 36.8 (CH_2-S), 68.0 (CH_2-O), 77.3 (CH-O), 79.3 (*C*HCH_2S), 80.3 (*C*HCHO), 109.9 (CMe_2), 110.1 (CMe_2), 126.0 (CH=), 129.0 (CH=), 129.1 (CH=), 136.8 (C=).

1-Deoxy-2,3:4,5-di-*O*-Isopropylidene-1-(2-naftylthio)-D-arabinitol (23). Yield: 5.3 g (87%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.39 (s, 6H, CH_3), 1.45 (s, 6H, CH_3), 3.19 (dd, 1H, CH_2-S, $^2J_{H-H}$ =13.6 Hz, $^3J_{H-H}$ =7.6 Hz), 3.60 (dd, 1H, CH_2-S, $^2J_{H-H}$ =14.4 Hz, $^3J_{H-H}$ =3.2 Hz), 3.83 (pt, 1H, C*H*CHO, $^3J_{H-H}$ =8.4 Hz), 4.00 (dd, 1H, CH_2-O, $^2J_{H-H}$ =8.4 Hz, $^3J_{H-H}$ =3.2 Hz), 4.07-4.11 (m, 1H, CH-O), 4.14-4.17 (m, 1H, CH_2-O), 4.23-4.27 (m, 1H, C*H*CH_2S), 7.41-7.49 (m, 3H, CH=), 7.24-7.80 (m, 3H, CH=), 7.84 (s, 1H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 25.6 (CH_3), 27.1 (CH_3), 27.4 (CH_3), 27.5 (CH_3), 36.7 (CH_2-S), 68.0 (CH_2-O), 77.4 (CH-O), 79.3 (*C*HCH_2S), 80.5 (*C*HCHO), 110.0 (CMe_2), 110.2 (CMe_2), 125.8 (CH=), 126.4 (CH=), 126.8 (CH=), 127.2 (CH=), 127.3 (CH=), 128.0 (CH=), 128.6 (CH=), 131.9 (C=), 134.1 (C=), 134.3 (C=).

3.2.4.11. General procedure for preparation of compound 37

Selenoeether-acetal compound **37** was synthesized as described above for compounds **9**-**10**.

1-Deoxy-2,3:4,5-di-*O*-isopropylidene-1-(1-naftylseleno)-D-arabinitol (37). Yield: 3.2 g (88%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.34 (s, 3H, CH_3), 1.37 (s, 6H, CH_3), 1.44 (s, 3H, CH_3), 3.18 (dd, 1H, CH_2-Se, $^2J_{H-H}$ =12.8 Hz, $^3J_{H-H}$ =7.2 Hz), 3.52 (dd, 1H, CH_2-Se, $^2J_{H-H}$ =12.8 Hz, $^3J_{H-H}$ =3.6 Hz), 3.80 (pt, 1H, C*H*CHO, $^3J_{H-H}$ =8.0 Hz), 3.95 (dd, 1H, CH_2-O, $^2J_{H-H}$ =8.0 Hz, $^3J_{H-H}$ =4.8 Hz), 4.04-4.08 (m, 1H, CH-O), 4.11-4.14 (m, 1H, CH_2-O), 4.23-4.26 (m, 1H, C*H*CH_2S), 7.44-7.48 (m, 2H, CH=), 7.60 (dd, 1H, CH=, $^3J_{H-H}$ =8.8 Hz, $^4J_{H-H}$ =1.6 Hz), 7.69-7.81 (m, 3H, CH=), 8.01 (s, 1H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 25.3 (CH_3), 26.7 (CH_3), 27.1 (CH_3), 27.3 (CH_3), 30.5 (CH_2-Se), 67.8 (CH_2-O), 77.0 (CH-O), 79.6 (*C*HCH_2Se), 80.8 (*C*HCHO), 109.7 (CMe_2), 125.9-133.9 (aromatic carbons).

3.2.4.12. General procedure for obtention of thiother compounds 24-25 and selenoether compound 39

The fully protected compound **22**, **23** and **37** (1.0 mmol) was stirred overnight at room temperature in 70% aq. acetic acid (3.5 mL). Then, the reaction mixture was neutralized with aq. $NaHCO_3$, and extracted with ethyl acetate (2 x 100 mL). The combined organic

extracts were washed with brine (20 mL), dried over anhydrous $MgSO_4$, concentrated under reduced pressure and purified by SiO_2-column chromatography (EtOAc/PE = 1/1) to afford the desired deprotected compounds colorless oil.

1-Deoxy-2,3-*O*-isopropylidene-1-phenylthio-D-arabinitol (24). Yield: 2.1 g (67%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.38 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 2.08 (b, 1H, OH), 2.65 (b, 1H, OH), 3.20 (dd, 1H, CH_2-S, $^2J_{H-H}$ =13.6 Hz, $^3J_{H-H}$ =6.0 Hz), 3.33 (dd, 1H, CH_2-S, $^2J_{H-H}$ =13.6 Hz, $^3J_{H-H}$ =4.8 Hz), 3.68 (dd, 1H, CH_2-O, $^2J_{H-H}$ =10.8 Hz, $^3J_{H-H}$ =5.2 Hz), 3.72-3.76 (m, 1H, CH-O), 3.80 (dd, 1H, CH_2-O, $^2J_{H-H}$ =10.4 Hz, $^3J_{H-H}$ =3.2 Hz), 3.87 (pt, 1H, C*H*CH-O, $^3J_{H-H}$ =6.8 Hz), 4.18-4.22 (m, 1H, C*H*CH_2S), 7.17-7.21 (m, 1H, CH=), 7.26-7.31 (m, 2H, CH=), 7.39-7.41 (m, 2H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 27.4 (CH_3), 27.5 (CH_3), 37.5 (CH_2-S), 64.2 (CH_2-O), 72.9 (CH-O), 78.5 (*C*HCH_2S), 80.7 (*C*HCHOH), 110.0 (CMe_2), 126.6 (CH=), 129.3 (CH=), 129.6 (CH=), 136.1 (C=).

1-Deoxy-2,3-*O*-Isopropylidene-1-(2-naftylthio)-D-arabinitol (25). Yield: 3.0 g (63%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.35 (s, 3H, CH_3), 1.41 (s, 3H, CH_3), 3.22 (dd, 1H, CH_2-S, $^2J_{H-H}$ =13.6 Hz, $^3J_{H-H}$ =7.2 Hz), 3.46 (dd, 1H, CH_2-S, $^2J_{H-H}$ =14.0 Hz, $^3J_{H-H}$ =4.4 Hz), 3.65 (dd, 1H, CH_2-O, $^2J_{H-H}$ =11.6 Hz, $^3J_{H-H}$ =6.0 Hz), 3.67-3.73 (m, 1H, CH-O), 3.79 (dd, 1H, CH_2-O, $^2J_{H-H}$ =10.8 Hz, $^3J_{H-H}$ =2.8 Hz), 3.86 (pt, 1H, C*H*CHO, $^3J_{H-H}$ =7.6 Hz), 4.24-4.29 (m, 1H, C*H*CH_2S), 7.36-7.44 (m, 3H, CH=), 7.69-7.74 (m, 3H, CH=), 7.81 (s, 1H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 27.1 (CH_3), 27.2 (CH_3), 37.0 (CH_2-S), 63.9 (CH_2-O), 72.8 (CH-O), 78.3 (*C*HCH_2S), 80.2 (*C*HCHOH), 109.8 (CMe_2), 125.7 (CH=), 126.6 (CH=), 126.7 (CH=), 127.1 (CH=), 127.7 (CH=), 128.5 (CH=), 131.7 (C=), 133.4 (C=), 133.7 (C=).

1-Deoxy-2,3-*O*-isopropylidene-1-(1-naftylseleno)-D-arabinitol (38). Yield: 2.8 g (58%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.37 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 2.40 (b, 2H, OH), 3.23 (dd, 1H, CH_2Se, $^2J_{H-H}$ =12.8 Hz, $^3J_{H-H}$ =6.4 Hz), 3.40 (dd, 1H, CH_2-Se, $^2J_{H-H}$ =12.4 Hz, $^3J_{H-H}$ =4.4 Hz), 3.65 (dd, 1H, CH_2-O, $^2J_{H-H}$ =10.8 Hz, $^3J_{H-H}$ =5.2 Hz), 3.70-3.73 (m, 1H, CH-O), 3.77 (dd, 1H, CH_2-O, $^2J_{H-H}$ =11.2 Hz, $^3J_{H-H}$ =3.2 Hz), 3.86 (pt, C*H*CHO, $^3J_{H-H}$ =6.8 Hz), 4.26-4.30 (m, 1H, C*H*CH_2Se), 7.42-7.48 (m, 2H, CH=), 7.58 (dd, 1H, CH=, $^3J_{H-H}$ =8.4 Hz, $^4J_{H-H}$ =1.6 Hz), 7.70-7.79 (m, 3H, CH=), 8.01 (s, 1H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 27.2 (CH_3), 27.3 (CH_3), 31.1 (CH_2-Se), 63.9 (CH_2-O), 73.0 (CH-O), 78.9 (*C*HCH_2Se), 80.6 (*C*HCHO), 109.7 (CMe_2), 126.0 (CH=), 126.5 (CH=), 127.2 (CH=), 127.8 (CH=), 128.5 (CH=), 129.8 (CH=), 130.8 (CH=), 132.1 (C=), 133.9 (C=).

3.2.4.13. Synthesis of hydroxyl-thioether compounds 31-32 and hydroxyl-selenoether compound 39

To a cooled solution (-15 °C) of compound **24**, **25** or **38** (1 mmol) in pyridine (0.27 mL. 3.4 mmol), a solution of *p*-toluenesulfonyl chloride (190.0 mg, 1 mmol) in DCM (2 mL) was slowly added. After stirring overnight, water was added and the reaction mixture was extracted with DCM (x3). The organic extract was washed with a solution of HCl 0.1 M (x1). The organic layer was dried over $MgSO_4$, evaporated to dryness and purified by SiO_2-flash chromatography (EtOAc/PE = 1/2) to produce the product as a white solid.

1-Deoxy-2,3-*O*-Isopropylidene-1-phenylthio-5-*O*-tosyl-D-arabinitol. Yield: 3.0 g (93%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.21 (s, 3H, CH_3), 1.27 (s, 3H, CH_3), 2.35 (s, 3H, CH_3, OTs), 2.58 (d, 1H, OH, $^3J_{H-H}$ =4.4 Hz), 3.02 (dd, 1H, CH_2-S, $^2J_{H-H}$ =14.0 Hz, $^3J_{H-H}$ =6.8 Hz), 3.24 (dd, 1H, CH_2-S, $^2J_{H-H}$ =13.6 Hz, $^3J_{H-H}$ =4.4 Hz), 3.62 (dd, 1H, C*H*CHO, $^3J_{H-H}$ =8.0 Hz, $^3J_{H-H}$ =6.4 Hz), 3.71-3.78 (m, 1H, CH-O), 3.94 (dd, 1H, CH_2-OTs, $^2J_{H-H}$ =10.4 Hz, $^3J_{H-H}$ =6.8 Hz), 4.06-4.09 (m, 1H, C*H*CH_2S), 4.18 (dd, 1H, CH_2-OTs, $^2J_{H-H}$ =10.4 Hz, $^3J_{H-H}$ =2.4 Hz), 7.06-7.10 (m, 1H, CH=), 7.15-7.19 (m, 2H, CH=), 7.24-7.28 (m, 4H, CH=), 7.69-7.71 (m, 2H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 21.9 (CH_3, OTs), 27.2 (CH_3), 27.4 (CH_3), 37.4 (CH_2-S), 71.8 (CH-O), 72.1 (CH_2-OTs), 78.8 (*C*HCHO), 79.2 (*C*HCH_2S), 110.3 (CMe_2), 126.4 (CH=), 128.2 (CH=), 129.2 (CH=), 129.4 (CH=), 130.2 (CH=), 132.6 (C=), 136.1 (C=), 145.4 (C=).

1-Deoxy-2,3-*O*-Isopropylidene-1-(2-naftylthio)-5-*O*-tosyl-D-arabinitol. Yield: 3.6 g (83%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.31 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 2.42 (s, 3H, CH_3, OTs), 3.20 (dd, 1H, CH_2-S, $^2J_{H-H}$ =14.4 Hz, $^3J_{H-H}$ =7.2 Hz), 3.47 (dd, 1H, CH_2-S, $^2J_{H-H}$ =14.0 Hz, $^3J_{H-H}$ =4.4 Hz), 3.76 (dd, 1H, C*H*CHO, $^3J_{H-H}$ =8.4 Hz, $^3J_{H-H}$ =6.8 Hz), 3.83-3.88 (m, 1H, CH-O), 4.06 (dd, 1H, CH_2-OTs, $^2J_{H-H}$ =10.8 Hz, $^3J_{H-H}$ =6.8 Hz), 4.22-4.26 (m, 1H, C*H*CH_2S), 4.29 (dd, 1H, CH_2-OTs, $^2J_{H-H}$ =10.4 Hz, $^3J_{H-H}$ =2.4 Hz), 7.31 (d, 2H, CH=, $^3J_{H-H}$ =8.8 Hz), 7.42-7.46 (m, 3H, CH=), 7.72-7.81 (m, 6H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 21.7 (CH_3, OTs), 27.0 (CH_3), 27.2 (CH_3), 36.9 (CH_2-S), 71.6 (CH-O), 72.0 (CH_2-O), 78.6 (*C*HCHOH), 78.9 (*C*HCH_2S), 110.2 (CMe_2), 125.7 (CH=), 126.5 (CH=), 126.6 (CH=), 127.1 (CH=), 127.7 (CH=), 128.0 (CH=), 128.5 (CH=), 130.0 (CH=), 131.7 (C=), 132.3 (C=), 133.4 (C=), 133.8 (C=), 145,2 (C=).

1-Deoxy-2,3-*O*-isopropylidene-1-(1-naftylseleno)-5-*O*-tosyl-D-arabinitol. Yield: 2.2 g (55%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.31 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 2.42 (s, 3H, CH_3, OTs), 3.19 (dd, 1H, CH_2-Se, $^2J_{H-H}$ =12.8 Hz, $^3J_{H-H}$ =6.4 Hz), 3.42 (dd, 1H, CH_2-Se, $^2J_{H-H}$ =12.4 Hz, $^3J_{H-H}$ =4.0 Hz), 3.76 (pt, 1H, C*H*CHO, $^3J_{H-H}$ =7.2 Hz), 3.84 (dd, 1H, CH-O, $^3J_{H-H}$ =8.8 Hz, $^2J_{H-H}$ =2.8 Hz), 4.04 (dd, 1H, CH_2-OTs, $^2J_{H-H}$ =10.8 Hz, $^3J_{H-H}$ =7.2 Hz), 4.24-4.30 (m, 2H, C*H*CH_2Se, CH_2-OTs), 7.30 (d, 2H, CH=, $^3J_{H-H}$ =7.6 Hz), 7.45-7.49 (m, 3H, CH=), 7.57 (dd, 1H, $^3J_{H-H}$ =8.4 Hz, $^4J_{H-H}$ =1.2 Hz), 7.70-7.79 (m, 5H, CH=), 8.00 (s, 1H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 21.7 (CH_3, OTs), 27.1 (CH_3), 27.3 (CH_3), 30.9 (CH_2-Se), 71.6 (CH-O), 72.0 (CH_2-O), 79.1 (*C*HCHO), 79.5 (*C*HCH_2Se), 110.0 (CMe_2), 126.0 (CH=), 126.5 (CH=), 127.2 (CH=), 127.6 (CH=), 127.9 (CH=), 128.5 (CH=), 129.8 (CH=), 130.8 (CH=), 132.2 (C=), 132.3 (C=), 133.9 (C=), 145.2 (C=).

To a cooled solution (0 °C) of the corresponding thioether-tosyl compound (1.0 mmol) in THF (2.5 mL), $LiAlH_4$ (56.9 mg, 1.5 mmol) was added portion-wise. The solution was stirred at reflux for 2h. Then, drops of water were carefully added and a white precipitate appeared which was filtered and clean three times with ethyl acetate. The organic phase was dried over $MgSO_4$ and evaporated to dryness. The crude product was purified by SiO_2-column chromatography (EtOAc/PE = 1/3) yielding the corresponding compounds as colorless oils.

1,5-Dideoxy-2,3-*O*-isopropylidene-5-methyl-1-phenylthio-D-arabinitol (31). Yield: 1.2 g (67%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.18 (d, 3H, CH_3, $^3J_{H-H}$ =6.8 Hz), 1.38 (s, 3H, CH_3), 1.41 (s,

3H, CH_3), 2.03 (b, 1H, OH), 3.15 (dd, 1H, CH_2-S, $^2J_{H-H}$ =13.6 Hz, $^3J_{H-H}$ =6.8 Hz), 3.26 (dd, 1H, CH_2-S, $^2J_{H-H}$ =13.6 Hz, $^3J_{H-H}$ =4.8 Hz), 3.74 (dd, 1H, C*H*CHO, $^3J_{H-H}$ =7.2 Hz, $^3J_{H-H}$ =5.2 Hz), 3.87-3.90 (m, 1H, CH-O), 4.13-4.18 (m, 1H, C*H*CH_2S), 7.14-7.18 (m, 1H, CH=), 7.23-7.28 (m, 2H, CH=), 7.36-7.39 (m, 2H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=19.5 (CH_3), 27.5 (CH_3), 27.6 (CH_3), 38.2 (CH_2-S), 68.2 (CH-O), 77.0 (*C*HCH_2S), 84.0 (*C*HCHO), 109.7 (CMe_2), 126.6 (CH=), 129.3 (CH=), 129.7 (CH=), 136.3 (C=).

1,5-Dideoxy-2,3-*O*-isopropylidene-5-methyl-1-(2-naftylthio)-D-arabinitol (32). Yield: 1.1 g (54%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.22 (d, 3H, CH_3, $^3J_{H-H}$ =6.8 Hz), 1.39 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 1.91 (b, 1H, OH), 3.26 (dd, 1H, CH_2-S, $^2J_{H-H}$ =13.6 Hz, $^3J_{H-H}$ =6.4 Hz), 3.39 (dd, 1H, CH_2-S, $^2J_{H-H}$ =13.6 Hz, $^3J_{H-H}$ =4.4 Hz), 3.79 (dd, 1H, C*H*CHO, $^3J_{H-H}$ =7.6 Hz, $^3J_{H-H}$ =5.6 Hz), 3.90-3.93 (m, 1H, CH-O), 4.21-4.24 (m, 1H, C*H*CH_2S), 7.40-7.48 (m, 3H, CH=), 7.72-7.82 (m, 4H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=19.3 (CH_3), 27.2 (CH_3), 27.3 (CH_3), 37.7 (CH_2-S), 68.0 (CH-O), 77.4 (*C*HCH_2S), 83.8 (*C*HCHO), 109.4 (CMe_2), 125.8 (CH=), 126.6 (CH=), 126.9 (CH=), 127.1 (CH=), 127.3 (CH=), 127.7 (CH=), 128.5 (CH=), 131.8 (C=), 133.5 (C=), 133.7 (C=).

1,5-Dideoxy-2,3-*O*-isopropylidene-5-methyl-1-(1-naftylseleno)-D-arabinitol (38). Yield: 731 mg (58%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.18 (d, 3H, CH_3, $^3J_{H-H}$ =6.8 Hz), 1.39 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 1.92 (b, 1H, OH), 3.21 (dd, 1H, CH_2-Se, $^2J_{H-H}$ =12.4 Hz, $^3J_{H-H}$ =6.4 Hz), 3.35 (dd, 1H, CH_2-Se, $^2J_{H-H}$ =12.4 Hz, $^3J_{H-H}$ =4.4 Hz), 3.78 (dd, 1H, C*H*CHO, $^3J_{H-H}$ =7.6 Hz, $^3J_{H-H}$ =5.2 Hz), 3.87-3.93 (m, 1H, CH-O), 4.24-4.29 (m, 1H, C*H*CH_2Se), 7.42-7.49 (m, 2H, CH=), 7.59 (dd, 1H, $^3J_{H-H}$ =8.4 Hz, $^4J_{H-H}$ =2.0 Hz), 7.71-7.80 (m, 3H, CH=), 8.01 (d, 1H, CH=, $^4J_{H-H}$ =1.6 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=19.2 (CH_3), 27.2 (CH_3), 27.4 (CH_3), 31.7 (CH_2-Se), 67.8 (CH-O), 77.0 (*C*HCH_2Se), 84.2 (*C*HCHO), 109.2 (CMe_2), 126.0 (CH=), 126.5 (CH=), 127.2 (CH=), 127.8 (CH=), 128.5 (CH=), 130.0 (CH=), 131.1 (CH=), 132.2 (C=), 133.9 (C=), 134.8 (C=).

3.2.4.14. General procedure for the synthesis of thioether-hydroxy compounds 26-30

The corresponding diol **24** or **25** (1 mmol) was solved in DMF (2 mL) in the presence of imidazole (2.5 mmol) and was cooled to -15 °C. A solution of the desired chlorosilane (1.2 mmol) in DMF (1 mL) was added and the reaction was stirred for 1.5 h. When chlorotrimethylsilane was used, the solution was cooled to -75 °C and the reaction mixture was stirred only 30 min. Then, water was added and the reaction mixture was extracted with Et_2O (x3). The organic layer was dried over $MgSO_4$, evaporated to dryness and purified by SiO_2-column chromatography (EtOAc/PE = 1/4) to produce the product as a colorless oil.

5-*O*-(*tert*-Butyldimethylsilyl)-1-deoxy-2,3-*O*-isopropylidene-1-phenylthio-D-arabinitol (26). Yield 263.3 mg (61%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.09 (s, 6H, CH_3, OTBDMS), 0.91 (s, 9H, CH_3, ^{t}Bu, OTBDMS), 1.38 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 2.62 (d, 1H, OH, $^3J_{H-H}$ =5.2 Hz), 3.12 (dd, 1H, CH_2-S, $^2J_{H-H}$ =13.6 Hz, $^3J_{H-H}$ =7.2 Hz), 3.46 (dd, 1H, CH_2-S, $^2J_{H-H}$ =10.4 Hz, $^3J_{H-H}$ =6.8 Hz), 3.62-3.68 (m, 2H, CH-O, CH_2-OTBDMS), 3.76-3.81 (m, 2H, C*H*CHO, CH_2-OTBDMS), 4.26 (m, 1H, C*H*CH_2S), 7.14-7.18 (m, 1H, CH=), 7.25-7.29 (m, 2H, CH=), 7.39-7.42 (m, 2H, CH=).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ=-5.2 (CH_3, OTBDMS), -5.1 (CH_3, OTBDMS), 18.5 (C, ^{t}Bu, OTBDMS), 26.1 (CH_3, ^{t}Bu, OTBDMS), 27.4 (CH_3), 27.5 (CH_3), 37.4 (CH_2-S), 64.5 (CH_2-OTBDMS), 73.3 (CH-O), 79.1 (*C*HCH_2S, *C*HCHO), 109.8 (CMe_2), 126.0 (CH=), 129.1 (CH=), 136.8 (C=).

5-*O*-(*tert*-Butyldimethylsilyl)-1-deoxy-2,3-*O*-isopropylidene-1-(2-naftylthio)-D-arabinitol (27). Yield 710.5 mg (69%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.08 (s, 3H, CH_3, OTBDMS), 0.09 (s, 3H, CH_3, OTBDMS), 0.91 (s, 9H, CH_3, ^{t}Bu, OTBDMS), 1.38 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 2.61 (b, 1H, OH), 3.21 (dd, 1H, CH_2-S, $^2J_{H\text{-}H}$ =13.6 Hz, $^3J_{H\text{-}H}$ =7.2 Hz), 3.59 (dd, 1H, CH_2-S, $^2J_{H\text{-}H}$ =13.2 Hz, $^3J_{H\text{-}H}$ =3.6 Hz), 3.64-3.69 (m, 2H, CH-O, CH_2-OTBDMS), 3.79-3.83 (m, 2H, C*H*CHO, CH_2-OTBDMS), 4.29-4.34 (m, 1H, C*H*CH_2S), 7.40-7.58 (m, 3H, CH=), 7.74-7.79 (m, 3H, CH=), 7.87 (s, 1H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=-5.4 (CH_3, OTBDMS), -5.3 (CH_3, OTBDMS), 18.3 (C, ^{t}Bu, OTBDMS), 25.9 (CH_3, ^{t}Bu, OTBDMS), 27.2 (CH_3), 27.3 (CH_3), 36.4 (CH_2-S), 64.3 (CH_2-OTBDMS), 73.2 (CH-O), 78.9 (*C*HCH_2S, *C*HCHOH), 109.7 (CMe_2), 125.5 (CH=), 126.2 (CH=), 126.5 (CH=), 127.1 (CH=), 127.7 (CH=), 128.3 (CH=), 131.6 (CH=), 133.8 (C=), 134.2 (C=).

5-*O*-(*tert*-Butyldiphenylsilyl)-1-deoxy-2,3-*O*-isopropylidene-1-(2-naftylthio)-D-arabinitol (28). Yield 913.3 mg (69%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.07 (s, 9H, CH_3, ^{t}Bu, OTBDPS), 1.30 (s, 3H, CH_3), 1.41 (s, 3H, CH_3), 2.76 (b, 1H, OH), 3.21 (dd, 1H, CH_2-S, $^2J_{H\text{-}H}$ =13.6 Hz, $^3J_{H\text{-}H}$ =7.2 Hz), 3.58 (dd, 1H, CH_2-S, $^2J_{H\text{-}H}$ =13.2 Hz, $^3J_{H\text{-}H}$ =2.8 Hz), 3.69 (b, 1H, CH-O), 3.76-3.91 (m, 3H, C*H*CHO, CH_2-OTBDPS), 4.28-4.31 (m, 1H, C*H*CH_2S), 7.38-7.50 (m, 8H, CH=), 7.68-7.87 (m, 9H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=19.4 (C, ^{t}Bu, OTBDPS), 27.2 (CH_3, ^{t}Bu, OTBDPS), 27.4 (CH_3), 27.6 (CH_3), 37.3 (CH_2-S), 65.5 (CH_2-OTBDPS), 73.6 (CH-O), 79.1 (*C*HCH_2S), 79.3 (*C*HCHO), 110.0 (CMe_2), 125.5 (CH=), 126.3 (CH=), 126.5 (CH=), 127.1 (CH=), 127.7 (CH=), 127.8 (CH=), 127.9 (CH=), 128.3 (CH=), 129.6 (CH=), 129.9 (CH=), 131.7-134.8 (C=), 135.5 (CH=), 135.6 (CH=).

1-Deoxy-2,3-*O*-isopropylidene-5-O-triisopropylsilyl-1-(2-naftylthio)-D-arabinitol)oxy)ethan-1-ol (29). Yield 823 mg (73%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.97-1.13 (m, 3H, CH, OTIPS), 1.04 (s, 9H, CH_3, OTIPS), 1.06 (s, 9H, CH_3, OTIPS), 1.37 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 2.72 (b, 1H, OH), 3.20 (dd, 1H, CH_2-S, $^2J_{H\text{-}H}$ =13.6 Hz, $^3J_{H\text{-}H}$ =7.6 Hz), 3.59 (dd, 1H, CH_2-S, $^2J_{H\text{-}H}$ =14.0 Hz, $^3J_{H\text{-}H}$ =3.2 Hz), 3.69 (b, 1H, CH-O), 3.76 (dd, 1H, CH_2-OTIPS, $^2J_{H\text{-}H}$ =10.0 Hz, $^3J_{H\text{-}H}$ =5.6 Hz), 3.84 (pt, 1H, C*H*CHO, $^3J_{H\text{-}H}$ =4.8 Hz), 3.88 (dd, 1H, CH_2-OTIPS, $^2J_{H\text{-}H}$ =10.0 Hz, $^3J_{H\text{-}H}$ =3.6 Hz), 4.29-4.33 (m, 1H, C*H*CH_2S), 7.38-7.48 (m, 3H, CH=), 7.73 (d, 2H, CH=, $^3J_{H\text{-}H}$ =8.4 Hz), 7.77 (d, 1H, CH=, $^3J_{H\text{-}H}$ =8.0 Hz), 7.84 (s, 1H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=11.9 (CH, OTIPS), 17.7 (CH_3, OTIPS), 17.9 (CH_3, OTIPS), 27.1 (CH_3), 27.2 (CH_3), 36.9 (CH_2-S), 64.5 (CH_2-OTIPS), 73.3 (CH-O), 78.8 (*C*HCH_2S), 78.9 (*C*HCHO), 109.7 (CMe_2), 125.5 (CH=), 126.2 (CH=), 126.4 (CH=), 127.1 (CH=), 127.7 (CH=), 128.3 (CH=), 131.6 (CH=), 133.8 (C=), 134.2 (C=).

3.2.4.15. Synthesis of hydroxyl-thioether compound 30

1-Deoxy-2,3-*O*-isopropylidene-1-(2-naftylthio)-5-*O*-trityl-D-arabinitol (30). Tritylchloride (940.2 mg, 3.5 mmol) was added to a solution of diol **25** (769.2 mg, 2.3 mmol) in pyridine (49.4 mmol, 4 mL). The reaction mixture was allowed to stir at room temperature for 36 h. Then dichloromethane was added and the solution was washed with a saturated $CuSO_4$ aqueous solution. The aqueous phase was extracted with dichloromethane once. All organic phases were washed with water, dried over $MgSO_4$ and concentrated. The resulting residue was purified by SiO_2-column chromatography (EtOAc/PE = 1/4) to yield the product as a colorless oil. Yield 415.8 mg (31%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.31 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 2.49 (b, 1H, OH), 3.17 (dd, 1H, CH_2-S, $^2J_{H-H}$ =13.6 Hz, $^3J_{H-H}$ =7.2 Hz), 3.32 (d, 1H, CH_2-OTr, $^3J_{H-H}$ =1.2 Hz), 3.34 (s, 1H, CH_2-OTr), 3.48 (dd, 1H, CH_2-S, $^2J_{H-H}$ =13.2 Hz, $^3J_{H-H}$ =3.2 Hz), 3.76-3.80 (m, 1H, CH-O), 3.94 (pt, 1H, C*H*CHO, $^3J_{H-H}$ =7.6 Hz), 4.24-4.29 (m, 1H, C*H*CH_2S), 7.21-7.30 (m, 10H, CH=), 7.40-7.44 (m, 8H, CH=), 7.70 (t, 2H, CH=, $^3J_{H-H}$ =8.4 Hz), 7.77 (dd, 2H, CH=, $^3J_{H-H}$ =6.0 Hz, $^4J_{H-H}$ =1.2 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 27.1 (CH_3), 27.4 (CH_3), 37.1 (CH_2-S), 65.1 (CH_2-OTr), 72.2 (CH-O), 78.3 (*C*HCH_2S), 79.8 (*C*HCHO), 87.4 (C, OTr), 109.7 (CMe_2), 125.6 (CH=), 126.4 (CH=), 126.5 (CH=), 127.1 (CH=), 127.2 (CH=), 127.7 (CH=), 128.0 (CH=), 128.3 (CH=), 128.7 (CH=), 131.7 (C=), 133.8 (C=), 134.1 (C=), 143.8 (C=).

3.2.4.16. Synthesis of hydroxyl-thioether compound 34 with inversion of configuration[25]

1,5-Dideoxy-2,3-*O*-isopropylidene-5-methyl-*O*-4-(p-nitrobenzoate)-1-phenylthio-D-xylitol. DIAD (3.1 mL, 16 mmol) was added dropwise to a solution of thioether-hydroxy **31** (1.1 g, 4 mmol), *p*-nitrobenzoic acid (2.7 g, 16 mmol), and PPh_3 (4.2 g, 16 mmol) in THF (33 mL) at 0 °C. After being stirred overnight at room temperature, the reaction mixture was concentrated and the residue was purifief by SiO_2-column chromatography (EtOAc/PE = 1/6) to yield the product as a colorless oil. Yield: 1.4 g (90%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.39 (d, 3H, CH_3, $^3J_{H-H}$ =6.0 Hz), 1.43 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 3.13 (dd, 1H, CH_2-S, $^2J_{H-H}$ =13.6 Hz, $^3J_{H-H}$ =5.6 Hz), 3.24 (dd, 1H, CH_2-S, $^2J_{H-H}$ =14.0 Hz, $^3J_{H-H}$ =5.6 Hz), 4.02-4.09 (m, 2H, C*H*CH_2S, C*H*CHOpNBA), 5.32-5.35 (m, 1H, CH-OpNBA), 7.07-7.09 (m, 1H, CH=), 7.15-7.20 (m, 2H, CH=), 7.29-7.32 (m, 2H, CH=), 8.10-8.12 (m, 2H, CH=), 8.20-8.23 (m, 2H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=16.7 (CH_3), 27.2 (CH_3), 27.5 (CH_3), 36.9 (CH_2-S), 70.9 (CH-OpNBA), 75.2 (*C*HCH_2S), 82.1 (*C*HCHOpNBA), 109.9 (CMe_2), 123.5 (CH=), 126.4 (CH=), 129.0 (CH=), 129.5 (CH=), 130.7 (CH=), 135.2 (C=), 135.3 (C=), 150.5 (C=), 163.9 (C=O, pNBA).

1,5-Dideoxy-2,3-*O*-isopropylidene-5-methyl-1-phenylthio-D-xylitol (33). 1,5-Dideoxy-2,3-O-isopropylidene-5-methyl-O-4-(p-nitrobenzoate)-1-phenylthio-D-xylitol (1.4 g, 3.6 mmol) was dissolved in MeOH (48.5 mL) and treated with NaOH (1.1 g, 26.9 mL) at room temperature. After being stirred overnight, the reaction mixture was concentrated and extracted with diethyl ether. The organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered, and evaporated. The residue was purified by SiO_2-column

chromatography (EtOAc/PE = 1/1) to yield the product as a colorless oil. Yield: 850 mg (87%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.17 (d, 3H, CH_3, $^{3}J_{H-H}$ =6.0 Hz), 1.40 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 2.29 (s, 1H, OH, $^{3}J_{H-H}$ =10.4 Hz), 3.10-3.23 (m, 2H, CH_2-S), 3.72-3.79 (m, 2H, C*H*CHO, CH-O), 4.11 (q, 1H, C*H*CH_2S, $^{3}J_{H-H}$ =6.0 Hz), 7.16-7.20 (m, 1H, CH=), 7.27 (t, 2H, CH=, , $^{3}J_{H-H}$ =7.2 Hz), 7.36-7.38 (m, 2H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 20.0 (CH_3), 27.4 (CH_3), 27.5 (CH_3), 37.3 (CH_2-S), 67.2 (CH-O), 76.0 (*C*HCH_2S), 84.1 (*C*HCHO), 109.7 (CMe_2), 126.4 (CH=), 129.1 (CH=), 129.5 (CH=), 135.7 (C=).

3.2.4.17. Typical procedure for the synthesis of compound 34

1-*O*-*tert*-Butyldiphenylsilyl-2,3:4,5-di-*O*-isopropylidene-D-arabinitol. Compound **2** (3.1 g, 13.4 mmol) was solved in DMF (20 mL) in the presence of imidazole (4.75 g, 33.4 mmol) and was cooled to -15 °C. A solution of *tert*-buthyl(chloro)diphenylsilane (4.2 mL, 16.0 mmol) in DMF (10 mL) was added and the reaction was stirred for 1.5 h. Then, water was added and the reaction mixture was extracted with Et_2O (x3). The organic layer was dried over $MgSO_4$, evaporated to dryness and purified by SiO_2-column chromatography (EtOAc/PE = 9.5/0.5) to produce the product as a white solid. Yield: 6.1 g (97%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.08 (s, 9H, CH_3, ^{t}Bu, OTBDPS), 1.33 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 1.41 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 3.76-3.80 (m, 1H, CH_2-OTBDPS), 3.92-3.95 (m, 1H, CH_2-OTBDPS), 3.96-3.98 (m, 1H, CH_2-O), 4.02-4.04 (m, 2H, CH-O, C*H*CH_2OTBDPS), 4.07-4.14 (m, 2H, CH_2-O, C*H*CHO), 7.36-7.45 (m, 6H, CH=), 7.70-7.75 (m, 4H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=19.3 (C, ^{t}Bu, OTBDPS), 25.3 (CH_3), 26.6 (CH_3), 26.8 (CH_3, ^{t}Bu, OTBDPS), 27.2 (CH_3), 27.4 (CH_3), 63.8 (CH_2-OTBDPS), 67.4 (CH_2-O), 77.0-80.9 (C*H*CH_2OTBDPS, C*H*CHO, CH-O), 109.5 (CMe_2), 127.6 (CH=), 129.6 (CH=), 129.7 (CH=), 133.3 (C=), 133.4 (C), 135.7 (CH=).

1-*O*-*tert*-Butyldiphenylsilyl-2,3-*O*-isopropylidene-D-arabinitol (34). The previously synthesized fully protected compound (4.7 g, 10.0 mmol) was stirred overnight at 55 °C in a mixture of 5:2:1 AcOH/THF/H_2O (30 mL). Then, the reaction mixture was cool down to room temperature and neutralized with aq. $NaHCO_3$, and extracted with ethyl acetate (2 x 100 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, concentrated under reduced pressure and purified by SiO_2-column chromatography (EtOAc/EP = 1/1) to afford the desired compound **34** as colorless oil. Yield: 1.6 g (37%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.07 (s, 9H, CH_3, ^{t}Bu, OTBDPS), 1.35 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 3.68-3.83 (m, 4H, CH_2-OTBDPS, CH-O, C*H*CH_2OTBDPS, C*H*CHO), 3.86 (dd, 1H, CH_2-OTBDPS, $^{2}J_{H-H}$ =10.4 Hz, $^{3}J_{H-H}$ =4.0 Hz), 3.93-3.96 (m, 1H, CH_2-O), 4.01-4.06 (m, 1H, CH_2-O), 7.38-7.48 (m, 6H, CH=), 7.66-7.69 (m, 4H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=19.4 (C, ^{t}Bu, OTBDPS), 27.1 (CH_3, CH_3, ^{t}Bu, OTBDPS), 27.2 (CH_3), 64.1-80.3 (CH_2-OTBDPS, CH_2-O, C*H*CH_2OTBDPS, C*H*CHO, CH-O), 109.7 (CMe_2), 128.2 (CH=), 130.4 (CH=), 129.7 (CH=), 132.5 (C=), 132.6 (C), 135.9 (CH=).

3.2.4.18. Preparation of the compound 35

1-*O*-*tert*-Butyldiphenylsilyl-2,3-*O*-isopropylidene-5-*O*-tosyl-D-arabinitol. To a cooled solution (-15 °C) of compound **34** (227.0 mg, 0.53 mmol) in pyridine (0.14 mL, 1.8 mmol), a

solution of *p*-toluenesulfonyl chloride (100.7 mg, 0.53 mmol) in DCM (1 mL) was slowly added. After stirring overnight, water was added and the reaction mixture was extracted with DCM (x3). The organic extract was washed with a solution of HCl 0.1 M (x1). The organic layer was dried over $MgSO_4$, evaporated to dryness and purified by SiO_2-flash chromatography (EtOAc/PE = 1/2) to produce the product as a white solid. Yield: 227 mg (41%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.04 (s, 9H, CH_3, ^{t}Bu, OTBDPS), 1.31 (s, 6H, CH_3), 2.41 (s, 3H, OTs), 3.13 (d, 1H, OH, $^3J_{H-H}$ =4.0 Hz), 3.72 (dd, 1H, CH_2-OTBDPS, $^2J_{H-H}$ =12.8 Hz, $^3J_{H-H}$ =6.0Hz), 3.78-3.82 (m, 2H, CH_2-OTBDPS, C*H*CH_2OTBDPS), 3.86 (pt, 1H, C*H*CHO, $^3J_{H-H}$ =8.4 Hz), 3.98-4.03 (m, 1H, CH-O), 4.08-4.13 (m, 1H, CH_2-OTs), 4.30 (dd, 1H, CH_2-OTs, $^2J_{H-H}$ =10.8 Hz, $^3J_{H-H}$ =2.4 Hz), 7.30 (d, 1H, CH=, $^3J_{H-H}$ =8.0 Hz), 7.36-7.44 (m, 6H, CH=), 7.65-7.68 (m, 5H, CH=), 7.81 (d, 2H, CH=, $^3J_{H-H}$ =8.4 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=19.1 (C, ^{t}Bu, OTBDPS), 21.6 (CH_3, OTs), 26.8 (CH_3, ^{t}Bu, OTBDPS), 26.9 (CH_3), 64.5 (CH_2-OTBDPS), 71.4 (C*H*CH_2OTBDPS), 71.7 (CH_2-O), 76.9 (C*H*CHO), 80.4 (CH-O), 109.6 (CMe_2), 127.8 (CH=), 128.0 (CH=), 129.8 (CH=), 129.9 (CH=), 130.0 (CH=), 132.6 (C=), 132.7 (C=), 132.8 (C=), 135.6 (CH=), 135.7 (CH=), 144.8 (C=).

1-*O*-*tert*-Butyldiphenylsilyl-5-deoxy-2,3-*O*-isopropylidene-5-methyl-D-arabinitol (35). To a cooled solution (0 °C) of the already prepared thioether-tosyl compound (3.6 g, 6.2 mmol) in THF (15.5 mL), $LiAlH_4$ (352.8 mg, 9.3 mmol) was added portion-wise. The solution was stirred at reflux for 2h. Then, drops of water were carefully added and a white precipitate appeared which was filtered and clean three times with ethyl acetate. The organic phase was dried over $MgSO_4$ and evaporated to dryness. The crude product was purified by SiO_2-column chromatography (EtOAc/PE = 1/3) yielding the corresponding compounds as colorless oils. Yield: 619 mg (24%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.10 (s, 9H, CH_3, ^{t}Bu, OTBDPS), 1.23 (d, 3H, CH_3, $^3J_{H-H}$ =6.4 Hz), 1.41 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 2.79 (b, 1H, OH), 3.78-3.86 (m, 3H, CH_2-OTBDPS, C*H*CHO), 3.90-3.94 (m, 1H, CH-O), 4.03-4.07 (m, 1H, C*H*CH_2OTBDPS), 7.40-7.48 (m, 6H, CH=), 7.70-7.73 (m, 4H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=19.0 (CH_3), 19.2 (C, ^{t}Bu, OTBDPS), 26.8 (CH_3, ^{t}Bu, OTBDPS), 27.0 (CH_3), 27.1 (CH_3), 64.8 (CH_2-OTBDPS), 67.9 (CH-O), 78.8 (*C*HCH_2OTBDPS), 82.6 (*C*HCHO), 108.8 (CMe_2), 127.8 (CH=), 127.9 (CH=), 129.9 (CH=), 130.0 (CH=), 132.6 (C=), 135.7 (CH=).

3.2.4.19. Preparation of compound 36

1-*O*-*tert*-Butyldiphenylsilyl-5-deoxy-2,3-*O*-isopropylidene-4-*O*-mesyl-5-methyl-D-arabinitol. To a cooled solution (0 °C) of compound **36** (1.1 g, 2.6 mmol) in DCM (18 mL), triethylamine (1.1 mL, 7.8 mmol) and methanesulfonyl chloride (0.65 mL, 7.8 mmol) in DCM was slowly added. After stirring 1h, water was added and the reaction mixture was extracted with DCM (x3). The organic layer was dried over $MgSO_4$, evaporated to dryness and purified by SiO_2-flash chromatography (EEtOAc/EP = 1/4) to produce the product as a colorless oil. Yield: 1.3 g (100%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.07 (s, 9H, CH_3, ^{t}Bu, OTBDPS), 1.41 (d, 3H, CH_3, $^3J_{H-H}$ =6.4 Hz), 1.42 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 2.97 (s, 3H, CH_3, OMs), 3.74 (dd, 1H, CH_2-OTBDPS, $^2J_{H-H}$ =11.2 Hz, $^3J_{H-H}$ =4.0 Hz), 3.88 (dd, 1H, CH_2-OTBDPS, $^2J_{H-}$

$_H$ =11.6 Hz, $^3J_{H-H}$ =4.0 Hz), 4.04-4.08 (m, 1H, C*H*CH_2OTBDPS), 4.19 (dd, 1H, C*H*CHOMs, $^2J_{H-H}$ =7.6 Hz, $^3J_{H-H}$ =4.0 Hz), 4.87-4.93 (m, 1H, CH-OMs), 7.37-7.44 (m, 6H, CH=), 7.67-7.71 (m, 4H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=17.3 (CH_3), 19.2 (C, ^{t}Bu, OTBDPS), 26.8 (CH_3, ^{t}Bu, OTBDPS), 27.1 (CH_3), 27.2 (CH_3), 64.0 (CH_2-OTBDPS), 77.9 (CH-OMs), 78.2 (*C*HCH_2OTBDPS), 78.6 (*C*HCHOMs), 109.7 (CMe_2), 127.8 (CH=), 129.8 (CH=), 129.9 (CH=), 132.9 (C=), 135.6 (CH=).

1-*O*-*tert*-Butyldiphenylsilyl-4,5-dideoxy-2,3-*O*-isopropylidene-5-methyl-4-phenylthio-D-xylitol. A suspension of NaH (494 mg, 12.4 mmol), washed three times in hexane, in THF (15 mL) was cooled to -15 °C, and thiophenol (0.64 mL) in THF (2 mL), at -15 °C was added. After 10 min a solution of compound 1-*O*-tert-Butyldiphenylsilyl-5-deoxy-2,3-O-isopropylidene-4-O-mesyl-5-methyl-D-arabinitol (1.3 g, 2.6 mmol) in THF (3 ml) was added at -15 °C. After stirring at -15 °C for 10 min, the reaction was warmed to 67 °C and stirred for 36h. The reaction was quenched with water and extracted with dichloromethane for three times. The extract was dried over anhydrous magnesium sulfate and concentrated. The residue was purified by SiO_2-column chromatography (EtOAc /PE = 0.5/9.5) to produce the desired product. Yield: 604 mg (46%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.11 (s, 9H, CH_3, ^{t}Bu, OTBDPS), 1.45 (d, 3H, CH_3, $^3J_{H-H}$ =7.2 Hz), 1.47 (s, 3H, CH_3), 1.55 (s, 3H, CH_3), 3.46-3.49 (m, 1H, CH-S), 3.86-3.93 (m, 2H, CH_2-OTBDPS), 4.21-4.24 (m, 1H, C*H*CHS), 4.27-4.31 (m, 1H, C*H*CH_2OTBDPS), 7.25-7.50 (m, 11H, CH=), 7.71-7.76 (m, 4H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=18.9 (CH_3), 19.3 (C, ^{t}Bu, OTBDPS), 26.9 (CH_3, ^{t}Bu, OTBDPS), 27.2 (CH_3), 27.3 (CH_3), 45.2 (CH-S), 64.9 (CH_2-OTBDPS), 78.6 (*C*HCH_2OTBDPS), 80.8 (*C*HCHS), 109.4 (CMe_2), 126.7 (CH=), 127.8 (CH=), 128.9 (CH=), 129.0 (CH=), 129.8 (CH=), 131.5 (CH=), 132.9 (C=), 133.1 (C=), 135.1 (C=), 135.7 (CH=).

4,5-Dideoxy-2,3-*O*-isopropylidene-5-methyl-4-phenylthio-D-xylitol (36). Treatment of silylated compound (604.0 mg, 1.2 mmol) in THF (5 mL) with a THF solution of TBAF (1 M, 1.8 mL, 1.8 mmol) provided deprotected compound **36**. The reaction was quenched with water and extracted with ethyl acetate (x3). The organic layer was dried over anhydrous $MgS0_4$, filtered and concentrated. The crude product was subjected to SiO_2-column chromatography (EtOAc /PE = 1/5) yielding pure thioether-hydroxy compound **36** as yellowish oil. Yield: 252 mg (76%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.42 (d, 3H, CH_3, $^3J_{H-H}$ =7.6 Hz), 1.44 (s, 3H, CH_3), 1.49 (s, 3H, CH_3), 2.51 (b, 1H, OH), 3.41-3.48 (m, 1H, CH-S), 3.68-3.74 (m, 1H, CH_2-O), 3.87-3.90 (m, 1H, CH_2-O), 4.04 (dd, 1H, C*H*CH-S, $^2J_{H-H}$ =8.0 Hz, $^3J_{H-H}$ =4.0 Hz), 4.17-4.21 (m, 1H, C*H*CH_2O), 7.24-7.34 (m, 3H, CH=), 7.45 (d, 2H, CH=, $^3J_{H-H}$ =7.2 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=17.5 (CH_3), 27.1 (CH_3), 27.2 (CH_3), 44.5 (CH-S), 63.1 (CH_2-O), 78.5 (*C*HCH_2O), 79.2 (*C*HCHS), 109.2 (CMe_2), 127.1 (CH=), 129.0 (CH=), 131.7 (CH=), 134.5 (C=).

3.2.4.20. General procedure for the asymmetric hydrogenation

In a typical run, the corresponding Rh-catalyst precursor (0.01 mmol), the corresponding ligand (0.011 mmol) and the corresponding substrate (1 mmol) were dissolved in dichloromethane (6 mL). The reaction mixture was then placed in the

autoclave and the autoclave was purged five times with hydrogen gas. Then, it was pressurized to the desired pressure. After the desired reaction time, the autoclave was depressurized and the solvent evaporated off. The residue was dissolved in Et_2O (2 mL) and filtered through a short celite plug. The enantiomeric excess was determined by chiral GC and conversions were determined by GC and confirmed by ^1H NMR. The enantiomeric excesses of hydrogenated products were determined using the conditions previously described.[26]

3.2.5. Acknowledgements

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UNIVERSITAT ROVIRA I VIRGILI
SCREENING OF MODULAR AND READILY AVAILABLE LIGAND LIBRARIES FOR C-X (X=H, C, N AND O) BOND FORMING REACTIONS. THE USE OF DFT STUDIES FOR CATALYSTS OPTIMIZATION
Jèssica Margalef Pallarès

3.3. Ir-Catalyzed asymmetric hydrogenation of olefins using phosphite-thioether/selenoether ligands

Jèssica Margalef, Carlota Borràs, Sabina Alegre, Oscar Pàmies and Montserrat Diéguez in manuscript to be submitted

***Abstract**: Phosphite-thioether/selenoether ligands, prepared from readily available L-(+)-tartaric acid and D-(+)-mannitol, were applied to the Ir-catalyzed asymmetric hydrogenation of minimally functionalized olefins. The catalytic results indicated that enantioselectivity is highly affected by the ligand parameters as well as the substrate. Although moderate enantioselectivities were achieved in model (E)- and (Z)-trisubstituted olefins, high ee's were achieved for other substrates containing poorly coordinative groups (i.e. alkenylboronic esters, α,β-unsaturated amides and esters, …) and also for more challenging disubstituted olefins. It should be noted the excellent enantioselectivities (up to 99% ee) achieved in the hydrogenation of β-aryl enamides, which gave access to 2-aminotetralines and 3-aminochromanes in almost enantiopure form.*

3.3.1. Introduction

The preparation of enantiomerically pure compounds is of great importance in several important fields such as pharmaceuticals, agrochemicals, fine chemicals and natural product chemistry. In this context, metal-catalyzed asymmetric transformations have become one of the most powerful tools for their preparation.[1] Among them, the asymmetric hydrogenation of prochiral olefins and ketones has turned out to be one of the most reliable catalytic methods for the synthesis of optically active compounds, mainly because of its perfect atom economy, operational simplicity and high efficiency.[1,2] This field has been dominated by the Rh/Ru-catalyzed asymmetric reduction of substrates with a good coordinating group close to the C=X bond, which its chelating ability is key in transferring the chiral information from the catalysts to the product. Today, a remarkable range of ligands is being applied to transform a broad range of functionalized substrates. Instead, the hydrogenation of cyclic β-aryl-*N*-acetyl enamides is still a challenge.[3] In contrast to Rh/Ru-hydrogenation, the asymmetric reduction of olefins that do not have an adjacent coordinative polar group - minimally functionalized olefins - is still challenging and requires more sophisticated ligand design.[4]

In 1977, Crabtree described the first metal-catalyst ($[Ir(cod)(Py)(PCy_3)]PF_6$ (cod = 1,5-cyclooctadiene)) able to hydrogenate a wide range of minimally functionalized olefins.[5] On the basis of this pioneering work, Pfaltz and coworkers used phosphine-oxazoline PHOX ligands (Figure 3.3.1) to design $[Ir(PHOX)(cod)]PF_6$, a chiral analogue of Crabtree's catalyst.[6] Although this catalyst hydrogenated prochiral olefins highly enantioselectively, it was unstable to the reaction conditions. Pfaltz and co-workers overcame this limitation by changing the hexafluorophosphate anion to $[(3,5\text{-}(CF_3)_2\text{-}C_6H_3)_4B]^-$ ($[BAr_F]^-$).[7] Since then, most of the research in this field has been dedicated to develop new Ir-catalysts modified with heterodonor P,N-ligands. The first successful P,N ligands contained a phosphine or phosphinite moiety as P-donor group and either an oxazoline,[8] oxazole,[9] thiazole[10] or

pyridine[11] as N-donor group (Figure 3.3.1). However, these iridium-phosphine/phosphinite,N catalysts were still highly substrate-dependent and the development of efficient chiral ligands that tolerate a broader range of substrates remained a challenge. Our group was able to overcome this drawback by incorporating a flexible biaryl-phosphite moiety in the ligand design.[12] Thus, the presence of biaryl-phosphite moieties in these P,N-ligands provided greater substrate versatility than previous Ir-phosphine/phosphinite,N catalyst systems. Although the number of substrates that can be successfully reduced increased, there is still important substrate classes that give unsatisfactory results with known catalysts. More research is therefore needed to find more versatile ligand systems that can be synthesized on an efficient and modular synthetic route using simple starting materials.

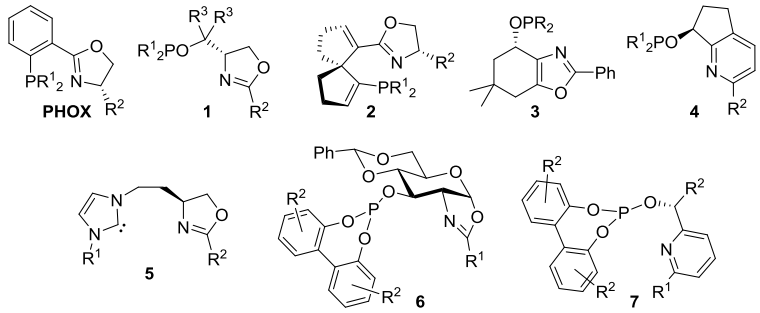


Figure 3.3.1. Representative P,N-ligands developed for this process.

In this respect, research focus on the possibility of changing the nature of the N-donor atom in these heterodonor ligands has not been contemplated until very recently. [13,14] Thus, we have recently developed novel phosphite-thioether ligands for the successful asymmetric Ir-catalyzed hydrogenation of model trisubstituted and terminal minimally functionalized olefins.[13a,b] Despite this success, a systematic study of the possibilities offered by phosphite-thioether as new ligands for this process is still needed. For this purpose in this chapter we report the synthesis and application of new Ir-complexes modified with a chiral phosphite-thioether/selenoether ligand library derived from L-(+)-tartaric acid and D-(+)-mannitol (**L1**-**L23a**-**g**; Figure 3.3.2). The modular ligand design allowed us to systematically investigate the effect of varying: (a) the electronic and steric properties of the thioether group (ligands **L1**-**L7**); (b) the substituents and the introduction of a new stereogenic centre in the alkyl backbone chain next to the phosphite moiety (ligands **L1**, **L7**, **L8**-**L9** and **L11**-**L18**); (c) the substituents and the introduction of a new stereogenic centre in the alkyl backbone chain next to the thioether moiety (ligands **L1**, **L2**, **L10** and **L19**); (d) the substituents and configurations in the biaryl phosphite moiety (**a**-**g**); and (e) the replacement of the thioether group by a selenoether moiety. By carefully selecting these elements, we achieved good activities and moderate-to-high enantioselectivities in the asymmetric hydrogenation of a wide range of minimally functionalized olefins.

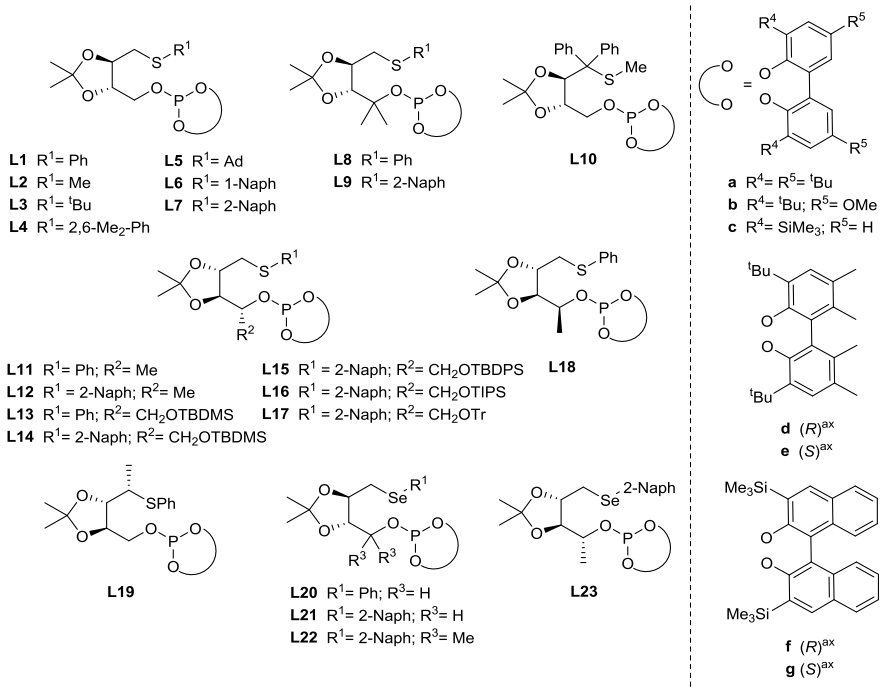
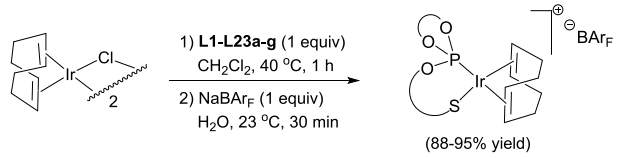


Figure 3.3.2. Phosphite-thioether/selenoether ligand library **L1**-**L23a**-**g**.

3.3.2. Results and discussion

3.3.2.1. Synthesis of Ir(I) catalyst precursors

The Ir-catalyst precursors were prepared in a two-step, one-pot procedure (Scheme 3.3.1). First, $[Ir(\mu\text{-}Cl)(cod)]_2$ reacts with one equivalent of the appropriate ligand. Then, Cl^- /BAr_F^- counterion exchange was achieved by reaction with $NaBAr_F$ in the presence of water. The iridium catalyst precursors were isolated in pure form as air-stable orange/red solids in excellent yields (89-95%) after simple extraction work-up. No further purification was needed. The HRMS-ESI spectra were in agreement with the assigned structures, displaying the heaviest ions at m/z which correspond to the loss of the BAr_F anion from the molecular species. The ^1H, ^{13}C, and ^{31}P NMR spectra show the expected pattern for these C_1-complexes. The VT-NMR in CD_2Cl_2 (+35 to -85 °C) spectra show that only one isomer is present in solution. In all cases, one singlet in the ^{31}P-{^1H} NMR spectra was observed.



Scheme 3.3.1. Synthesis of catalyst precursors [Ir(cod)(**L1**-**L23a**-**g**)]BAr_F.

3.3.2.2. Asymmetric hydrogenation of trisubstituted olefins

In a first set of experiments we studied the potential of phosphite-thioether/selenoether ligands **L1**-**L23a**-**g** in the Ir-catalyzed hydrogenation of (*E*)-2-(4-methoxyphenyl)-2-butene **S1**. Substrate **S1** was chosen as a model for the hydrogenation of trisubstituted olefins because it has been reduced with a wide range of ligands, which enable the efficiency of the various ligand systems to be compared directly.[4h] The results, which are summarized in Table 3.3.1, indicate that enantioselectivities are highly affected by a subtle balance of the thioether/selenoether substituent, the substituents/configurations at the alkyl backbone chain next to the phosphite and next to the thioether/selenoether moieties as well as the configuration of the biaryl phosphite moiety. Both enantiomers of the hydrogenated product could be therefore achieved in moderate enantioselectivities (up to 73%) by correctly choosing the ligand parameters.

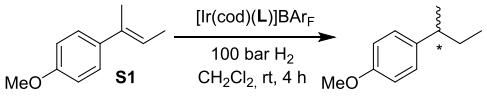
The effect of the substituents and configuration of the biaryl phosphite moiety was mainly investigated using **L1a**-**g** (Table 3.3.1, entries 1-7). The results indicated that the substituents at the biaryl phosphite moiety have little impact on enantioselectivity and that the presence of chiral biaryl moieties is necessary to achieve the highest level of enantioselectivity. The latter indicates that the chiral ligand backbone is not able to control the tropoisomerism of the biphenyl phosphite moiety. This is the case for all ligands except for those containing a substituent at the carbon next to the phosphite moiety with an (*R*)-configuration (ligands **L11**-**L17**). The presence of an (*R*)-configurated stereogenic carbon therefore facilitates the control of the tropoisomerism of the biphenyl phosphite group (i.e. entries 31 vs 32 and 33). Nevertheless, we can conclude that in general ligands containing an (*R*)-biaryl phosphite moiety provide the highest enantioselectivities.

The results using ligands **L1**-**L7** indicate that enantioselectivity is affected by the thioether substituent. The presence of aromatic rather than alkyl substituent has a positive effect on enantioselectivity (i.e. entry 4 vs 9, 12 and 17).

The results using ligands **L8** and **L9** indicated that the presence of two methyl substituents attached to the carbon close to the phosphite moiety had a negative effect on enantioselectivity (Table 3.3.1; entries 24, 25 vs 4 and 5), which contrast with the positive effect observed in the Rh-catalyzed hydrogenation of functionalized olefins (Chapter 3.2). Similarly, the use of ligands **L10** and **L19**, with substituents attached to the carbon next to the thioether group, also had a detrimental effect on enantioselectivity (entries 29, 30 and 46-48). Nevertheless, the results using ligands **L11** and **L18** indicated that there is a cooperative effect between the configuration of the carbon adjacent to the phosphite group and the ligand backbone that results in a matched combination for ligands **L18** (i.e. entry 44 vs 32).

Finally, comparing the results using phosphite-selenoether ligands **L20**-**L23** with their thioether counterparts indicate that the catalytic performance is hardly affected by the replacement of the sulfur by selenium (entries 49-57).

Table 3.3.1. Selected results for the Ir-catalyzed hydrogenation of **S1** using the phosphite-thioether ligand library **L1**-**L23a**-**g**[a]



Entry	Ligand	% Conv[b]	% ee[b]	Entry	Ligand	% Conv[b]	% ee[b]
1	**L1a**	99	6 (*R*)	30	**L10g**	100	10 (*R*)
2	**L1b**	100	5 (*R*)	31	**L11a**	100	58 (*S*)
3	**L1c**	100	6 (*R*)	32	**L11f**	100	58 (*R*)
4	**L1d**	100	66 (*R*)	33	**L11g**	100	44 (*S*)
5	**L1e**	99	29 (*S*)	34	**L12a**	100	53 (*S*)
6	**L1f**	92	53 (*R*)	35	**L12f**	100	61 (*R*)
7	**L1g**	88	40 (*S*)	36	**L12g**	100	41 (*S*)
8	**L2a**	100	19 (*R*)	37	**L13a**	100	72 (*S*)
9	**L2f**	100	38 (*R*)	38	**L14a**	100	73 (*S*)
10	**L2g**	100	45 (*S*)	39	**L14g**	100	44 (*S*)
11	**L3a**	100	0	40	**L15g**	100	60 (*S*)
12	**L3d**	100	33 (*R*)	41	**L16g**	100	50 (*S*)
13	**L3e**	99	10 (*S*)	42	**L17g**	100	64 (*S*)
14	**L4a**	95	25 (*S*)	43	**L18a**	96	47 (*R*)
15	**L4d**	100	69 (*R*)	44	**L18f**	95	70 (*R*)
16	**L4e**	100	70 (*S*)	45	**L18g**	92	47 (*S*)
17	**L5d**	100	21 (*R*)	46	**L19a**	100	3 (*S*)
18	**L5e**	99	11 (*R*)	47	**L19f**	100	24 (*R*)
19	**L6d**	100	50 (*R*)	48	**L19g**	100	28 (*S*)
20	**L6e**	98	31 (*S*)	49	**L20a**	100	5 (*S*)
21	**L7d**	100	60 (*R*)	50	**L20f**	100	52 (*R*)
22	**L7e**	100	35 (*S*)	51	**L20g**	100	47 (*S*)
23	**L8a**	100	25 (*S*)	52	**L21f**	100	44 (*R*)
24	**L8d**	100	27 (*R*)	53	**L21g**	100	43 (*S*)
25	**L8e**	100	36 (*S*)	54	**L22f**	100	37 (*R*)
26	**L9a**	98	19 (*S*)	55	**L22g**	100	51 (*S*)
27	**L9f**	100	32 (*R*)	56	**L23f**	100	70 (*R*)
28	**L9g**	100	31 (*R*)	57	**L23g**	100	7 (*R*)
29	**L10f**	100	13 (*R*)	58[c]	**L14a**	98	72 (*S*)

[a] Reactions carried out using 0.5 mmol of **S1** and 2 mol% of Ir-catalyst precursor.[b] Conversion and enantiomeric excesses determined by chiral GC. [c] Reaction carried out at 0.5 mol% of Ir-catalyst precursor.

We next studied the asymmetric hydrogenation of other (*E*)- and (*Z*)-trisubstituted olefins (**S2**-**S16**), including examples containing neighboring polar groups, by using ligands **L1**-**L23a**-**g**. The most noteworthy results are shown in Figure 3.3.3. We found that the correct choice of the ligand parameters is crucial to achieve the highest levels of enantioselectivity. We initially studied the hydrogenation of (*E*)-substrates **S2**-**S3**, related to **S1,** that differ in the substituents in both the aryl ring and the substituents *trans* to the aryl group. Enantioselectivities followed the same trends as those observed for substrate **S1**. Enantioselectivities were thus best with ligand **L14a** (ee's up to 76%).

In order to assess the potential of the new ligand library for (*Z*)-trisubstituted isomers, which are usually hydrogenated less enantioselectively than the corresponding (*E*)-isomers,

we chose substrates **S4**-**S5**. The reduction of the model (*Z*)-substrate **S4** proceeded with moderate enantiocontrol and followed a different trend than that observed with *E*-substrates **S1**-**S3**. The enantioselectivities were therefore best with ligands **L17g** (ee's up to 56%). The reduction of dehydronaphthalene **S5**, which has also a (*Z*)-configuration, proceeded with lower enantiocontrol (ee's up to 21%).

We next studied the reduction of a range of trisubstituted olefins containing several types of neighboring poorly coordinative groups **S6**-**S16** (Figure 3.3.3). The hydrogenation of this type of substrates is especially relevant, because they allow for further functionalization and could therefore led to important intermediates for the synthesis of more complex chiral molecules. We found that enantioselectivities up to 85% could be achieved in the reduction of allylic alcohol **S6** using Ir-**L23g** catalytic system.

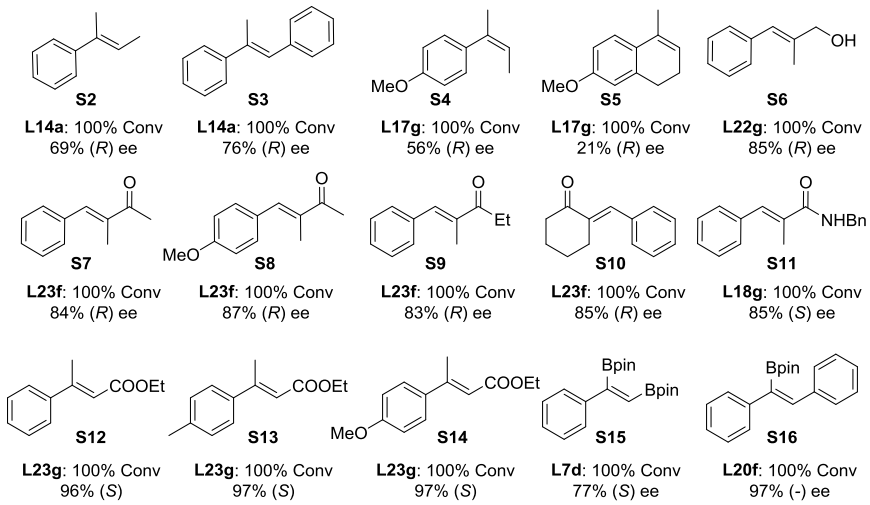


Figure 3.3.3. Selected results for the hydrogenation of trisubstituted olefins **S2**-**S16** using [Ir(cod)(**L1**-**L23a**-**g**)]BAr_F catalyst precursors. Reaction conditions: 2 mol % catalyst precursor, CH_2Cl_2 as solvent, 100 bar H_2, 4 h.

A range of α,β-unsaturated ketones (**S7**-**S10**) were also hydrogenated in good enantioselectivities (ee's ranging from 83 % to 87 %). It should be noted that ee's are highly independent of the nature of the alkyl substituent and the electronic nature of the substrate phenyl ring. This represents an important entry point to the synthesis of ketones with stereogenic centers in the α-position to the carbonyl group. Despite this, they have been less studied than other trisubstituted olefins with neighboring polar groups.[15] α,β-Unsaturated amide **S11** represents another challenging substrate that has been overlooked, despite amides with stereogenic centers in the α-position are present in several natural products and that the amide group can be easily transformed into other useful compounds (i.e. amines)[16]. Interestingly the reduction of **S11** proceeded with similar good enantiocontrol than α,β-unsaturated ketones, albeit the highest ee (up to 85%) was achieved with Ir-**L18g** catalyst. We were pleased to find out that a range of α,β-unsaturated esters (**S12**-**S14**) could be efficiently hydrogenated (ee's ranging from 96% to 97%).[17] These results are noteworthy because the resulting chiral carboxylic ester derivatives are present

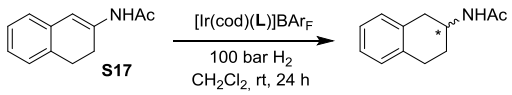
in many relevant products. Finally, we evaluated our new ligand library in the reduction of alkenylboronic esters **S15** and **S16**.[18] Full conversions and good-to-high enantioselectivities (up to 97% ee) were achieved. The hydrogenation of alkenylboronic esters provides easy access to chiral borane compounds, which are valuable organic intermediates since the C-B bond can be easily transformed to C-O, C-N and C-C bonds with retention of the chirality.

Encouraged by these results, we made the decision to explore the hydrogenation functionalized cyclic β-aryl-*N*-acetyl enamides **S17**-**S23**. The hydrogenation of this substrate class is still a challenge because in contrast to the parent α-enamides most of the Rh- and Ru-catalysts provided low enantiomeric excesses; nevertheless, some successful protocols are available.[19] Thus, for instance, Tang and coworkers have designed a new P-stereogenic diphosphine ligand with deep chiral pockets that has shown high efficiency in the Rh-catalyzed hydrogenation of this substrate class (ee's ranging from 94% to 98%). As a model, we choose *N*-(3,4-dihydronaphthalen-2-yl)acetamide **S17** to assess the potential of the new ligand library. The results are summarized in Table 3.3.2.

The results indicate that although enantioselectivities are controlled by the same ligand parameters than the hydrogenation of **S1**, their effect on enantioselectivity is different. Thus, for example and in contrast to the reduction of **S1**, ligands containing an (*S*)-biaryl phosphite moiety provide the highest enantioselectivities (i.e. entries 6 and 7). The highest enantioselectivity of the ligand series (ee's up to 97%) was achieved using ligand **L14g**.

We next studied the asymmetric hydrogenation of other β-aryl-*N*-acetyl enamides **S18**-**S23** using [Ir(cod)(**L14g**)]BAr_F as catalyst precursor (Figure 3.3.4). Advantageous, the results indicate that both activities and enantioselectivities are relatively insensitive to the different substitution pattern in the aryl ring. Ir-**L14g** catalytic system is therefore able to give access to a range of 2-aminotetralines and 3-aminochromanes in excellent enantioselectivities (ee's ranging from 95% to 99%). This is of great importance because both moieties are present in numerous biologically active natural products and therapeutic agents, such as Rotigotine[20] and Robalzotan (NAD-299)[21].

Table 3.3.2. Selected results for the Ir-catalyzed hydrogenation of **S17** using the phosphite-thioether ligand library **L1**-**L23a**-**g**.[a]



Entry	Ligand	% Conv[b]	% ee[b]	Entry	Ligand	% Conv[b]	% ee[b]
1	**L1a**	100	11 (*S*)	12	**L14g**	100	97 (*R*)
2	**L1f**	100	34 (*R*)	13	**L16g**	100	91 (*R*)
3	**L1g**	100	59 (*S*)	14	**L17g**	100	94 (*R*)
4	**L8d**	100	45 (*R*)	15	**L18f**	95	80 (*S*)
5	**L8e**	100	83 (*S*)	16	**L18g**	92	6 (*R*)
6	**L9f**	100	77 (*S*)	17	**L20f**	100	44 (*R*)
7	**L9g**	100	90 (*R*)	18	**L20g**	100	64 (*S*)
8	**L10f**	100	33 (*S*)	19	**L22f**	100	77 (*S*)
9	**L10g**	100	84 (*R*)	20	**L22g**	100	81 (*R*)
10	**L11f**	100	50 (*S*)	21	**L23f**	100	35 (*S*)
11	**L11g**	100	90 (*R*)	22	**L23g**	100	91 (*R*)

[a] Reactions carried out using 0.5 mmol of **S17** and 1 mol% of Ir-catalyst precursor. [b] Conversion determined by ^{1}H NMR. [c] Enantiomeric excesses determined by chiral HPLC.

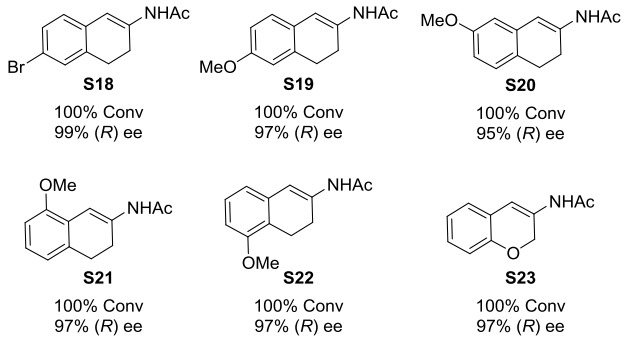
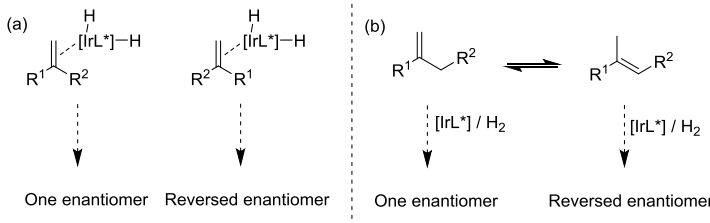


Figure 3.3.4. Asymmetric hydrogenation of β-aryl-*N*-acetyl enamides using [Ir(cod)(**L14g**)]BAr$_F$ as catalyst precursor. Reaction conditions: 1 mol % catalyst precursor, CH_2Cl_2 as solvent, 100 bar H_2, 24 h.

3.3.2.3. Asymmetric hydrogenation of disubstituted olefins

To further study the potential of the phosphite-thioether/selenoether ligand library **L1**-**L23a**-**g**, we also screened it in the Ir-catalyzed hydrogenation of terminal olefins.[4e,h] Enantioselectivity is more difficult to control in these substrates than in trisubstituted olefins. There are two main reasons for this: a) the two substituents in the substrate can easily exchange positions in the chiral environment formed by the catalysts, thus reversing the face selectivity (Scheme 3.3.2(a)); and b) the terminal double bond can isomerize to form the more stable internal (*E*)-alkene, which usually leads to the predominant formation of the opposite enantiomer of the hydrogenated product (Scheme 3.3.2(b)). Few known catalytic systems provide high enantioselectivities for these substrates, and those that do are usually limited in substrate scope. In contrast to the hydrogenation of trisubstituted

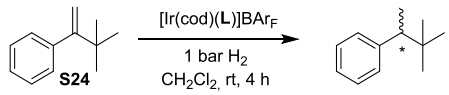
olefins, the enantioselectivity in the reduction of terminal alkenes is highly pressure dependent. Therefore, hydrogenation at an atmospheric pressure of H_2 gave, in general, significantly higher ee values than at higher pressures.[8a,g]



Scheme 3.3.2. Proposed reasons for the low enantioselectivities associated with the hydrogenation of terminal olefins.

As a model substrate, we have chosen the 3,3-dimethyl-2-phenyl-1-butene **S24** to assess the potential of the new ligand library. The results are summarized in Table 3.3.3. In contrast to the reduction of the trisubstituted olefins, the results indicated that the use of selenoether ligands led to lower ee's than the thioether counterparts (i.e. entries 27-28 vs 54-55) and that enantioselectivities are mainly controlled by the configuration of the biaryl phosphite moiety. Ligands containing enantiopure (*R*)- and (*S*)-biaryl phosphite moieties led to excellent enantioselectivities. In addition, the configuration of the biaryl phosphite controls the sense of enantioselectivity, which gives access to both enantiomers of the hydrogenated products (up to 99%; i.e. entries 22 and 29). In summary, we have been therefore able to fine-tune the ligand parameters to produce both enantiomers of the hydrogenated product in high activities and enantioselectivities (ee's up to 99%) at low hydrogen pressures (1 bar).

Table 3.3.3. Selected results for the Ir-catalyzed hydrogenation of **S24** using the phosphite-thioether ligand library **L1**-**L23a**-**g**.[a]



Entry	Ligand	% Conv[b]	% ee[b]	Entry	Ligand	% Conv[b]	% ee[b]
1	**L1a**	94	14 (*S*)	30	**L10g**	100	33 (*R*)
2	**L1b**	97	16 (*S*)	31	**L11a**	100	92 (*R*)
3	**L1c**	75	19 (*S*)	32	**L11f**	92	90 (*S*)
4	**L1d**	100	94 (*S*)	33	**L11g**	100	93 (*R*)
5	**L1e**	65	93 (*R*)	34	**L12a**	100	81 (*R*)
6	**L1f**	100	95 (*S*)	35	**L12f**	100	93 (*S*)
7	**L1g**	60	88 (*R*)	36	**L12g**	100	93 (*R*)
8	**L2a**	100	20 (*S*)	37	**L13a**	100	96 (*R*)
9	**L2f**	100	95 (*S*)	38	**L14a**	100	93 (*R*)
10	**L2g**	100	96 (*R*)	39	**L14g**	100	93 (*R*)
11	**L3a**	55	23 (*S*)	40	**L15g**	100	93 (*R*)
12	**L3d**	100	90 (*S*)	41	**L16g**	100	95 (*R*)
13	**L3e**	96	88 (*R*)	42	**L17g**	100	91 (*R*)
14	**L4a**	100	39 (*R*)	43	**L18a**	100	84 (*S*)
15	**L4d**	100	92 (*S*)	44	**L18f**	100	92 (*S*)
16	**L4e**	100	93 (*R*)	45	**L18g**	100	86 (*R*)
17	**L5d**	100	90 (*S*)	46	**L19a**	100	30 (*R*)
18	**L5e**	100	89 (*R*)	47	**L19f**	100	90 (*S*)
19	**L6d**	100	91 (*S*)	48	**L19g**	100	98 (*R*)
20	**L6e**	100	93 (*R*)	49	**L20a**	100	15 (*R*)
21	**L7d**	100	96 (*S*)	50	**L20f**	100	91 (*S*)
22	**L7e**	100	98 (*R*)	51	**L20g**	100	85 (*R*)
23	**L8a**	100	6 (*R*)	52	**L21f**	100	82 (*S*)
24	**L8d**	100	94 (*S*)	53	**L21g**	100	62 (*R*)
25	**L8e**	100	96 (*R*)	54	**L22f**	100	53 (*S*)
26	**L9a**	100	10 (*R*)	55	**L22g**	100	45 (*R*)
27	**L9f**	100	95 (*S*)	56	**L23f**	100	36 (*S*)
28	**L9g**	100	94 (*R*)	57	**L23g**	100	66 (*R*)
29	**L10f**	100	99 (*S*)	58[c]	**L7e**	91	98 (*R*)

[a] Reactions carried out using 0.5 mmol of **S24** and 2 mol% of Ir-catalyst precursor.[b] Conversion and enantiomeric excesses determined by chiral GC. [c] Reaction carried out at 0.5 mol% of Ir-catalyst precursor.

We next studied the asymmetric hydrogenation of other terminal disubstituted olefins (Figure 3.3.5). The results with several α-alkylstyrenes bearing decreasingly sterically demanding alkyl substituents (**S24**-**S26**) indicated that enantioselectivity is affected by the nature of the alkyl chain (ee's ranging from 68% to 99%). A plausible explanation is the competition between direct hydrogenation and isomerization. This is supported by the fact that the hydrogenation of substrate **S24** bearing a *tert*-butyl group, which cannot isomerize, provides the highest enantioselectivity. We then studied several α-*tert*-butylstyrene type substrates (**S27**-**S32**) to evaluate how the electronic and steric properties of the aryl group of the substrate affected the catalytic performance. The results indicated that the presence of *ortho* substituents at the aryl ring (**S32**) led to low activities.

Nevertheless, enantioselectivity is hardly unaffected by the substitution pattern and the electronic nature of the substituents (ee's ranging 97% to 99%). Interestingly, the excellent activities and enantioselectivities were maintained when introducing a heteroaromatic group instead of the phenyl moiety. This is of great importance because *N*-containing heterocycles are present in many relevant compounds such us pharmaceuticals and natural products. Finally, we tested our ligands in the hydrogenation of the aryl-boronic ester **S34**. This substrate type, which is very appealing due to the importance of chiral organoboranes, is still a challenge.[12c,18a] We were pleased to find that our ligands are able to hydrogenate this substrate with enantioselectivities as high as 86%.

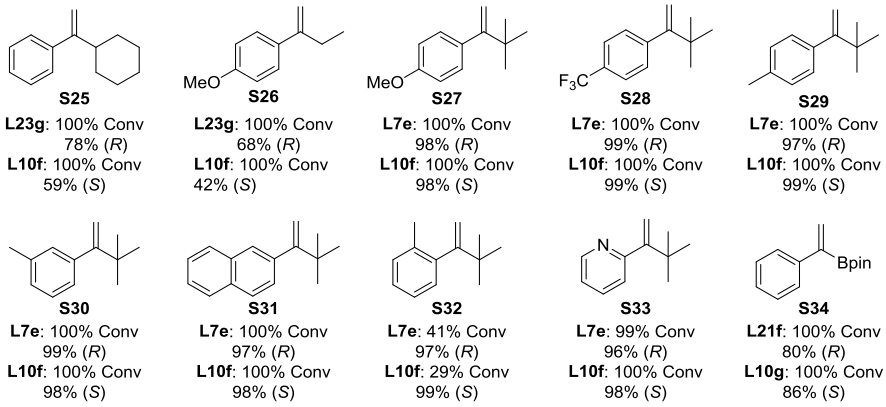


Figure 3.3.5. Selected results for the hydrogenation of disubstituted olefins **S25**-**S34** using [Ir(cod)(**L1**-**L23a**-**g**)]BAr_F catalyst precursors. Reaction conditions: 2 mol % catalyst precursor, CH_2Cl_2 as solvent, 1 bar H_2, 4 h.

3.3.3. Conclusions

We have successfully applied new Ir(I)-catalyst precursors ([Ir(cod)(**L1**-**L23a**-**g**)]BAr_F), modified with easily accessible phosphite-thioether/selenoether ligands, for the asymmetric hydrogenation of minimally functionalized alkenes. The catalytic results indicated that enantioselectivity is highly affected by the ligand parameters as well as the substrate. Although moderate enantioselectivities were achieved in model (*E*)- and (*Z*)-trisubstituted olefins, high ee's were achieved for other relevant substrates containing poorly coordinative groups (i.e. alkenylboronic esters, α,β-unsaturated amides and esters, …) and also for more challenging disubstituted olefins. On the other hand, it should be noted the excellent enantioselectivities achieved in the hydrogenation of β-aryl enamides, which gave access to 2-aminotetralines and 3-aminochromanes in enantioselectivities up to 99%.

3.3.4. Experimental section

3.3.4.1. General considerations

All reactions were carried out using standard Schlenk techniques under an argon atmosphere. Commercial chemicals were used as received. Solvents were dried by means of standard procedures and stored under argon. ^{1}H, $^{13}C\{^{1}H\}$ and $^{31}P\{^{1}H\}$ NMR spectra were

recorded using a Varian Mercury-400 MHz spectrometer. Chemical shifts are relative to that of $SiMe_4$ (^1H and $^{13}C\{^1H\}$) as an internal standard or H_3PO_4 ($^{31}P\{^1H\}$) as an external standard. ^1H and ^{13}C assignments were made on the basis of ^1H-^1H gCOSY and ^1H-^{13}C gHSQC experiments. The synthesis of ligands **L1**-**L23a**-**g** is described in Chapter 3.2.

3.3.4.2. Typical procedure for the preparation of [Ir(cod)(L1-L23a-g)]BAr_F

The corresponding ligand (0.037 mmol) was dissolved in CH_2Cl_2 (2.5 mL) and [Ir(μ-Cl)(cod)]$_2$ (12.5 mg, 0.0185 mmol) was added. The reaction was refluxed at 50 °C for 1 hour. After 5 min at room temperature, $NaBAr_F$ (38.6 mg, 0.041 mmol) and water (2.5 mL) were added and the reaction mixture was stirred vigorously for 30 min at room temperature. The phases were separated and the aqueous phase was extracted twice with CH_2Cl_2. The combined organic phases were dried with $MgSO_4$, filtered through a plug of celite and the solvent was evaporated to give the products as red-orange solids.

[Ir(cod)(L1a)]BAr_F. Yield: 62 mg (91%). ^{31}P NMR (400 MHz, $CDCl_3$) δ: 101.8 (s). ^1H NMR ($CDCl_3$), δ: 1.25 (s, 3H, CH_3), 1.28 (s, 3H, CH_3), 1.36 (s, 9H, CH_3, ^{t}Bu), 1.37 (s, 9H, CH_3, ^{t}Bu), 1.54 (s, 9H, CH_3, ^{t}Bu), 1.71 (s, 9H, CH_3, ^{t}Bu), 1.86 (m, 2H, CH_2, COD), 2.01 (m, 2H, CH_2, COD), 2.1 (m, 4H, $2CH_2$, COD), 3.74-3.79 (m, 2H, CH_2-O), 3.80-3.83 (m, 1H, CH_2-S), 3.96(m, 1H, CH=, COD), 4.11 (m, 1H, C*H*CH_2S), 4.13-4.17 (m, 1H, CH_2-S), 4.24-4.28 (m, 1H, C*H*CH_2O), 4.46(m, 1H, CH=, COD), 4.57 (m, 1H, CH=, COD), 4.71 (m, 1H, CH=, COD), 7.18-7.70 (m, 21H, CH=). ^{13}C NMR ($CDCl_3$), δ: 26.4 (CH_3), 27.8(CH_2, COD), 29.7(CH_2, COD), 31.4 (CH_3, ^{t}Bu), 31.5 (CH_3, ^{t}Bu), 31.7 (CH_2, COD), 32.0 (CH_3, ^{t}Bu), 33.8 (CH_2, COD), 35.0 (C, ^{t}Bu), 35.1 (C, ^{t}Bu), 35.6 (C, ^{t}Bu), 47.8 (CH_2-S), 69.1 (CH_2-O), 69.3 (CH=, COD), 74.1 (CH=, COD), 77.4 (*C*HCH_2S), 79.6 (*C*HCH_2S), 102.8 (CH=, COD), 104.1 (CH=, COD), 110.7 (CMe_2), 117.6-149.9 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^1J_{C\text{-}B}$= 49 Hz). MS HR-ESI [found 993.4238, $C_{49}H_{69}IrO_5PS$ $(M)^+$ requires 993.4233].

[Ir(cod)(L1b)]BAr_F. Yield: 62 mg (93%). ^{31}P NMR (400 MHz, $CDCl_3$) δ: 102.6 (s). ^1H NMR ($CDCl_3$), δ: 1.25 (s, 3H, CH_3), 1.28 (s, 3H, CH_3), 1.50 (s, 9H, CH_3, ^{t}Bu), 1.67 (s, 9H, CH_3, ^{t}Bu), 1.85 (m, 2H, CH_2, COD), 2.01 (m, 2H, CH_2, COD), 2.15 (m, 4H, $2CH_2$, COD), 3.82 (s, 6H, O-CH_3), 3.87-3.95 (m, 4H, CH_2-S, CH_2-O, CH= COD), 4.11 (m, 2H, CH_2-S, C*H*CH_2S), 4.25 (m, 1H, C*H*CH_2O), 4.44 (m, 1H, CH=, COD), 4.54 (m, 1H, CH=, COD), 4.71 (m, 1H, CH=, COD), 6.70-7.69 (m, 21H, CH=). ^{13}C NMR ($CDCl_3$), δ: 26.4 (CH_3), 27.5 (CH_2, COD), 29.5 (CH_2, COD), 29.6 (CH_2, COD), 31.1 (CH_3, ^{t}Bu), 31.6 (CH_3, ^{t}Bu), 33.7 (CH_2, COD), 35.4 (C, ^{t}Bu), 47.7 (CH_2-S), 55.5 (O-CH_3), 55.6 (O-CH_3), 68.2 (CH=, COD), 69.2 (d, CH_2-O, $J_{C\text{-}P}$= 14.7 Hz), 73.8 (CH=, COD), 77.1 (*C*HCH_2S), 79.4 (*C*HCH_2O), 102.7 (CH=, COD), 103.9 (CH=, COD), 110.4 (CMe_2), 113.7-157.2 (aromatic carbons), 161.5 (q, C-B, BAr_F, $^1J_{C\text{-}B}$= 49 Hz). MS HR-ESI [found 941.3195, $C_{43}H_{57}IrO_7PS$ $(M)^+$ requires 941.3192].

[Ir(cod)(L1c)]BAr_F. Yield: 59 mg (90%). ^{31}P NMR (400 MHz, $CDCl_3$) δ: 102.6 (s). ^1H NMR ($CDCl_3$), δ: 0.40 (s, 9H, CH_3, $SiMe_3$), 0.56 (s, 9H, CH_3, $SiMe_3$),1.19 (s, 3H, CH_3), 1.21 (s, 3H, CH_3), 1.73 (m, 2H, CH_2, COD), 1.98 (m, 2H, CH_2, COD), 2.15 (m, 4H, $2CH_2$, COD), 3.63-3.85 (m, 3H, CH_2-O, CH_2-S), 3.95-4.06 (m, 3H, CH_2-S, CH= COD, C*H*CH_2S), 4.06 (m, 1H, C*H*CH_2O), 4.38 (m, 2H, CH=, COD), 4.74 (m, 1H, CH=, COD), 7.18-7.63 (m, 23H, CH=). ^{13}C NMR ($CDCl_3$), δ: 0.0 ($SiMe_3$), 0.9 ($SiMe_3$), 26.3 (CH_3), 26.4 (CH_3), 26.9 (CH_2, COD), 29.6 (CH_2, COD), 30.1 (CH_2, COD), 34.3 (CH_2, COD), 48.0 (CH_2-S), 69.1 (d, CH_2-O, $J_{C\text{-}P}$= 13 Hz), 69.7 (CH=, COD), 74.2

(CH=, COD), 77.1 (*C*HCH$_2$S), 79.5 (*C*HCH$_2$O), 103.4 (CH=, COD), 110.5 (CMe$_2$), 117.3-152.4 (aromatic carbons) , 161. 6 (q, C-B, BAr$_F$, $^1J_{C\text{-}B}$= 50 Hz). MS HR-ESI [found 913.2524, $C_{39}H_{53}IrO_5PSSi_2$ $(M)^+$ requires 913.2519].

[Ir(cod)(L1d)]BAr$_F$. Yield: 60 mg (90%). ^{31}P NMR (400 MHz, CDCl$_3$) δ: 94.0 (s). ^{1}H NMR (CDCl$_3$), δ: 1.21 (s, 3H, CH$_3$), 1.22 (s, 3H, CH$_3$), 1.36 (s, 9H, CH$_3$, ^{t}Bu), 1.54 (m, 2H, CH$_2$, COD), 1.63 (s, 9H, CH$_3$, ^{t}Bu), 1.70 (s, 3H, CH$_3$), 1.74 (s, 3H, CH$_3$), 1.91 (m, 4H, CH$_2$, COD), 2.07 (m, 2H, CH$_2$, COD), 2.19 (s, 3H, CH$_3$), 2.20 (s, 3H, CH$_3$), 3.44 (m, 1H, CH$_2$-O), 3.50 (m, 1H, CH$_2$-S), 3.62 (m, 1H, CH=, COD), 3.81-3.87 (m, 1H, C*H*CH$_2$S), 3.94 (m, 1H, CH$_2$-O), 4.01 (m, 1H, CH$_2$-S), 4.17 (m, 1H, C*H*CH$_2$O), 4.49 (m, 3H, CH=, COD), 7.17-7.63 (m, 19H, CH=). ^{13}C NMR (CDCl$_3$), δ: 16.3 (CH$_3$), 16.6 (CH$_3$), 20.3 (CH$_3$), 20.4 (CH$_3$), 26.4 (CH$_3$), 28.1 (CH$_2$, COD), 29.0 (CH$_2$, COD), 29.6 (CH$_2$, COD), 31.3 (CH$_3$, ^{t}Bu), 32.2 (CH$_3$, ^{t}Bu), 33.0 (CH$_2$, COD), 34.7 (C, ^{t}Bu), 35.1 (C, ^{t}Bu), 46.3(CH$_2$-S), 68.0 (CH=, COD), 68.3 (CH$_2$-O), 74.7 (CH=, COD), 77.2 (*C*HCH$_2$S), 79.9 (*C*HCH$_2$O), 101.2 (CH=, COD), 101.4 (CH=, COD), 111.3 (CMe$_2$), 117.4-144.6 (aromatic carbons), 161.5 (q, C-B, BAr$_F$, $^1J_{C\text{-}B}$= 49 Hz). MS HR-ESI [found 937.3611, $C_{45}H_{61}IrO_5PS$ $(M)^+$ requires 937.3607].

[Ir(cod)(L1e)]BAr$_F$. Yield: 63 mg (95%). ^{31}P NMR (400 MHz, CDCl$_3$) δ: 96.7 (s). ^{1}H NMR (CDCl$_3$), δ: 1.20 (s, 3H, CH$_3$), 1.22 (s, 3H, CH$_3$), 1.38 (s, 9H, CH$_3$, ^{t}Bu), 1.52 (m, 2H, CH$_2$, COD), 1.64 (s, 9H, CH$_3$, ^{t}Bu), 1.72 (s, 3H, CH$_3$), 1.74 (s, 3H, CH$_3$), 1.84-2.12 (m, 6H, CH$_2$, COD), 2.21 (s, 3H, CH$_3$), 2.19 (s, 3H, CH$_3$), 3.33 (m, 1H, CH=, COD), 3.55 (m, 2H, CH$_2$-O), 3.71 (m, 1H, CH$_2$-S), 4.06 (m, 2H, CH$_2$-S, C*H*CH$_2$S), 4.18 (m, 1H, C*H*CH$_2$O), 4.26 (m, 1H, CH=, COD), 4.47 (m, 1H, CH=, COD), 4.60 (m, 1H, CH=, COD), 7.18-7.63 (m, 19H, CH=). ^{13}C NMR (CDCl$_3$), δ: 16.4 (CH$_3$), 16.6 (CH$_3$), 20.3 (CH$_3$), 20.4 (CH$_3$), 26.4 (CH$_3$), 26.9 (CH$_2$, COD), 30.0 (CH$_2$, COD), 30.9 (CH$_2$, COD), 31.4 (CH$_3$, ^{t}Bu), 32.1 (CH$_3$, ^{t}Bu), 34.2 (CH$_2$, COD), 34.7 (C, ^{t}Bu), 48.3 (CH$_2$-S), 67.6 (CH=, COD), 69.1 (CH$_2$-O), 74.9 (CH=, COD), 77.6 (*C*HCH$_2$S), 79.5 (*C*HCH$_2$O), 102.6 (CH=, COD), 103.1 (CH=, COD), 110.2 (CMe$_2$), 117.3-143.8 (aromatic carbons), 161.7 (q, C-B, BAr$_F$, $^1J_{C\text{-}B}$= 49 Hz). MS HR-ESI [found 937.3609, $C_{45}H_{61}IrO_5PS$ $(M)^+$ requires 937.3607].

[Ir(cod)(L1f)]BAr$_F$. Yield: 63 mg (91%).^{31}P NMR (161.9 MHz, CDCl$_3$): δ=100.6 (s). ^{1}H NMR (400 MHz, CDCl$_3$): δ=0.55 (s, 9H, CH$_3$, SiMe$_3$), 0.73 (s, 9H, CH$_3$, SiMe$_3$), 1.28 (s, 6H, CH$_3$), 1.88 (b, 3H, CH$_2$, cod), 1.94-2.22 (m, 5H, CH$_2$, cod), 3.55-3.58 (m, 1H, CH$_2$-O), 3.68 (b, 1H, CH$_2$-O), 3.74 (d, 1H, CH$_2$-S, $^2J_{H\text{-}H}$ =10.8 Hz), 3.85-3.90 (m, 1H, CH$_2$-S), 3.98-4.10 (m, 2H, CH= cod, C*H*CH$_2$O), 4.34 (b, 1H, CH=, cod), 4.59 (b, 1H, C*H*CH$_2$S), 4.65 (b, 1H, CH=, cod), 4.77 (b, 1H, CH=, cod), 7.04-8.20 (m, 27H, CH= aromatic). ^{13}C NMR (100.6 MHz, CDCl$_3$): δ=0.0 (CH$_3$, SiMe$_3$), 1.2 (CH$_3$, SiMe$_3$), 26.4 (CH$_3$), 26.6 (CH$_3$), 27.9 (CH$_2$, cod), 29.4 (CH$_2$, cod), 31.7 (d, CH$_2$, cod, $J_{C\text{-}P}$ =3.1 Hz), 33.5 (d, CH$_2$, cod, $J_{C\text{-}P}$ =5.3 Hz), 46.4 (CH$_2$-S), 68.9 (d, CH$_2$-O, $^2J_{C\text{-}P}$ =13.8 Hz), 69.3 (CH=, cod), 76.4 (*C*HCH$_2$S), 77.2 (*C*HCH$_2$O), 79.11 (CH=, cod), 102.0 (d, CH=, cod, $J_{C\text{-}P}$ =16.1 Hz), 106.3 (d, CH=, cod, $J_{C\text{-}P}$ =16.1 Hz), 112.0 (CMe$_2$), 117.4-150.9 (aromatic carbons), 161.7 (q, C-B, BAr$_F$, $^1J_{C\text{-}B}$ =49.7 Hz). MS HR-ESI [found 1113.2835, $C_{47}H_{57}IrO_5PSSi_2$ $(M)^+$ requires 1013.2832].

[Ir(cod)(L1g)]BAr$_F$. Yield: 64 mg (93%).^{31}P NMR (161.9 MHz, CDCl$_3$): δ=103.7 (s). ^{1}H NMR (400 MHz, CDCl$_3$): δ=0.54 (s, 9H, CH$_3$, SiMe$_3$), 0.78 (s, 9H, CH$_3$, SiMe$_3$), 1.25 (s, 6H, CH$_3$), 1.61-1.72 (m, 3H, CH$_2$, cod), 1.97-2.24 (m, 5H, CH$_2$, cod), 3.50-3.64 (m, 3H, CH$_2$-O, CH= cod), 3.83 (d, 1H, CH$_2$-S, $^2J_{H\text{-}H}$ =14.0 Hz), 4.05-4.11 (m, 2H, CH$_2$-S, C*H*CH$_2$O), 4.23 (pt, 1H, C*H*CH$_2$S, $^3J_{H\text{-}H}$ =7.6 Hz), 4.42-4.50 (m, 2H, CH=, cod), 4.81 (b, 1H, CH=, cod), 7.07-8.21 (m, 27H, CH=

aromatic). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=0.0 (CH_3, $SiMe_3$), 1.4 (CH_3, $SiMe_3$), 26.4 (CH_3), 26.5 (CH_3), 29.7 (CH_2, cod), 30.1 (CH_2, cod), 30.8 (CH_2, cod), 35.1 (CH_2, cod), 48.8 (CH_2-S), 68.6 (CH=, cod), 69.1 (d, CH_2-O, $^2J_{C\text{-}P}$ =14.5 Hz), 75.4 (CH=, cod), 77.5 (*C*HCH$_2$O), 79.8 (*C*HCH$_2$S), 103.2 (d, CH=, cod, $J_{C\text{-}P}$ =17.5 Hz), 104.4 (d, CH=, cod, $J_{C\text{-}P}$ =14.5 Hz), 110.4 (CMe_2), 117.4-150.3 (aromatic carbons), 161.6 (q, C-B, BAr_F, $^1J_{C\text{-}B}$ =49.7 Hz). MS HR-ESI [found 1113.2834, $C_{47}H_{57}IrO_5PSSi_2$ $(M)^+$ requires 1013.2832].

[Ir(cod)(L2a)]BAr$_F$. Yield: 59 mg (90%). ^{31}P NMR (400 MHz, $CDCl_3$) δ: 103.4 (s). ^{1}H NMR ($CDCl_3$), δ: 1.24 (s, 6H, CH_3), 1.33 (s, 18H, CH_3, ^{t}Bu), 1.48 (s, 9H, CH_3, ^{t}Bu), 1.57 (s, 9H, CH_3, ^{t}Bu), 2.11 (m, 8H, CH_2, COD), 2.5 (s, 3H, CH_3), 3.43 (m, 2H, CH_2-S), 3.84-3.99 (m, 2H, CH_2-O, C*H*CH$_2$S), 4.15 (m, 1H, CH=, COD), 4.22 (m, 1H, C*H*CH$_2$O), 4.52 (m, 1H, CH=, COD), 5.09 (m, 2H, CH=, COD), 7.15-7.69 (m, 16H, CH=).^{13}C NMR ($CDCl_3$), δ: 19.7 (CH_3), 26.6 (CH_3), 26.7 (CH_3), 28.7 (CH_2, COD), 29.8 (CH_2, COD), 30.3 (CH_2, COD), 31.5 (CH_3, ^{t}Bu), 31.6 (CH_3, ^{t}Bu), 31.8 (CH_3, ^{t}Bu), 33.2 (CH_2, COD), 35.0 (C, ^{t}Bu), 35.6 (C, ^{t}Bu), 35.7 (C, ^{t}Bu), 44.5 (CH_2-S), 68.1 (d, CH_2-O, $J_{C\text{-}P}$= 12.4 Hz), 72.2 (CH=, COD), 74.8 (CH=, COD), 77.1 (*C*HCH$_2$S), 77.4 (*C*HCH$_2$O), 99.8 (CH=, COD), 100.9 (CH=, COD), 110.9 (CMe_2), 117.6- 149.6 (aromatic carbons), 161.8 (q, C-B, BAr_F, $^1J_{C\text{-}B}$= 49 Hz). MS HR-ESI [found 931.4078, $C_{44}H_{67}IrO_5PS$ $(M)^+$ requires 931.4076].

[Ir(cod)(L2f)]BAr$_F$. Yield: 62 mg (92%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ=101.6 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.49 (s, 9H, CH_3, $SiMe_3$), 0.63 (s, 9H, CH_3, $SiMe_3$), 1.26 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 1.31 (s, 3H, CH_3), 1.91 (b, 2H, CH_2, cod), 2.07 (b, 3H, CH_2, cod), 2.21 (b, 3H, CH_2, cod), 3.24-3.31 (m, 2H, CH_2-S), 3.63 (b, 2H, CH_2-O, CH= cod), 3.99 (dd, 1H, CH_2-O, $^2J_{H\text{-}H}$ =21.2 Hz, $^3J_{H\text{-}H}$ =10.4 Hz), 4.08 (b, 1H, C*H*CH$_2$O), 4.22 (b, 1H, C*H*CH$_2$S), 4.67 (b, 1H, CH=, cod), 5.21 (b, 1H, CH=, cod), 5.27 (b, 1H, CH=, cod), 6.99-8.16 (m, 22H, CH= aromatic). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=0.0 (CH_3, $SiMe_3$), 1.0 (CH_3, $SiMe_3$), 26.4 (CH_3), 26.6 (CH_3), 29.0 (CH_2, cod), 29.4 (CH_2, cod), 30.0 (CH_3), 32.1 (CH_2, cod), 32.7 (CH_2, cod), 44.8 (CH_2-S), 68.9 (d, CH_2-O, $^2J_{C\text{-}P}$ =13.8 Hz), 70.0 (CH=, cod), 77.2 (*C*HCH$_2$O), 78.1 (CH=, cod), 78.8 (*C*HCH$_2$S), 100.5 (d, CH=, cod, $J_{C\text{-}P}$ =17.6 Hz), 104.0 (d, CH=, cod, $J_{C\text{-}P}$ =16.8 Hz), 110.0 (CMe_2), 117.4-150.8 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^1J_{C\text{-}B}$ =49.7 Hz). MS HR-ESI [found 951.2679, $C_{42}H_{55}IrO_5PSSi_2$ $(M)^+$ requires 951.2676].

[Ir(cod)(L2g)]BAr$_F$. Yield: 64 mg (95%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ=105.3 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.48 (s, 9H, CH_3, $SiMe_3$), 0.65 (s, 9H, CH_3, $SiMe_3$), 1.25 (s, 3H, CH_3), 1.29 (s, 3H, CH_3), 1.31 (s, 3H, CH_3), 1.72 (b, 2H, CH_2, cod), 1.87 (b, 1H, CH_2, cod), 2.11 (b, 3H, CH_2, cod), 2.31 (b, 2H, CH_2, cod), 3.43-3.62 (m, 4H, CH_2-S, CH_2-O, CH= cod), 3.73-3.80 (m, 1H, CH_2-O), 3.98-4.04 (m, 1H, C*H*CH$_2$O), 4.16 (pt, 1H, C*H*CH$_2$S, $^3J_{H\text{-}H}$ =7.2 Hz), 4.48 (b, 1H, CH=, cod), 5.01 (b, 1H, CH=, cod), 5.27 (b, 1H, CH=, cod), 7.02-8.18 (m, 22H, CH= aromatic). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=0.1 (CH_3, $SiMe_3$), 1.2 (CH_3, $SiMe_3$), 26.5 (CH_3), 27.2 (CH_3), 29.7 (CH_2, cod), 30.0 (CH_2, cod), 31.3 (CH_3), 34.5 (CH_2, cod), 45.7 (CH_2-S), 68.2 (d, CH_2-O, $^2J_{C\text{-}P}$ =12.7 Hz), 70.5 (CH=, cod), 76.2 (CH=, cod), 77.6 (*C*HCH$_2$O), 78.2 (*C*HCH$_2$S), 100.2 (d, CH=, cod, $J_{C\text{-}P}$ =18.1 Hz), 101.8 (d, CH=, cod, $J_{C\text{-}P}$ =13.8 Hz), 110.5 (CMe_2), 117.5-148.8 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^1J_{C\text{-}B}$ =50.4 Hz). MS HR-ESI [found 951.2678, $C_{42}H_{55}IrO_5PSSi_2$ $(M)^+$ requires 951.2676].

[Ir(cod)(L3a)]BAr$_F$. Yield: 63 mg (93%).^{31}P NMR (400 MHz, $CDCl_3$) δ: 104.1 (s). ^{1}H NMR ($CDCl_3$), δ: 1.29 (s, 6H, CH_3), 1.35 (s, 9H, CH_3, ^{t}Bu), 1.36 (s, 9H, CH_3, ^{t}Bu), 1.44 (s, 9H, CH_3,

^{t}Bu), 1.63 (s, 18H, CH_3, ^{t}Bu), 1.73 (m, 2H, CH_2, COD), 1.86 (m, 2H, CH_2, COD), 2.01 (m, 2H, $2CH_2$, COD), 2.25 (m, 2H, $2CH_2$, COD), 3.27 (dd, 1H, $^2J_{H\text{-}H}$= 15.2 Hz, $^3J_{H\text{-}H}$= 3.2 Hz, CH_2-S), 3.50-3.56 (m, 1H, CH_2-O), 3.62 (dd, 1H, $^2J_{H\text{-}H}$= 12.4 Hz, $^3J_{H\text{-}H}$= 2.8 Hz, CH_2-S), 3.80-3.86 (m, 1H, CH_2-O), 3.96-4.02 (m, 1H, C*H*CH_2O), 4.04-4.07 (m, 1H, C*H*CH_2S), 4.56(m, 2H, CH=, COD), 5.56 (m, 1H, CH=, COD), 6.02 (m, 1H, CH=, COD), 7.18-7.72 (m, 16H, CH=). ^{13}C NMR ($CDCl_3$), δ: 26.6 (CH_3), 27.7(CH_2, COD), 29.9(CH_2, COD), 30.9 (CH_3, ^{t}Bu), 31.1 (CH_3, ^{t}Bu), 31.5 (CH_3, ^{t}Bu), 32.5 (CH_2, COD), 33.9 (CH_2, COD), 35.0 (C, ^{t}Bu), 35.5 (C, ^{t}Bu), 35.7 (C, ^{t}Bu), 36.3 (CH_2-S), 66.5 (CH_2-O), 71.1 (CH=, COD), 71.7 (CH=, COD), 76.3 (*C*HCH_2S), 78.0 (*C*HCH_2O), 93.9 (CH=, COD), 98.6 (CH=, COD), 110.4 (CMe_2), 117.6-149.8 (aromatic carbons), 161.6 (q, C-B, BAr_F, $^1J_{C\text{-}B}$= 49 Hz). MS HR-ESI [found 973.4549, $C_{47}H_{33}IrO_5PS$ $(M)^+$ requires 973.4546].

[Ir(cod)(L3d)]BAr_F. Yield: 62 mg (94%). ^{31}P NMR (400 MHz, $CDCl_3$) δ: 103.2(s), 92.7 (s). ^{1}H NMR ($CDCl_3$), δ: 1.04 (m, 2H, CH_2, COD), 1.19 (s, 3H, CH_3), 1.25 (s, 3H, CH_3), 1.30 (s, 9H, CH_3, ^{t}Bu), 1.39 (s, 9H, CH_3, ^{t}Bu), 1.52 (s, 9H, CH_3, ^{t}Bu), 1.64 (s, 3H, CH_3), 1.75 (s, 3H, CH_3), 1.84-2.02 (m, 4H, CH_2, COD), 2.03 (s, 3H, CH_3), 2.17 (s, 3H, CH_3), 2.43 (m, 2H, CH_2, COD), 2.89-3.07 (m, 2H, CH_2-O, CH_2-S), 3.25-3.30 (m, 1H, CH_2-S), 3.51 (m, 1H, C*H*CH_2S), 3.64 (m, 1H, C*H*CH_2O), 3.84-3.91 (m, 1H, CH_2-O), 4.32 (m, 2H, CH=, COD), 5.20 (m, 1H, CH=, COD), 5.96 (m, 1H, CH=, COD), 7.14-7.60 (m, 14H, CH=). ^{13}C NMR ($CDCl_3$), δ: 16.4 (CH_3), 16.6 (CH_3), 20.3 (CH_3), 26.3 (CH_3), 28.0 (CH_2, COD), 30.2 (CH_2, COD), 30.9 (CH_3, ^{t}Bu), 31.7 (CH_3, ^{t}Bu), 32.2 (CH_3, ^{t}Bu), 32.5 (CH_2, COD), 32.9 (C, ^{t}Bu), 34.9 (C, ^{t}Bu), 34.2 (CH_2, COD), 34.4 (CH_2, COD), 35.9 (CH_2-S), 67.6 (CH_2-O), 70.6 (CH=, COD), 72.8 (CH=, COD), 77.1 (*C*HCH_2S), 84.6 (*C*HCH_2O), 91.4 (CH=, COD), 99.3 (CH=, COD), 110.3 (CMe_2), 117.4-143.4 (aromatic carbons), 161.5 (q, C-B, BAr_F, $^1J_{C\text{-}B}$= 49 Hz). MS HR-ESI [found 917.3922, $C_{43}H_{65}IrO_5PSSi_2$ $(M)^+$ requires 917.3920].

[Ir(cod)(L3e)]BAr_F. Yield: 60 mg (92%). ^{31}P NMR (400 MHz, $CDCl_3$) δ: 98.6 (s). ^{1}H NMR ($CDCl_3$), δ: 1.30 (s, 6H, CH_3), 1.37 (s, 9H, CH_3, ^{t}Bu), 1.50 (s, 9H, CH_3, ^{t}Bu), 1.61 (s, 9H, CH_3, ^{t}Bu), 1.75 (s, 3H, CH_3), 1.81 (s, 3H, CH_3), 2.04 (m, 6H, CH_2, COD), 2.25 (s, 3H, CH_3), 2.26 (s, 3H, CH_3), 2.4 (m, 2H, CH_2, COD), 3.25 (m, 1H, CH_2-S), 3.31 (m, 1H, CH_2-O), 3.65-3.70 (m, 1H, CH_2-S), 3.75-3.81 (m, 1H, CH_2-O), 3.98 (m, 1H, C*H*CH_2S), 4.08-4.11 (m, 2H, C*H*CH_2O, CH= COD), 4.43 (m, 1H, CH=, COD), 5.36 (m, 1H, CH=, COD), 6.09 (m, 1H, CH=, COD), 7.19-7.69 (m, 14H, CH=). ^{13}C NMR ($CDCl_3$), δ: 16.6 (CH_3), 16.8 (CH_3), 20.3 (CH_3), 20.5 (CH_3), 26.6 (CH_3), 26.7 (CH_3), 28.8 (CH_2, COD), 29.9 (CH_2, COD), 31.1 (CH_3, ^{t}Bu), 31.4 (CH_3, ^{t}Bu), 32.2 (CH_3, ^{t}Bu), 33.8 (CH_2, COD), 34.8 (C, ^{t}Bu), 35.1 (C, ^{t}Bu), 35.1 (CH_2, COD), 36.8 (CH_2-S), 66.2 (CH_2-O), 69.8 (CH=, COD), 72.8 (CH=, COD), 76.1 (*C*HCH_2S), 77.5 (*C*HCH_2O), 99.4 (CH=, COD), 99.5 (CH=, COD), 110.5 (CMe_2), 117.6-144.5 (aromatic carbons), 161.6 (q, C-B, BAr_F, $^1J_{C\text{-}B}$= 49 Hz). MS HR-ESI [found 917.3924, $C_{43}H_{65}IrO_5PSSi_2$ $(M)^+$ requires 917.3920].

[Ir(cod)(L4a)]BAr_F. Yield: 64 mg (92%). ^{31}P NMR (400 MHz, $CDCl_3$) δ: 101.5 (s). ^{1}H NMR ($CDCl_3$), δ: 1.22 (s, 3H, CH_3), 1.24 (s, 3H, CH_3), 1.33 (s, 18H, CH_3, ^{t}Bu), 1.54 (s, 9H, CH_3, ^{t}Bu), 1.62 (s, 9H, CH_3, ^{t}Bu), 1.78 (m, 2H, CH_2, COD), 1.96 (m, 2H, CH_2, COD), 2.11 (m, 2H, CH_2, COD), 2.22 (m, 2H, CH_2, COD), 2.60 (s, 3H, CH_3), 2.68 (s, 3H, CH_3), 3.43 (m, 1H, CH_2-S), 3.69-3.76 (m, 1H, CH_2-O), 3.95-4.06 (m, 4H, CH_2-S, CH= COD, C*H*CH_2S), 4.12-4.16 (m, 4H, CH COD, CH_2-O, C*H*CH_2O), 4.43 (m, 1H, CH=, COD), 4.57 (m, 1H, CH=, COD), 7.18-7.68 (m, 19H, CH=). ^{13}C NMR ($CDCl_3$), δ: 22.7 (CH_3), 23.0 (CH_3), 26.9 (CH_3), 30.7 (CH_2, COD), 30.9 (CH_2, COD), 31.4 (CH_3, ^{t}Bu), 31.5 (CH_3, ^{t}Bu), 31.9 (CH_3, ^{t}Bu), 34.6 (CH_2, COD), 35.0 (C, ^{t}Bu), 35.1 (C, ^{t}Bu), 35.5 (C, ^{t}Bu), 35.6 (C, ^{t}Bu), 47.3 (CH_2-S), 69.3 (CH_2-O), 77.4 (*C*HCH_2S), 80.2 (*C*HCH_2O), 103.7 (CH=,

COD), 110.9 (CMe_2), 117.6-149.9 (aromatic carbons), 161.5 (q, C-B, BAr_F, $^1J_{C-B}$= 49 Hz). MS HR-ESI [found 1021.4547, $C_{51}H_{73}IrO_5PS$ $(M)^+$ requires 1021.4546].

[Ir(cod)(L4d)]BAr_F. Yield: 63 mg (93%). ^{31}P NMR (400 MHz, $CDCl_3$) δ: 93.6 (s). ^1H NMR ($CDCl_3$), δ: 1.18 (s, 3H, CH_3), 1.22 (s, 3H, CH_3), 1.36 (s, 9H, CH_3, ^{t}Bu), 1.56 (m, 2H, CH_2, COD), 1.61 (s, 9H, CH_3, ^{t}Bu), 1.71 (s, 3H, CH_3), 1.73 (s, 3H, CH_3), 1.87 (m, 2H, CH_2, COD), 2.08 (m, 2H, CH_2, COD), 2.18 (s, 3H, CH_3), 2.19 (s, 3H, CH_3), 2.25 (m, 2H, CH_2, COD), 2.53 (s, 3H, CH_3), 2.69 (s, 3H, CH_3), 3.02 (m, 1H, CH_2-S), 3.32 (m, 1H, CH=, COD), 3.46-3.49 (m, 1H, CH_2-O), 3.79-3.82 (m, 1H, C*H*CH_2S), 3.87-3.92 (m, 1H, CH=, COD), 3.95 (m, 1H, CH_2-S), 4.00-4.08 (m, 2H, C*H*CH_2O, CH_2-O), 4.49 (m, 1H, CH=, COD), 4.76 (m, 1H, CH=, COD), 7.08-7.63 (m, 17H, CH=). ^{13}C NMR ($CDCl_3$), δ: 16.5 (CH_3), 16.8 (CH_3), 20.5 (CH_3), 20.6 (CH_3), 22.7 (CH_3), 22.9 (CH_3), 26.8 ($2CH_3$), 27.0 (CH_2, COD), 29.9 (CH_2, COD), 31.5 (CH_3, ^{t}Bu), 31.6 (CH_2, COD), 32.6 (CH_3, ^{t}Bu), 34.3 (CH_2, COD), 34.9 (C, ^{t}Bu), 35.2 (C, ^{t}Bu), 44.5 (CH_2-S), 65.4 (CH=, COD), 69.4 (CH_2-O), 74.6 (CH=, COD), 77.4 (*C*HCH_2S), 79.6 (*C*HCH_2O), 103.1 (CH=, COD), 105.6 (CH=, COD), 112.1 (CMe_2), 117.6-145.0 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^1J_{C-B}$= 49 Hz). MS HR-ESI [found 965.3922, $C_{47}H_{65}IrO_5PS$ $(M)^+$ requires 965.3920].

[Ir(cod)(L4e)]BAr_F. Yield: 60 mg (89%). ^{31}P NMR (400 MHz, $CDCl_3$) δ: 97.0 (s). ^1H NMR ($CDCl_3$), δ: 0.85 (s, 3H, CH_3), 0.90 (s, 3H, CH_3), 0.90 (m, 2H, CH_2, COD),1.07 (s, 9H, CH_3, ^{t}Bu), 1.26 (s, 9H, CH_3, ^{t}Bu), 1.36 (m, 2H, CH_2, COD),1.39 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 1.57 (m, 2H, CH_2, COD), 1.73 (m, 2H, CH_2, COD), 1.74 (s, 3H, CH_3), 1.87 (s, 3H, CH_3), 2.20 (s, 3H, CH_3), 2.21 (s, 3H, CH_3), 3.15 (m, 1H, CH_2-S), 3.18 (m, 1H, CH=, COD), 3.22 (m, 2H, CH_2-O), 3.47-3.52 (m, 1H, CH_2-S), 3.66 (m, 1H, CH=, COD), 3.68 (m, 1H, C*H*CH_2S), 3.76-3.78 (m, 1H, C*H*CH_2O), 4.00 (m, 1H, CH=, COD), 4.18 (m, 1H, CH=, COD), 6.78-7.30 (m, 17H, CH=). ^{13}C NMR ($CDCl_3$), δ: 16.4 (CH_3), 16.6 (CH_3), 20.3 (CH_3), 20.4 (CH_3), 22.4 (CH_3), 22.5 (CH_3), 26.4 (CH_3), 26.8 (CH_2, COD), 29.6 (CH_2, COD), 30.7 (CH_2, COD), 31.5 (CH_3, ^{t}Bu), 32.6 (CH_3, ^{t}Bu), 34.4 (CH_2, COD), 34.7 (C, ^{t}Bu), 48.0 (CH_2-S), 67.9 (CH=, COD), 68.6 (CH_2-O), 74.7 (CH=, COD), 77.5 (*C*HCH_2S), 80.4 (*C*HCH_2O), 101.8 (CH=, COD), 103.3 (CH=, COD), 110.3 (CMe_2), 117.4-140.7 (aromatic carbons), 161.6 (q, C-B, BAr_F, $^1J_{C-B}$= 49 Hz). MS HR-ESI [found 965.3921, $C_{47}H_{65}IrO_5PS$ $(M)^+$ requires 965.3920].

[Ir(cod)(L5d)]BAr_F. Yield: 64 mg (93%). ^{31}P NMR (400 MHz, $CDCl_3$) δ: 92.9 (s). ^1H NMR ($CDCl_3$), δ: 1.30 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 1.40 (s, 9H, CH_3, ^{t}Bu), 1.46 (m, 2H, CH_2, COD), 1.64 (s, 9H, CH_3, ^{t}Bu), 1.70 (m, 2H, CH_2, COD), 1.74 (s, 3H, CH_3), 1.77-181 (m, 6H, CH_2, Ad), 1.85 (s, 3H, CH_3), 2.00-2.06 (m, 6H, CH_2, Ad), 2.16 (m, 2H, CH_2, COD), 2.23 (m, 3H, CH, Ad), 2.27 (s, 6H, CH_3), 2.36 (m, 2H, CH_2, COD), 2.50 (m, 1H, CH_2-S), 3.05 (m, 1H, CH_2-O), 3.22 (m, 1H, CH_2-S), 3.6 (m, 1H, C*H*CH_2S), 3.73 (m, 1H, C*H*CH_2O), 3.98 (m, 1H, CH_2-O), 4.38 (m, 2H, CH=, COD), 5.45 (m, 1H, CH=, COD), 6.12 (m, 1H, CH=, COD), 7.17-7.71 (m, 14H, CH=). ^{13}C NMR ($CDCl_3$), δ: 16.4 (CH_3), 16.6 (CH_3), 20.3 ($2CH_3$), 26.0 (CH_2, COD), 26.3 ($2CH_3$), 27.9 (CH_2, COD), 29.7 (CH_2, COD), 30.0 (3CH, Ad), 30.9 (CH_3, ^{t}Bu), 31.8 (CH_3, ^{t}Bu), 32.8 (CH_2-S), 34.2 (CH_2, COD), 34.4 (C, ^{t}Bu), 35.0 (C, ^{t}Bu), 35.3 (3 CH_2, Ad), 42.5 (3 CH_2, Ad), 58.4 (C, Ad), 67.5 (d, CH_2-O, J_{C-P}= 15.5 Hz), 70.1 (CH=, COD), 72.7 (CH=, COD), 78.2 (*C*HCH_2S), 84.8 (*C*HCH_2O), 91.2 (CH=, COD), 99.2 (CH=, COD), 110.2 (C), 117.3-145.0 (aromatic carbons), 161.6 (q, C-B, BAr_F, $^1J_{C-B}$= 49 Hz). MS HR-ESI [found 995.4392, $C_{49}H_{71}IrO_5PS$ $(M)^+$ requires 995.4389].

[Ir(cod)(L5e)]BAr_F. Yield: 62 mg (92%). ^{31}P NMR (400 MHz, $CDCl_3$) δ: 98.5 (s). ^1H NMR ($CDCl_3$), δ: 1.25 (s, 3H, CH_3), 1.32 (s, 3H, CH_3), 1.38 (s, 9H, CH_3, ^{t}Bu), 1.45 (m, 2H, CH_2, COD),

1.63 (s, 9H, CH_3, ^{t}Bu), 1.71 (s, 3H, CH_3), 1.76 (m, 3H, CH_2, Ad), 1.82 (s, 3H, CH_3), 1.93 (m, 2H, CH_2, COD), 2.04 (m, 3H, CH_2, Ad), 2.14 (m, 2H, CH_2, COD), 2.21 (m, 3H, CH, Ad), 2.26 (s, 6H, CH_3), 2.34 (m, 2H, CH_2, COD), 3.29 (m, 2H, CH_2-S, CH_2-O), 3.60 (m, 1H, CH_2-S), 3.82 (m, 1H, CH_2-O), 4.02-4.11 (m, 3H, C*H*CH_2O, C*H*CH_2S, CH=, COD), 4.43 (m, 1H, CH=, COD), 5.58 (m, 1H, CH=, COD), 6.16 (m, 1H, CH=, COD), 7.24-7.71 (m, 14H, CH=). ^{13}C NMR ($CDCl_3$), δ: 16.4 (CH_3), 16.6 (CH_3), 20.3 (CH_3), 26.4 (CH_3), 26.5 (CH_3), 26.7 (CH_2, COD), 28.7 (CH_2, COD), 29.6 (CH_2, COD), 30.3 (3CH, Ad), 31.1 (CH_3, ^{t}Bu), 32.1 (CH_3, ^{t}Bu), 33.5 (CH_2, COD), 33.9 (CH_2-S), 34.6 (C, ^{t}Bu), 34.9 (C, ^{t}Bu), 35.3 (CH_2, Ad), 43.2 (CH_2, Ad), 58.5 (C, Ad), 66.0 (CH_2-O, $J_{C\text{-}P}$= 15 Hz), 69.1 (CH=, COD), 72.5 (CH=, COD), 76.0 (*C*HCH_2S), 77.1 (*C*HCH_2O), 99.0 (CH=, COD), 99.1 (CH=, COD), 110.2 (CMe_3), 117.3-144.4 (aromatic carbons), 161.6 (q, C-B, BAr_F, $^1J_{C\text{-}B}$= 49 Hz). MS HR-ESI [found 995.4391, $C_{49}H_{71}IrO_5PS$ $(M)^+$ requires 995.4389].

[Ir(cod)(L6d)]BAr_F. Yield: 61 mg (90%). ^{31}P NMR (400 MHz, $CDCl_3$) δ: 94.2 (s). ^{1}H NMR ($CDCl_3$), δ: 1.15 (s, 3H, CH_3), 1.21 (s, 3H, CH_3), 1.31 (m, 2H, CH_2, COD),1.45 (s, 9H, CH_3, ^{t}Bu), 1.67 (s, 9H, CH_3, ^{t}Bu), 1.72 (s, 3H, CH_3), 1.74 (s, 3H, CH_3), 1.87-2.13 (m, 6H, CH_2, COD), 2.20 (s, 6H, CH_3), 3.34-3.51 (m, 3H, CH_2-S, CH_2-O, CH=, COD), 3.85 (m, 1H, C*H*CH_2S), 4.06 (m, 2H, CH_2-O, CH=, COD), 4.16 (m, 1H, C*H*CH_2O), 4.57 (m, 2H, CH_2-O, CH=, COD), 5.17 (m, 1H, CH=, COD), 7.05-8.42 (m, 21H, CH=). ^{13}C NMR ($CDCl_3$), δ: 16.3 (CH_3), 16.6 (CH_3), 20.3 (CH_3), 20.4 (CH_3), 26.5 (CH_3), 29.3 (CH_2, COD), 29.5 (CH_2, COD), 29.7 (CH_2, COD), 31.4 (CH_3, ^{t}Bu), 34.0 (CH_2, COD), 34.7 (C, ^{t}Bu), 35.1 (C, ^{t}Bu), 45.1 (CH_2-S), 66.2 (CH=, COD), 69.0 (CH_2-O), 75.7 (CH=, COD), 77.2 (*C*HCH_2S), 79.0 (*C*HCH_2O), 105.7 (CH=, COD), 111.9 (CMe_2), 117.4-144.9 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^1J_{C\text{-}B}$= 49 Hz). MS HR-ESI [found 987.3765, $C_{49}H_{63}IrO_5PS$ $(M)^+$ requires 987.3763].

[Ir(cod)(L6e)]BAr_F. Yield: 64 mg (91%). ^{31}P NMR (400 MHz, $CDCl_3$) δ: 96.9 (s). ^{1}H NMR ($CDCl_3$), δ: 0.87 (m, 2H, CH_2, COD), 1.18 (s, 6H, CH_3), 1.43 (s, 9H, CH_3, ^{t}Bu), 1.52 (m, 2H, CH_2, COD), 1.70 (s, 6H, CH_3), 1.75 (s, 9H, CH_3, ^{t}Bu), 2.06 (m, 4H, CH_2, COD), 2.22 (s, 6H, CH_3), 3.29 (m, 1H, CH=, COD), 3.57 (m, 2H, CH_2-O, CH=, COD), 3.74 (m, 1H, CH_2-S), 3.95-4.34 (m, 3H, CH_2-O, C*H*CH_2S, C*H*CH_2O), 4.44 (m, 1H, CH=, COD), 4.54 (m, 1H, CH_2-O), 4.71 (m, 1H, CH=, COD), 7.17-8.37 (m, 21H, CH=). ^{13}C NMR ($CDCl_3$), δ: 16.4 (CH_3), 16.6 (CH_3), 20.3 (CH_3), 20.4 (CH_3), 26.3 (CH_3), 26.4 (CH_3), 29.6 (CH_2, COD), 30.5 (CH_2, COD), 31.4 (CH_3, ^{t}Bu), 32.1 (C, ^{t}Bu), 32.3 (C, ^{t}Bu), 34.8 (CH_2, COD), 48.5 (CH_2-S), 67.1 (CH=, COD), 68.8 (CH_2-O), 74.9 (CH=, COD), 77.9 (*C*HCH_2S), 80.2 (*C*HCH_2O), 102.2 (CH=, COD), 104.8 (CH=, COD), 110.2 (CMe_2), 117.4-159.3 (aromatic carbons), 161.6 (q, C-B, BAr_F, $^1J_{C\text{-}B}$= 49 Hz). MS HR-ESI [found 987.3763, $C_{49}H_{63}IrO_5PS$ $(M)^+$ requires 987.3763].

[Ir(cod)(L7d)]BAr_F. Yield: 58 mg (89%). ^{31}P NMR (400 MHz, $CDCl_3$) δ: 94.1 (s). ^{1}H NMR ($CDCl_3$), δ: 1.49 (s, 6H, CH_3), 1.66 (s, 9H, CH_3, ^{t}Bu), 1.83 (m, 2H, CH_2, COD), 1.96 (s, 9H, CH_3, ^{t}Bu), 2.00 (s, 3H, CH_3), 2.04 (s, 3H, CH_3), 2.20 (m, 4H, CH_2, COD), 2.35 (m, 2H, CH_2, COD), 2.49 (s, 6H, CH_3), 3.78 (m, 1H, CH_2-O), 3.90 (m, 2H, CH_2-S, CH=, COD), 4.16 (m, 1H, C*H*CH_2S), 4.25 (m, 1H, CH_2-O), 4.40-4.34 (m, 1H, CH_2-S), 4.53 (m, 1H, C*H*CH_2O), 4.78 (m, 1H, CH=, COD), 4.86 (m, 2H, CH=, COD), 7.47-8.23 (m, 21H, CH=). ^{13}C NMR ($CDCl_3$), δ: 16.3 (CH_3), 16.6 (CH_3), 20.3 (2CH_3), 26.5 (2CH_3), 28.2 (CH_2, COD), 28.8 (CH_2, COD), 29.7 (CH_2, COD), 31.3 (CH_3, ^{t}Bu), 32.3 (CH_3, ^{t}Bu), 32.9 (CH_2, COD), 34.7 (C, ^{t}Bu), 35.1 (C, ^{t}Bu), 46.5 (CH_2-S), 67.9 (CH=, COD), 68.3 (CH_2-O, $J_{C\text{-}P}$= 14.4 Hz), 75.0 (CH=, COD), 77.2 (*C*HCH_2S), 79.9 (*C*HCH_2O), 101.5

(CH=, COD), 104.4 (CH=, COD), 111.4 (CMe_2), 117.4-144.7 (aromatic carbons), 161.6 (q, C-B, BAr_F, $^1J_{C-B}$= 49 Hz). MS HR-ESI [found 987.3766, $C_{49}H_{63}IrO_5PS$ $(M)^+$ requires 987.3763].

[Ir(cod)(L7e)]BAr_F. Yield: 61 mg (90%). ^{31}P NMR (400 MHz, $CDCl_3$) δ: 96.9 (s). ^{1}H NMR ($CDCl_3$), δ: 1.28 (s, 6H, CH_3), 1.48 (s, 9H, CH_3, ^{t}Bu), 1.60 (m, 2H, CH_2, COD), 1.76 (s, 9H, CH_3, ^{t}Bu), 1.81 (s, 3H, CH_3), 1.84 (s, 3H, CH_3), 1.93 (m, 2H, CH_2, COD), 2.14 (m, 4H, CH_2, COD), 2.3 (s, 6H, CH_3), 3.45 (m, 1H, CH=, COD), 3.64 (m, 2H, CH_2-O), 3.87 (m, 1H, CH_2-S) 4.18 (m, 2H, CH_2-S, C*H*CH_2S), 4.31 (m, 1H, C*H*CH_2O), 4.40 (m, 1H, CH=, COD), 4.58 (m, 1H, CH=, COD), 4.74 (m, 1H, CH=, COD), 7.26-8.06 (m, 21H, CH=). ^{13}C NMR ($CDCl_3$), δ: 16.4 (CH_3), 16.6 (CH_3), 20.3 (CH_3), 20.4 (CH_3), 26.4 (CH_3), 27.0 (CH_2, COD), 29.6 (CH_2, COD), 30.0 (CH_2, COD), 31.0 (CH_2, COD), 31.4 (CH_3, ^{t}Bu), 32.1 (CH_3, ^{t}Bu), 34.3 (C, ^{t}Bu), 34.7 (C, ^{t}Bu), 48.3 (CH_2-S), 67.8 (CH=, COD), 69.1 (CH_2-O, J_{C-P}= 14.4 Hz), 75.0 (CH=, COD), 77.6 (*C*HCH_2S), 79.6 (*C*HCH_2O), 102.9 (CH=, COD), 103.1 (CH=, COD), 110.3 (CMe_2), 117.4-143.9 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^1J_{C-B}$= 49 Hz). MS HR-ESI [found 987.3764, $C_{49}H_{63}IrO_5PS$ $(M)^+$ requires 987.3763].

[Ir(cod)(L8a)]BAr_F. Yield: 63 mg (90%). ^{31}P NMR (400 MHz, $CDCl_3$) δ: 99.1 (s). ^{1}H NMR ($CDCl_3$), δ: 0.88 (m, 2H, CH_2, COD), 1.25 (s, 3H, CH_3), 1.28 (s, 3H, CH_3), 1.33 (s, 9H, CH_3, ^{t}Bu), 1.36 (s, 9H, CH_3, ^{t}Bu), 1.52 (s, 9H, CH_3, ^{t}Bu), 1.56 (s, 9H, CH_3, ^{t}Bu), 1.77 (s, 3H, CH_3), 1.99 (m, 2H, CH_2, COD), 2.09 (m, 2H, CH_2, COD), 2.1 (m, 2H, $2CH_2$, COD), 3.80 (m, 1H, CH=, COD), 3.95 (m, 1H, CH_2-S), 4.19 (m, 2H, CH_2-S, C*H*CMe_2O), 4.33 (m, 1H, C*H*CH_2S), 4.42 (m, 1H, CH=, COD), 4.50 (m, 1H, CH=, COD), 4.70 (m, 1H, CH=, COD), 7.15-7.71 (m, 21H, CH=). ^{13}C NMR ($CDCl_3$), δ: 22.7 (CH_2, COD), 26.4 (CH_3), 26.5 (CH_3), 27.5 (CH_3), 29.6 ($2CH_2$, COD), 31.2 (CH_3, ^{t}Bu), 31.6 ($2CH_3$, ^{t}Bu), 31.9 (CH_3, ^{t}Bu), 33.8 (CH_2, COD), 34.8 (C, ^{t}Bu), 35.4 (C, ^{t}Bu), 35.5 (C, ^{t}Bu), 47.9 (CH_2-S), 75.9 (CH=, COD), 76.8 (CH=, COD), 77.2 (*C*HCH_2S), 83.7 (*C*HCMe_2O), 91.3 (d, *C*Me_2O, J_{C-P}= 21.2 Hz), 100.5 (CH=, COD), 100.7 (CH=, COD), 109.2 (CMe_2), 117.4-149.5 (aromatic carbons), 161.6 (q, C-B, BAr_F, $^1J_{C-B}$= 49 Hz). MS HR-ESI [found 1021.4547, $C_{57}H_{73}IrO_5PS$ $(M)^+$ requires 1021.4546].

[Ir(cod)(L8d)]BAr_F. Yield: 60 mg (91%). ^{31}P NMR (400 MHz, $CDCl_3$) δ: 92.2 (s). ^{1}H NMR ($CDCl_3$), δ: 0.85 (m, 2H, CH_2, COD), 1.25 (s, 3H, CH_3), 1.31 (s, 3H, CH_3), 1.32 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 1.43 (s, 9H, CH_3, ^{t}Bu), 1.59 (m, 2H, CH_2, COD), 1.68 (s, 9H, CH_3, ^{t}Bu), 1.73 (s, 3H, CH_3), 1.84 (s, 3H, CH_3), 2.16 (m, 4H, $2CH_2$, COD), 2.27 (s, 3H, CH_3), 2.28 (s, 3H, CH_3), 3.44 (m, 1H, CH=, COD), 3.66 (d, 1H, C*H*CMe_2O, $^3J_{H-H}$= 8 Hz), 3.77-3.89 (m, 2H, CH_2-S), 4.14 (m, 1H, CH=, COD), 4.37-4.42 (m, 1H, C*H*CH_2S), 4.58 (m, 1H, CH=, COD), 4.72 (m, 1H, CH=, COD), 7.22-7.70 (m, 19H, CH-Ar). ^{13}C NMR ($CDCl_3$), δ: 16.2 (CH_3), 16.4 (CH_3), 20.2 (CH_3), 20.4 (CH_3), 22.8 (CH_3), 26.5 (CH_3), 26.6 (CH_3), 27.9 (CH_2, COD), 29.6 (CH_2, COD), 29.9 (CH_2, COD), 30.8 (CH_2, COD), 31.3 (CH_3, ^{t}Bu), 32.4 (CH_3, ^{t}Bu), 33.6 (C, ^{t}Bu), 34.8 (C, ^{t}Bu), 45.5 (CH_2-S), 68.9 (CH=, COD), 76.5 (*C*HCH_2S), 77.2 (CH=, COD), 85.5 (*C*HCMe_2O), 92.1 (d, *C*Me_2O, J_{C-P}= 21.2 Hz), 99.6 (CH=, COD), 100.2 (CH=, COD), 109.9 (CMe_2), 117.4-136.9 (aromatic carbons), 161.6 (q, C-B, BAr_F, $^1J_{C-B}$= 49 Hz). MS HR-ESI [found 965.3923, $C_{47}H_{65}IrO_5PS$ $(M)^+$ requires 965.3920].

[Ir(cod)(L8e)]BAr_F. Yield: 63 mg (93%). ^{31}P NMR (400 MHz, $CDCl_3$) δ: 94.0 (s). ^{1}H NMR ($CDCl_3$), δ: 0.85 (m, 2H, CH_2, COD), 1.25 (s, 3H, CH_3), 1.28 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 1.46 (s, 9H, CH_3, ^{t}Bu), 1.56 (s, 3H, CH_3), 1.67 (m, 2H, CH_2, COD), 1.74 (s, 3H, CH_3), 1.75 (s, 9H, CH_3, ^{t}Bu), 1.77 (s, 3H, CH_3), 2.17 (m, 4H, $2CH_2$, COD), 2.26 (s, 3H, CH_3), 2.28 (s, 3H, CH_3), 3.26

(m, 1H, CH=, COD), 3.33 (m, 1H, CH_2-S), 4.13-4.20 (m, 2H, C*H*CMe_2O, CH_2-S), 4.29-4.37 (m, 2H, C*H*CH_2S, CH=, COD), 4.45 (m, 1H, CH=, COD), 4.61 (m, 1H, CH=, COD), 7.26-7.71 (m, 19H, CH=). ^{13}C NMR ($CDCl_3$), δ: 16.1 (CH_3), 16.4 (CH_3), 20.2 (CH_3), 20.3 (CH_3), 22.7 (CH_3), 22.8 (CH_3), 26.4 (CH_3), 26.5 (CH_3), 27.0 (CH_2, COD), 29.8 (CH_2, COD), 30.1 (CH_2, COD), 30.7 (CH_2, COD), 31.6 (CH_3, ^{t}Bu), 32.2 (CH_3, ^{t}Bu), 34.3(C, ^{t}Bu), 34.7 (C, ^{t}Bu), 48.3 (CH_2-S), 69.1 (CH=, COD), 75.8 (*C*HCH_2S), 76.0 (CH=, COD), 83.9 (*C*HCMe_2O), 91.2 (d, *C*Me_2O, $J_{C\text{-}P}$= 20.5 Hz), 99.9 (CH=, COD), 100.5 (CH=, COD), 109.2 (CMe_2), 117.4-145.2 (aromatic carbons), 161.6 (q, C-B, BAr_F, $^1J_{C\text{-}B}$= 49 Hz). MS HR-ESI [found 965.3922, $C_{47}H_{65}IrO_5PS$ $(M)^+$ requires 965.3920].

[Ir(cod)(L9f)]BAr_F. Yield: 66 mg (91%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ=98.8 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.55 (s, 9H, CH_3, $SiMe_3$), 0.77 (s, 9H, CH_3, $SiMe_3$), 0.79 (s, 3H, CH_3), 1.18 (s, 3H, CH_3), 1.27 (s, 3H, CH_3), 1.31 (s, 3H, CH_3), 1.67-1.75 (m, 2H, CH_2, cod), 1.90-2.19 (m, 6H, CH_2, cod), 3.50 (b, 1H, CH=, cod), 3.87 (dd, 1H, CH_2-S, $^2J_{H\text{-}H}$ =12.8 Hz, $^3J_{H\text{-}H}$ =9.6 Hz), 3.94 (d, 1H, C*H*CMe_2O, $^3J_{H\text{-}H}$ =7.2 Hz), 4.01 (dd, 1H, CH_2-S, $^2J_{H\text{-}H}$ =12.8 Hz, $^3J_{H\text{-}H}$ =2.0 Hz), 4.49-4.56 (m, 2H, C*H*CH_2S, CH= cod), 4.61 (b, 1H, CH=, cod), 4.79 (b, 1H, CH=, cod), 6.96-8.21 (m, 29H, CH= aromatic). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=0.2 (CH_3, $SiMe_3$), 1.5 (CH_3, $SiMe_3$), 22.4 (CH_3), 26.6 (CH_3), 26.8 (CH_3), 27.5 (CH_2, cod), 28.6 (CH_3), 30.1 (CH_2, cod), 31.1 (CH_2, cod), 34.0 (d, CH_2, cod, $J_{C\text{-}P}$ =4.9 Hz), 46.9 (CH_2-S), 69.2 (CH=, cod), 76.2 (*C*HCH_2S), 77.2 (CH=, cod), 85.4 (d, *C*HCMe_2O, $^3J_{C\text{-}P}$ =10.0 Hz), 92.9 (d, CMe_2O, $^2J_{C\text{-}P}$ =21.4 Hz), 100.5 (d, CH=, cod, $J_{C\text{-}P}$ =16.8 Hz), 102.4 (d, CH=, cod, $J_{C\text{-}P}$ =16.0 Hz), 111.1 (CMe_2), 117.4-150.5 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^1J_{C\text{-}B}$ =50.5 Hz). MS HR-ESI [found 1091.3305, $C_{53}H_{63}IrO_5PSSi_2$ $(M)^+$ requires 1091.3302].

[Ir(cod)(L9g)]BAr_F. Yield: 64 mg (89%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ=102.1 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.38 (s, 3H, CH_3), 0.56 (s, 9H, CH_3, $SiMe_3$), 0.86 (s, 9H, CH_3, $SiMe_3$), 1.24 (s, 3H, CH_3), 1.28 (s, 3H, CH_3), 1.31 (s, 3H, CH_3), 1.61 (m, 2H, CH_2, cod), 1.94-2.02 (m, 1H, CH_2, cod), 2.05-2.18 (m, 4H, CH_2, cod), 2.21-2.30 (m, 1H, CH_2, cod), 3.53 (b, 1H, CH=, cod), 4.04 (d, 1H, CH_2-S, $^2J_{H\text{-}H}$ =14.4 Hz) 4.10 (d, 1H, C*H*CMe_2O, $^3J_{H\text{-}H}$ =8.4 Hz), 4.19 (dd, 1H, CH_2-S, $^2J_{H\text{-}H}$ =14.8 Hz, $^3J_{H\text{-}H}$ =8.4 Hz), 4.37 (pt, 1H, C*H*CH_2S, $^3J_{H\text{-}H}$ =7.2 Hz), 4.48-4.53 (m, 1H, CH=, cod), 4.60 (b, 1H, CH=, cod), 4.73 (b, 1H, CH=, cod), 7.00-8.23 (m, 29H, CH= aromatic). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=0.3 (CH_3, $SiMe_3$), 1.6 (CH_3, $SiMe_3$), 23.0 (d, CH_3, $^3J_{H\text{-}H}$ =6.1 Hz), 26.4 (CH_3), 26.7 (CH_2, cod), 29.7 (CH_3), 29.9 (CH_2, cod), 31.1 (CH_2, cod), 35.1 (CH_2, cod), 48.3 (CH_2-S), 70.2 (CH=, cod), 75.8 (*C*HCH_2S, CH= cod), 84.4 (*C*HCMe_2O), 92.0 (d, CMe_2O, $^2J_{C\text{-}P}$ =20.6 Hz), 100.2 (d, CH=, cod, $J_{C\text{-}P}$ =17.6 Hz), 102.3 (d, CH=, cod, $J_{C\text{-}P}$ =15.3 Hz), 109.4 (CMe_2), 117.4-150.5 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^1J_{C\text{-}B}$ =49.7 Hz). MS HR-ESI [found 1091.3304, $C_{53}H_{63}IrO_5PSSi_2$ $(M)^+$ requires 1091.3302].

[Ir(cod)(L10f)]BAr_F. Yield: 65 mg (89%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ=99.7 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.59 (s, 9H, CH_3, $SiMe_3$), 0.72 (s, 9H, CH_3, $SiMe_3$), 0.91 (s, 3H, CH_3), 1.32 (s, 3H, CH_3), 1.40-1.67 (m, 2H, CH_2, cod), 1.74 (m, 1H, CH_2, cod), 1.93-2.08 (m, 4H, CH_2, cod), 2.18 (b, 1H, CH_2, cod), 2.36 (s, 3H, CH_3), 3.45 (b, 1H, CH=, cod), 3.84-3.89 (m, 1H, CH_2-O), 4.12 (b, 1H CH=, cod), 4.34-4.44 (m, 2H, CH_2-O, C*H*CH_2O), 4.55 (b, 1H, CH=, cod), 4.94-5.10 (m, 1H, CH=, cod), 5.65 (d, 1H, C*H*CPh_2S, $^3J_{H\text{-}H}$ =3.5 Hz), 6.89-8.17 (m, 32H, CH= aromatic). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=0.1 (CH_3, $SiMe_3$), 1.3 (CH_3, $SiMe_3$), 14.8 (CH_3), 26.1 (CH_3), 26.4 (CH=, cod), 28.3 (CH_2, cod), 28.8 (CH_2, cod), 31.6 (CH_2, cod), 35.0 (CH_2, cod), 64.7 (d, CH_2-O, $^2J_{C\text{-}P}$ =10.7 Hz), 71.8 (CH=, cod), 74.8 (CPh_2-S), 75.0 (d, *C*HCH_2O, $^3J_{C\text{-}P}$ =4.6 Hz), 78.0 (CH=,

cod), 83.9 (*C*HCPh$_2$S), 102.1 (d, CH=, cod, $J_{C\text{-}P}$ =15.3 Hz), 105.8 (d, CH=, cod, $J_{C\text{-}P}$ =16.0 Hz), 112.7 (CMe$_2$), 117.4-151.0 (aromatic carbons), 161.7 (q, C-B, BAr$_F$, $^1J_{C\text{-}B}$ =49.7 Hz). MS HR-ESI [found 1103.3304, $C_{54}H_{63}IrO_5PSSi_2$ $(M)^+$ requires 1103.3302].

[Ir(cod)(L10g)]BAr$_F$. Yield: 67 mg (92%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ=109.5 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.52 (s, 3H, CH$_3$), 0.59 (s, 9H, CH$_3$, SiMe$_3$), 0.63 (s, 9H, CH$_3$, SiMe$_3$), 1.47 (s, 3H, CH$_3$), 1.26-1.38 (m, 2H, CH$_2$, cod), 1.60-1.71 (m, 2H, CH$_2$, cod), 1.75-1.81 (m, 2H, CH$_2$, cod), 1.86 (b, 1H, CH$_2$, cod), 2.03-2.13 (m, 1H, CH$_2$, cod), 2.41 (s, 3H, CH$_3$), 3.11-3.18 (m, 1H, CH=, cod), 3.35-3.38 (m, 1H, CH=, cod), 3.84 (d, 1H, C*H*CH$_2$O, $^3J_{H\text{-}H}$ =8.8 Hz), 4.31-4.37 (m, 1H, CH$_2$-O), 4.63-4.66 (m, 1H, CH=, cod), 4.90-5.00 (m, 2H, CH$_2$-O, CH=, cod), 5.69 (d, 1H, C*H*CPh$_2$S, $^3J_{H\text{-}H}$ =8.8 Hz), 6.96-8.20 (m, 32H, CH= aromatic). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=0.9 (CH$_3$, SiMe$_3$), 1.4 (CH$_3$, SiMe$_3$), 13.7 (CH$_3$), 25.2 (CH$_3$), 27.3 (CH$_3$), 28.5 (CH$_2$, cod), 30.1 (CH$_2$, cod), 30.8 (CH$_2$, cod), 32.4 (CH$_2$, cod), 64.7 (d, CH$_2$-O, $^2J_{C\text{-}P}$ =5.3 Hz), 72.8 (CH=, cod), 74.0 (CPh$_2$-S), 75.2 (d, *C*HCH$_2$O, $^3J_{C\text{-}P}$ =3.8 Hz), 75.7 (*C*HCPh$_2$S), 79.0 (CH=, cod), 99.9 (d, CH=, cod, $J_{C\text{-}P}$ =16.8 Hz), 103.8 (d, CH=, cod, $J_{C\text{-}P}$ =14.5 Hz), 109.6 (CMe$_2$), 117.4-150.5 (aromatic carbons), 161.7 (q, C-B, BAr$_F$, $^1J_{C\text{-}B}$ =50.5 Hz). MS HR-ESI [found 1103.3304, $C_{54}H_{63}IrO_5PSSi_2$ $(M)^+$ requires 1103.3302]. MS HR-ESI [found 1103.3306, $C_{54}H_{63}IrO_5PSSi_2$ $(M)^+$ requires 1103.3302].

[Ir(cod)(L11a)]BAr$_F$. Yield: 64 mg (92%). ^{31}P NMR (161.9 MHz, C_2DCl_2): δ=102.8 (s). ^{1}H NMR (400 MHz, C_2DCl_2): δ=0.29 (d, 3H, CH$_3$, $^3J_{H\text{-}H}$ =6.0 Hz), 1.13 (s, 3H, CH$_3$), 1.19 (s, 3H, CH$_3$), 1.25 (s, 27H, CH$_3$, ^{t}Bu), 1.38 (s, 9H, CH$_3$, ^{t}Bu), 1.80 (b, 2H, CH$_2$, cod), 2.00 (b, 4H, CH$_2$, cod), 2.10 (m, 1H, CH$_2$, cod), 2.25 (m, 1H, CH$_2$, cod), 2.97 (b, 1H, CH=, cod), 3.63 (pt, 1H, C*H*CHO, $^3J_{H\text{-}H}$ =8.4 Hz), 3.71 (d, 1H, CH$_2$-S, $^2J_{H\text{-}H}$ =12.8 Hz), 4.00 (dd, 1H, CH$_2$-S, $^2J_{H\text{-}H}$ =12.4 Hz, $^3J_{H\text{-}H}$ =6.4 Hz), 4.07 (b, 1H, CH=, cod), 4.24-4.29 (m, 1H, CH=, cod), 4.37-4.42 (m, 2H, CH-O, C*H*CH$_2$S), 4.79 (b, 2H, CH=, cod), 7.05-7.66 (m, 21H, CH= aromatic). ^{13}C NMR (100.6 MHz, C_2DCl_2): δ=19.0 (CH$_3$), 27.0 (CH$_3$), 27.1 (CH$_3$), 28.4 (CH$_2$, cod), 30.3 (b, CH$_2$, cod), 31.2 (b, CH$_2$, cod), 31.6 (CH$_3$, ^{t}Bu), 32.3 (CH$_3$, ^{t}Bu), 34.1 (CH$_2$, cod), 35.2 (C, ^{t}Bu), 35.4 (C, ^{t}Bu), 35.8 (C, ^{t}Bu), 36.4 (C, ^{t}Bu), 46.3 (CH$_2$-S), 69.7 (CH=, cod), 77.1 (CH=, cod), 79.1 (*C*HCH$_2$S), 81.4 (CH-O), 83.9 (*C*HCHO), 102.4 (d, CH=, cod, $J_{C\text{-}P}$ =16.1 Hz), 104.3 (d, CH=, cod, $J_{C\text{-}P}$ =17.5 Hz), 112.0 (CMe$_2$), 118.0-140.7 (aromatic carbons), 162.1 (q, C-B, BAr$_F$, $^1J_{C\text{-}B}$ =49.9 Hz). MS HR-ESI [found 1007.4390, $C_{50}H_{71}IrO_5PS$ $(M)^+$ requires 1007.4389].

[Ir(cod)(L11f)]BAr$_F$. Yield: 64 mg (91%).^{31}P NMR (161.9 MHz, $CDCl_3$): δ=102.9 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.41 (d, 3H, CH$_3$, $^3J_{H\text{-}H}$ =7.2 Hz), 0.54 (s, 9H, CH$_3$, SiMe$_3$), 0.80 (s, 9H, CH$_3$, SiMe$_3$), 1.27 (s, 3H, CH$_3$), 1.29 (s, 3H, CH$_3$), 1.68 (b, 2H, CH$_2$, cod), 1.94-2.15 (m, 6H, CH$_2$, cod), 3.22 (b, 1H, CH=, cod), 3.94 (m, 2H, CH$_2$-S, C*H*CHO), 4.10 (dd, 1H, CH$_2$-S, $^2J_{H\text{-}H}$ =14.4 Hz, $^3J_{H\text{-}H}$ =7.6 Hz), 4.26 (m, 2H, CH-O, C*H*CH$_2$S), 4.51 (b, 2H, CH=, cod), 4.61 (b, 1H, CH=, cod), 6.98-8.21 (m, 27H, CH= aromatic). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=0.0 (CH$_3$, SiMe$_3$), 1.6 (CH$_3$, SiMe$_3$), 18.4 (CH$_3$), 26.5 (CH$_3$), 26.6 (CH$_3$), 29.7 (CH$_2$, cod), 30.1 (d, CH$_2$, cod, $J_{C\text{-}P}$ =2.7 Hz), 30.7 (d, CH$_2$, cod, $J_{C\text{-}P}$ =2.6 Hz), 34.8 (d, CH$_2$, cod, $J_{C\text{-}P}$ =5.0 Hz), 48.4 (CH$_2$-S), 69.7 (CH=, cod), 77.0 (CH=, cod), 80.2 (*C*HCH$_2$S), 82.3 (*C*HCHO), 84.2 (d, CH-O, $^2J_{C\text{-}P}$ =19.1 Hz), 101.3 (d, CH=, cod, $J_{C\text{-}P}$ =17.5 Hz), 102.8 (d, CH=, cod, $J_{C\text{-}P}$ =16.0 Hz), 109.9 (CMe$_2$), 117.4-150.3 (aromatic carbons), 161.7 (q, C-B, BAr$_F$, $^1J_{C\text{-}B}$ =49.7 Hz). MS HR-ESI [found 1027.2993, $C_{48}H_{59}IrO_5PSSi_2$ $(M)^+$ requires 1027.2989].

[Ir(cod)(L11g)]BAr$_F$. Yield: 67mg (95%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ= 99.3 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.56 (s, 3H, CH_3), 0.55 (s, 9H, CH_3, $SiMe_3$), 0.69 (s, 9H, CH_3, $SiMe_3$), 1.29 (s, 3H, CH_3), 1.32 (s, 3H, CH_3), 1.78 (b, 2H, CH_2, cod), 1.91-1.95 (m, 2H, CH_2, cod), 2.00-2.07 (m, 2H, CH_2, cod), 2.13-2.28 (m, 2H, CH_2, cod), 3.50 (pt, 1H, CH_2-S, $^3J_{H-H}$ =10.0 Hz), 3.55-3.57 (m, 1H, CH=, cod), 3.89-3.93 (m, 2H, CH_2-S, C*H*CHO), 4.26-4.31 (m, 1H, CH=, cod), 4.38-4.45 (m, 1H, CH-O), 4.47-4.52 (m, 1H, C*H*CH_2S), 4.81 (b, 1H, CH=, cod), 5.12 (b, 1H, CH=, cod), 7.00-8.17 (m, 27H, CH= aromatic). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=0.2 (CH_3, $SiMe_3$), 0.9 (CH_3, $SiMe_3$), 19.1 (CH_3), 26.4 (CH_3), 26.8 (CH_3), 27.9 (CH_2, cod), 29.4 (d, CH_2, cod, J_{C-P} =2.3 Hz), 32.1 (d, CH_2, cod, J_{C-P} =4.8 Hz), 33.2 (d, CH_2, cod, J_{C-P} =4.1 Hz), 45.6 (CH_2-S), 69.5 (CH=, cod), 77.2 (*C*HCH_2S), 79.1 (CH=, cod), 79.9 (d, CH-O, $^2J_{C-P}$ =14.5 Hz), 82.9 (d, *C*HCHO, $^3J_{C-P}$ =6.1 Hz), 102.2 (d, CH=, cod, J_{C-P} =16.0 Hz), 105.5 (d, CH=, cod, J_{C-P} =16.0 Hz), 112.5 (CMe_2), 117.4-150.8 (aromatic carbons), 162.1 (q, C-B, BAr_F, $^1J_{C-B}$ =41.8 Hz). MS HR-ESI [found 1027.2992, $C_{48}H_{59}IrO_5PSSi_2$ $(M)^+$ requires 1027.2989].

[Ir(cod)(L12a)]BAr$_F$. Yield: 66 mg (93%).^{31}P NMR (161.9 MHz, $CDCl_3$): δ=101.0 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.47 (d, 3H, CH_3, $^3J_{H-H}$ =6.0 Hz), 1.25 (s, 3H, CH_3), 1.28 (s, 3H, CH_3), 1.36 (s, 9H, CH_3, ^{t}Bu), 1.38 (s, 9H, CH_3, ^{t}Bu), 1.51 (s, 9H, CH_3, ^{t}Bu), 1.76 (s, 9H, CH_3, ^{t}Bu), 1.84 (b, 2H, CH_2, cod), 2.01-2.17 (b, 5H, CH_2, cod), 2.33 (m, 1H, CH_2, cod), 3.72 (pt, 1H, C*H*CHO, $^3J_{H-H}$ =8.8 Hz), 3.83 (dd, 1H, CH_2-S, $^2J_{H-H}$ =13.2 Hz, $^3J_{H-H}$ =2.4 Hz), 4.08 (m, 1H, CH_2-S), 4.11 (b, 1H, CH=, cod), 4.44 (m, 1H, CH=, cod), 4.49 (m, 2H, CH-O, C*H*CH_2S), 4.86 (b, 1H, CH=, cod), 4.97 (b, 1H, CH=, cod), 7.15-8.06 (m, 23H, CH= aromatic). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=18.8 (CH_3), 26.9 (CH_3), 27.0 (CH_3), 28.1 (d, CH_2, cod, J_{C-P} =3.0 Hz), 29.9 (b, CH_2, cod), 31.5 (CH_3, ^{t}Bu), 31.6 (CH_3, ^{t}Bu), 32.0 (d, CH_2, cod, J_{C-P} =2.1 Hz), 32.2(CH_3, ^{t}Bu), 33.8 (d, CH_2, cod, J_{C-P} =3.8 Hz), 35.1 (C, ^{t}Bu), 35.2 (C, ^{t}Bu), 35.6 (C, ^{t}Bu), 36.2 (C, ^{t}Bu), 46.5 (CH_2-S), 69.5 (CH=, cod), 77.5 (CH=, cod), 78.7 (*C*HCH_2S), 81.3 (d, CH-O, $^2J_{C-P}$ =14.5 Hz), 83.6 (d, *C*HCHO, $^3J_{C-P}$ =6.0 Hz), 102.1 (d, CH=, cod, J_{C-P} =15.3 Hz), 103.9 (d, CH=, cod, J_{C-P} =16.8 Hz), 111.9 (CMe_2), 120.8-150.7 (aromatic carbons), 162.1 (q, C-B, BAr_F, $^1J_{C-B}$ =49.3 Hz). MS HR-ESI [found 1057.4547, $C_{54}H_{73}IrO_5PS$ $(M)^+$ requires 1057.4546].

[Ir(cod)(L12f)]BAr$_F$. Yield: 65 mg (91%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ=102.9 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.45 (d, 3H, CH_3, $^3J_{H-H}$ =6.4 Hz), 0.57 (s, 9H, CH_3, $SiMe_3$), 0.86 (s, 9H, CH_3, $SiMe_3$), 1.26 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 1.62 (b, 2H, CH_2, cod), 1.95 (m, 1H, CH_2, cod), 2.00 (b, 4H, CH_2, cod), 2.20 (m, 1H, CH_2, cod), 3.27 (b, 1H, CH=, cod), 4.01 (m, 2H, CH_2-S, C*H*CHO), 4.19 (dd, 1H, CH_2-S, $^2J_{H-H}$ =14.4 Hz, $^3J_{H-H}$ =6.0 Hz), 4.30 (m, 2H, CH-O, C*H*CH_2S), 4.57 (b, 2H, CH=, cod), 4.71 (b, 1H, CH=, cod), 7.02-8.24 (m, 29H, CH= aromatic). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=0.28 (CH_3, $SiMe_3$), 1.93 (CH_3, $SiMe_3$), 18.7 (CH_3), 26.8 (CH_3), 26.9 (CH_3), 30.1 (b, CH_2, cod), 30.4 (b, CH_2, cod), 31.2 (b, CH_2, cod), 35.3 (d, CH_2, cod, J_{C-P} =4.6 Hz), 48.8 (CH_2-S), 70.3 (CH=, cod), 77.6 (CH=, cod), 80.5 (*C*HCH_2S), 82.7 (*C*HCHO), 84.7 (d, CH-O, $^2J_{C-P}$ =20.1 Hz), 101.4 (d, CH=, cod, J_{C-P} =17.5 Hz), 103.4 (d, CH=, cod, J_{C-P} =15.3 Hz), 110.2 (CMe_2), 120.8-150.7 (aromatic carbons), 162.1 (q, C-B, BAr_F, $^1J_{C-B}$ =49.3 Hz). MS HR-ESI [found 1077.3148, $C_{52}H_{61}IrO_5PSSi_2$ $(M)^+$ requires 1077.3145].

[Ir(cod)(L12g)]BAr$_F$. Yield: 64 mg (89%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ= 99.6 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.56 (b, 3H, CH_3), 0.58 (s, 9H, CH_3, $SiMe_3$), 0.73 (s, 9H, CH_3, $SiMe_3$), 1.29 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 1.74-1.81 (b, 2H, CH_2, cod), 1.89-2.05 (m, 3H, CH_2, cod), 2.16-2.36 (b, 3H, CH_2, cod), 3.59 (b, 1H, CH=, cod), 3.62 (m, 1H, CH_2-S), 3.94 (pt,

1H, C*H*CHO, $^{3}J_{H-H}$ =7.2 Hz), 4.02 (dd, 1H, CH_2-S, $^{2}J_{H-H}$ =11.6 Hz, $^{3}J_{H-H}$ =3.2 Hz), 4.36 (m, 1H, CH=, cod), 4.46 (m, 1H, CH-O), 4.55 (m, 1H, C*H*CH_2S), 4.83 (b, 1H, CH=, cod), 5.19 (b, 1H, CH=, cod), 7.00-8.19 (m, 29H, CH= aromatic). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=0.44 (CH_3, $SiMe_3$), 1.21 (CH_3, $SiMe_3$), 19.3 (CH_3), 26.6 (CH_3), 27.0 (CH_3), 28.2 (CH_2, cod), 29.5 (CH_2, cod), 32.4 (CH_2, cod), 33.3 (CH_2, cod), 46.2 (CH_2-S), 69.7 (CH=, cod), 69.5 (CH=, cod), 79.0 (*C*HCH_2S), 80.0 (CH=, cod), 80.1 (CH-O), 82.9 (d, *C*HCHO, $^{2}J_{C-P}$ =20.1 Hz), 101.4 (d, CH=, cod, J_{C-P} =17.5 Hz), 103.4 (d, CH=, cod, J_{C-P} =15.3 Hz), 110.2 (CMe_2), 120.8-150.7 (aromatic carbons), 162.1 (q, C-B, BAr_F, $^{1}J_{C-B}$ =49.3 Hz). MS HR-ESI [found 1077.3147, $C_{52}H_{61}IrO_5PSSi_2$ $(M)^+$ requires 1077.3145].

[Ir(cod)(L13a)]BAr_F. Yield: 66 mg (89%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ=102.1 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ=-0.04 (s, 3H, CH_3, OTBDMS), 0.00 (s, 3H, CH_3, OTBDMS), 0.88 (s, 9H, CH_3, ^{t}Bu, OTBDMS), 1.25 (s, 3H, CH_3), 1.26 (s, 3H, CH_3), 1.35 (s, 9H, CH_3, ^{t}Bu), 1.37 (s, 9H, CH_3, ^{t}Bu), 1.51 (s, 9H, CH_3, ^{t}Bu), 1.72 (s, 9H, CH_3, ^{t}Bu), 1.86 (b, 2H, CH_2, cod), 1.94 (d, 1H, CH_2-OTBDMS, $^{2}J_{H-H}$ =12.0 Hz), 2.04-2.13 (b, 5H, CH_2, cod), 2.33-2.38 (m, 1H, CH_2, cod), 3.22 (d, 1H, CH_2-OTBDMS, $^{2}J_{H-H}$ =11.6 Hz), 3.73 (dd, 1H, CH_2-S, $^{2}J_{H-H}$ =12.8 Hz, $^{3}J_{H-H}$ =2.8 Hz), 3.87 (dd, 1H, CH_2-S, $^{2}J_{H-H}$ =13.2 Hz, $^{3}J_{H-H}$ =6.4 Hz), 4.11 (b, 1H, CH=, cod), 4.23 (pt, 1H, C*H*CHO, $^{3}J_{H-H}$ =8.8 Hz), 4.31-4.37 (m, 2H, CH= cod, CH-O), 4.53-4.57 (m, 1H, C*H*CH_2S), 4.97 (b, 2H, CH=, cod), 7.10-7.71 (m, 21H, CH= aromatic). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=-5.7 (CH_3, OTBDMS), -5.0 (CH_3, OTBDMS), 18.3 (C, ^{t}Bu, OTBDMS), 25.8 (CH_3, ^{t}Bu, OTBDMS), 26.5 (CH_3), 26.8 (CH_3), 27.7 (CH_2, cod), 30.8 (CH_3, ^{t}Bu), 30.9 (CH_2, cod), 31.2 (CH_3, ^{t}Bu), 31.4 (CH_3, ^{t}Bu), 31.6 (d, CH_2, cod, J_{C-P} =3.8 Hz), 31.8 (CH_3, ^{t}Bu), 33.6 (d, CH_2, cod, J_{C-P} =4.3 Hz), 34.8 (C, ^{t}Bu), 34.9 (C, ^{t}Bu), 35.2 (C, ^{t}Bu), 35.8 (C, ^{t}Bu), 45.6 (CH_2-S), 60.5 (CH_2-OTBDMS), 68.8 (CH=, cod), 76.0 (d, *C*HCHO, $^{3}J_{C-P}$ =5.3 Hz), 77.0 (CH=, cod), 77.2 (*C*HCH_2S), 83.1 (d, CH-O, $^{2}J_{C-P}$ =15.3 Hz), 101.8 (d, CH=, cod, J_{C-P} =16.1 Hz), 103.8 (d, CH=, cod, J_{C-P} =17.5 Hz), 111.8 (CMe_2), 117.4-149.8 (aromatic carbons), 161.6 (q, C-B, BAr_F, $^{1}J_{C-B}$ =50.5 Hz). MS HR-ESI [found 1137.5207, $C_{56}H_{85}IrO_6PSSi$ $(M)^+$ requires 1137.5203].

[Ir(cod)(L14a)]BAr_F. Yield: 69 mg (91%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ=102.3 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ=-0.03 (s, 3H, CH_3, OTBDMS), -0.02 (s, 3H, CH_3, OTBDMS), 0.89 (s, 9H, CH_3, ^{t}Bu, OTBDMS), 1.26 (s, 6H, CH_3), 1.37 (s, 9H, CH_3, ^{t}Bu), 1.38 (s, 9H, CH_3, ^{t}Bu), 1.54 (s, 9H, CH_3, ^{t}Bu), 1.77 (s, 9H, CH_3, ^{t}Bu), 1.82 (b, 2H, CH_2, cod), 1.99 (b, 3H, CH_2-OTBDMS, CH_2, cod), 2.13 (b, 3H, CH_2, cod), 2.37 (b, 1H, CH_2, cod), 3.23 (d, 1H, CH_2-OTBDMS, $^{2}J_{H-H}$ =12.0 Hz), 3.81 (d, 1H, CH_2-S, $^{2}J_{H-H}$ =11.8 Hz), 3.99 (dd, 1H, CH_2-S, $^{2}J_{H-H}$ =12.8 Hz, $^{3}J_{H-H}$ =6.4 Hz), 4.13 (m, 1H, CH=, cod), 4.26 (pt, 1H, C*H*CHO, $^{3}J_{H-H}$ =8.4 Hz), 4.36-4.41 (m, 2H, CH-O, CH=, cod), 4.61 (b, 1H, C*H*CH_2S), 4.98 (b, 1H, CH=, cod), 5.07 (b, 1H, CH=, cod), 7.12-8.07 (m, 23H, CH= aromatic). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=-5.7 (CH_3, $SiMe_3$, OTBDMS), -5,0 (CH_3, $SiMe_3$, OTBDMS), 18.3 (C, ^{t}Bu, OTBDMS), 25.8 (CH_3, ^{t}Bu, OTBDMS), 26.5 (CH_3), 26.8 (CH_3), 27.7 (CH_2, cod), 29.7 (CH_2, cod), 30.9 (CH_3, ^{t}Bu), 31.2 (CH_3, ^{t}Bu), 31.4 (CH_3, ^{t}Bu), 31.7 (CH_2, cod), 31.9 (CH_3, ^{t}Bu), 33.6 (CH_2, cod), 34.8 (C, ^{t}Bu), 35.0 (C, ^{t}Bu), 35.2 (C, ^{t}Bu), 35.9 (C, ^{t}Bu), 45.8 (CH_2-S), 60.5 (CH_2-OTBDMS), 68.8 (CH=, cod), 76.1 (d, *C*HCHO, $^{3}J_{C-P}$ =4.5 Hz), 77.2 (*C*HCH_2S, CH= cod), 83.2 (d, CH-O, $^{2}J_{C-P}$ =14.5 Hz), 101.9 (d, CH=, cod, J_{C-P} =14.6 Hz), 103.8 (d, CH=, cod, J_{C-P} =16.9 Hz), 111.8 (CMe_2), 117.4-149.8 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^{1}J_{C-B}$ =49.7 Hz). MS HR-ESI [found 1087.5363, $C_{60}H_{87}IrO_6PSSi$ $(M)^+$ requires 1087.5359].

[Ir(cod)(L14g)]BAr$_F$. Yield: 71 mg (93%).^{31}P NMR (161.9 MHz, $CDCl_3$): δ=101.0 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ=-0.09 (s, 3H, CH_3, OTBDMS), -0.02 (s, 3H, CH_3, OTBDMS), 0.63 (s, 9H, CH_3, $SiMe_3$), 0.71 (s, 9H, CH_3, $SiMe_3$), 0.86 (s, 9H, CH_3, ^{t}Bu, OTBDMS), 1.27 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 1.72-2.07 (m, 6H, CH_2, cod), 2.05 (d, 1H, CH_2-OTBDMS, $^2J_{H\text{-}H}$ =12.0 Hz), 2.17-2.21 (m, 1H, CH_2, cod), 2.29-2.32 (m, 1H, CH_2, cod), 3.18 (d, 1H, CH_2-OTBDMS, $^2J_{H\text{-}H}$ =11.6 Hz), 3.55-3.60 (m, 1H, CH_2-S), 3.69 (b, 1H, CH=, cod), 4.03 (dd, 1H, CH_2-S, $^2J_{H\text{-}H}$ =11.2 Hz, $^3J_{H\text{-}H}$ =3.2 Hz), 4.30 (m, 2H, CH-O, CH=, cod), 4.44 (pt, 1H, C*H*CHO, $^3J_{H\text{-}H}$ =8.4 Hz), 4.57 (b, 1H, C*H*CH_2S), 4.93 (b, 1H, CH=, cod), 5.30 (b, 1H, CH=, cod), 6.98-8.18 (m, 29H, CH= aromatic). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=-5.9 (CH_3, $SiMe_3$, OTBDMS), -5,3 (CH_3, $SiMe_3$, OTBDMS), 0.0 (CH_3, $SiMe_3$), 0.9 (CH_3, $SiMe_3$), 18.4 (C, ^{t}Bu, OTBDMS), 25.8 (CH_3, ^{t}Bu, OTBDMS), 26.2 (CH_3), 26.8 (CH_3), 27.8 (CH_2, cod), 29.6 (d, CH_2, cod, $J_{C\text{-}P}$ =13.0 Hz), 31.9 (CH_2, cod), 33.4 (CH_2, cod), 45.6 (CH_2-S), 61.2 (CH_2-OTBDMS), 69.5 (CH=, cod), 76.2 (d, *C*HCHO, $^3J_{C\text{-}P}$ =5.3 Hz), 76.6 (*C*HCH_2S), 79.2 (CH=, cod), 82.5 (d, CH-O, $^2J_{C\text{-}P}$ =14.5 Hz), 102.6 (d, CH=, cod, $J_{C\text{-}P}$ =17.6 Hz), 105.5 (d, CH=, cod, $J_{C\text{-}P}$ =15.3 Hz), 112.4 (CMe_2), 117.4-151.6 (aromatic carbons), 162.2 (q, C-B, BAr_F, $^1J_{C\text{-}B}$ =63.4 Hz). MS HR-ESI [found 1207.3964, $C_{58}H_{75}IrO_6PSSi_3$ $(M)^+$ requires 1207.3959].

[Ir(cod)(L15f)]BAr$_F$. Yield: 73 mg (90%).^{31}P NMR (161.9 MHz, $CDCl_3$): δ=100.5 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.55 (s, 9H, CH_3, $SiMe_3$), 0.70 (s, 9H, CH_3, $SiMe_3$), 1.09 (s, 9H, CH_3, ^{t}Bu, OTBDPS), 1.18 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 1.70 (b, 1H, CH_2, cod), 1.85 (b, 2H, CH_2, cod), 2.01 (b, 1H, CH_2, cod), 2.11-2.22 (m, 3H, CH_2, cod), 2.30-2.36 (m, 1H, CH_2, cod), 2.51 (d, 1H, CH_2-OTBDPS, $^2J_{H\text{-}H}$ =12.0 Hz), 3.37 (d, 1H, CH_2-OTBDPS, $^2J_{H\text{-}H}$ =11.6 Hz), 3.44-3.49 (m, 1H, CH_2-S), 3.74 (b, 1H, CH=, cod), 4.11 (d, 1H, CH_2-S, $^2J_{H\text{-}H}$ =9.9 Hz), 4.32 (b, 2H, CH-O, CH=, cod), 4.68 (b, 2H, C*H*CH_2S, C*H*CHO), 4.97 (b, 1H, CH=, cod), 5.34 (b, 1H, CH=, cod), 6.93-8.17 (m, 39H, CH= aromatic). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=-0.1 (CH_3, $SiMe_3$), -0.8 (CH_3, $SiMe_3$), 19.8 (C, ^{t}Bu, OTBDPS), 26.0 (CH_3), 26.7 (CH_3), 27.1 (CH_3, ^{t}Bu, OTBDPS), 27.7 (CH_2, cod), 29.8 (CH_2, cod), 31.8 (CH_2, cod), 33.6 (CH_2, cod), 45.6 (CH_2-S), 62.5 (CH_2-OTBDPS), 70.0 (CH=, cod), 75.7 (*C*HCHO, *C*HCH_2S), 80.0 (CH=, cod), 82.2 (d, CH-O, $^2J_{C\text{-}P}$ =14.6 Hz), 102.6 (d, CH=, cod, $J_{C\text{-}P}$ =16.0 Hz), 105.6 (d, CH=, cod, $J_{C\text{-}P}$ =16.0 Hz), 112.4 (CMe_2), 117.4-151.0 (aromatic carbons), 161.8 (q, C-B, BAr_F, $^1J_{C\text{-}B}$ =49.7 Hz). MS HR-ESI [found 1331.4276, $C_{68}H_{79}IrO_6PSSi_3$ $(M)^+$ requires 1331.4272].

[Ir(cod)(L16g)]BAr$_F$. Yield: 71 mg (91%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ=100.4 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.62 (s, 9H, CH_3, $SiMe_3$), 0.71 (s, 9H, CH_3, $SiMe_3$), 0.97 (s, 21H, CH, CH_3, OTIPS), 1.27 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 1.69 (b, 1H, CH_2, cod), 1.84 (b, 2H, CH_2, cod), 2.00 (b, 1H, CH_2, cod), 2.11 (b, 3H, CH_2, cod), 2.34 (b, 1H, CH_2, cod), 2.51 (d, 1H, CH_2-OTIPS, $^2J_{H\text{-}H}$ =11.2 Hz), 3.30 (d, 1H, CH_2-OTIPS, $^2J_{H\text{-}H}$ =10.4 Hz), 3.45-3.50 (m, 1H, CH_2-S), 3.72 (b, 1H, CH=, cod), 4.08 (dd, 1H, CH_2-S, $^2J_{H\text{-}H}$ =10.8 Hz, $^3J_{H\text{-}H}$ =2.8 Hz), 4.30-4.38 (m, 2H, CH-O, CH=, cod), 4.57 (pt, 1H, C*H*CHO, $^3J_{H\text{-}H}$ =8.4 Hz), 4.65 (m, 1H, C*H*CH_2S), 4.96 (b, 1H, CH=, cod), 5.31 (b, 1H, CH=, cod), 6.94-8.17 (m, 29H, CH= aromatic). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=-0.1 (CH_3, $SiMe_3$), 0.8 (CH_3, $SiMe_3$), 12.0 (CH, OTIPS), 17.9 (CH_3, OTIPS), 26.2 (CH_3), 26.8 (CH_3), 27.6 (CH_2, cod), 29.8 (b, CH_2, cod), 31.8 (CH_2, cod), 33.6 (CH_2, cod), 45.5 (CH_2-S), 62.3 (CH_2-OTr), 69.8 (CH=, cod), 76.1 (*C*HCH_2S), 77.0 (*C*HCHO), 80.0 (CH=, cod), 82.5 (d, CH-O, $^2J_{C\text{-}P}$ =14.5 Hz), 102.5 (d, CH=, cod, $J_{C\text{-}P}$ =16.8 Hz), 105.3 (d, CH=, cod, $J_{C\text{-}P}$ =16.1 Hz), 112.6 (CMe_2),

117.4-151.1 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^1J_{C-B}$ =49.7 Hz). MS HR-ESI [found 1249.4431, $C_{61}H_{81}IrO_6PSSi_3$ $(M)^+$ requires 1249.4428].

[Ir(cod)(L17g)]BAr_F. Yield: 73 mg (90%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ= 99.5 (s). ^1H NMR (400 MHz, $CDCl_3$): δ=0.46 (s, 9H, CH_3, $SiMe_3$), 0.70 (s, 9H, CH_3, $SiMe_3$), 1.34 (s, 3H, CH_3), 1.37 (s, 3H, CH_3), 1.66 (b, 1H, CH_2, cod), 1.81 (b, 2H, CH_2, cod), 1.98-2.17 (m, 4H, CH_2, cod), 2.29-2.36 (m, 1H, CH_2, cod), 2.52 (dd, 1H, CH_2-OTr, $^2J_{H-H}$ =11.2 Hz, $^3J_{H-H}$ =4.0 Hz), 3.06 (dd, 1H, CH_2-OTr, $^2J_{H-H}$ =11.8 Hz, $^3J_{H-H}$ =2.8 Hz), 3.48-3.53 (m, 1H, CH_2-S), 3.66 (b, 1H, CH_2, cod), 4.10 (dd, 1H, CH_2-S, $^2J_{H-H}$ =11.2 Hz, $^3J_{H-H}$ =3.2 Hz), 4.33 (m, 1H, CH=, cod), 4.43 (m, 1H, CH-O), 4.71 (m, 2H, C*H*CHO, C*H*CH_2S), 4.89 (b, 1H, CH=, cod) 5.30 (b, 1H, CH=, cod), 6.85-8.15 (m, 44H, CH= aromatic). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=-0.1 (CH_3, $SiMe_3$), 0.9 (CH_3, $SiMe_3$), 26.3 (CH_3), 26.7 (CH_3), 27.6 (CH_2, cod), 29.8 (d, CH_2, cod, J_{C-P} =19.1 Hz), 31.7 (CH_2, cod), 33.7 (CH_2, cod), 45.1 (CH_2-S), 63.0 (CH_2-OTr), 70.2 (CH=, cod), 76.0 (*C*HCH_2S), 78.3 (*C*HCHO), 80.7 (CH=, cod), 81.2 (d, CH-O, $^2J_{C-P}$ =15.3 Hz), 87.3 (C, OTr), 102.5 (d, CH=, cod, J_{C-P} =16.1 Hz), 105.2 (d, CH=, cod, J_{C-P} =16.1 Hz), 112.5 (CMe_2), 117.4-150.8 (aromatic carbons), 162.7 (q, C-B, BAr_F, $^1J_{C-B}$ =49.7 Hz). MS HR-ESI [found 1335.4193, $C_{71}H_{75}IrO_6PSSi_2$ $(M)^+$ requires 1335.4190].

[Ir(cod)(L18a)]BAr_F. Yield: 62 mg (91%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ=105.2 (s). ^1H NMR (400 MHz, $CDCl_3$): δ=0.83 (d, 3H, CH_3, $^3J_{H-H}$ =6.4 Hz), 1.24 (s, 3H, CH_3), 1.26 (s, 3H, CH_3), 1.36 (s, 9H, CH_3, ^{t}Bu), 1.37 (s, 9H, CH_3, ^{t}Bu), 1.47 (s, 9H, CH_3, ^{t}Bu), 1.75 (s, 9H, CH_3, ^{t}Bu), 1.85 (b, 2H, CH_2, cod), 1.95-2.10 (b, 4H, CH_2, cod), 2.14-2.31 (m, 2H, CH_2, cod), 3.95 (dd, 1H, CH_2-S, $^2J_{H-H}$ =14.0 Hz, $^3J_{H-H}$ =4.8 Hz), 4.05 (d, 1H, CH_2-S, $^2J_{H-H}$ =14.0 Hz), 4.14-4.19 (m, 1H, CH=, cod), 4.23-4.91 (m, 3H, C*H*CH_2S, C*H*CHO, CH-O), 4.43-4.38 (m, 1H, CH=, cod), 4.77 (b, 2H, CH=, cod), 7.15-7.71 (m, 21H, CH= aromatic). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=14.2 (CH_3), 26.6 (CH_3), 28.3 (CH_2, cod), 28.6 (CH_2, cod), 31.3 (CH_3, ^{t}Bu), 31.6 (CH_3, ^{t}Bu), 32.1 (CH_3, ^{t}Bu), 33.2 (d, CH_2, cod, J_{C-P} =3.6 Hz), 33.3 (d, CH_2, cod, J_{C-P} =4.8 Hz), 35.1 (C, ^{t}Bu), 35.2 (C, ^{t}Bu), 35.5 (C, ^{t}Bu), 35.8 (C, ^{t}Bu), 47.6 (CH_2-S), 69.2 (CH=, cod), 74.2 (C*H*CHO), 75.5 (CH=, cod), 77.4 (*C*HCH_2S), 79.1 (CH-O), 102.5 (d, CH=, cod, J_{C-P} =15.8 Hz), 103.4 (d, CH=, cod, J_{C-P} =16.5 Hz), 110.3 (CMe_2), 117.7-150.4 (aromatic carbons), 162.0 (q, C-B, BAr_F, $^1J_{C-B}$ =50.2 Hz). MS HR-ESI [found 1007.4392, $C_{50}H_{71}IrO_5PS$ $(M)^+$ requires 1007.4389].

[Ir(cod)(L18f)]BAr_F. Yield: 64 mg (92%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ=103.8 (s). ^1H NMR (400 MHz, $CDCl_3$): δ=0.52 (s, 9H, CH_3, $SiMe_3$), 0.76 (s, 9H, CH_3, $SiMe_3$), 0.92 (d, 3H, CH_3, $^3J_{H-H}$ =6.8 Hz), 1.22 (s, 3H, CH_3), 1.25 (s, 3H, CH_3), 1.70 (b, 2H, CH_2, cod), 1.94-2.22 (m, 6H, CH_2, cod), 3.66 (b, 1H, CH=, cod), 3.90 (d, 1H, CH_2-S, $^2J_{H-H}$ =14.4 Hz), 4.03 (dd, 1H, CH_2-S, $^2J_{H-H}$ =14.0 Hz, $^3J_{H-H}$ =6.8 Hz), 4.07-4.13 (m, 1H, C*H*CH_2S), 4.22 (pt, 1H, CH-O, $^3J_{H-H}$ =5.2 Hz), 4.30 (pt, 1H, C*H*CHO, $^3J_{H-H}$ =7.6 Hz), 4.39-4.44 (m, 1H, CH=, cod), 4.52 (b, 1H, CH=, cod), 4.80 (b, 1H, CH=, cod), 6.99-8.19 (m, 27H, CH= aromatic). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=0.3 (CH_3, $SiMe_3$), 1.6 (CH_3, $SiMe_3$), 14.5 (d, CH_3, $^3J_{C-P}$ =4.9 Hz), 26.6 (CH_3), 26.8 (CH_2, cod), 26.9 (CH_3), 30.4 (CH_2, cod), 31.0 (CH_2, cod), 35.1 (d, CH_2, cod, J_{C-P} =5.3 Hz), 49.2 (CH_2-S), 69.1 (CH=, cod), 75.3 (*C*HCHO), 75.7 (CH=, cod), 77.4 (*C*HCH_2S), 79.6 (CH-O), 102.8 (d, CH=, cod, J_{C-P} =17.6 Hz), 104.2 (d, CH=, cod, J_{C-P} =15.0 Hz), 110.4 (CMe_2), 117.6-150.9 (aromatic carbons), 162.0 (q, C-B, BAr_F, $^1J_{C-B}$ =49.9 Hz). MS HR-ESI [found 1027.2992, $C_{48}H_{59}IrO_5PSSi_2$ $(M)^+$ requires 1027.2989].

[Ir(cod)(L18g)]BAr_F. Yield: 62 mg (90%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ=103.6 (s). ^1H NMR (400 MHz, $CDCl_3$): δ=0.53 (s, 9H, CH_3, $SiMe_3$), 0.73 (s, 9H, CH_3, $SiMe_3$), 0.88 (d, 3H, CH_3,

$^3J_{H-H}$ =6.4 Hz), 1.29 (s, 3H, CH_3), 1.39 (s, 3H, CH_3), 1.55 (b, 1H, CH_2, cod), 1.69-1.77 (m, 1H, CH_2, cod), 1.77-1.87 (m, 1H, CH_2, cod), 1.91-2.12 (m, 3H, CH_2, cod), 2.24-2.29 (m, 2H, CH_2, cod), 3.73 (d, 1H, CH_2-S, $^2J_{H-H}$ =13.6 Hz), 3.89 (b, 1H, CH=, cod), 3.99 (dd, 1H, CH_2-S, $^2J_{H-H}$ =14.0 Hz, $^3J_{H-H}$ =5.6 Hz), 4.08-4.14 (m, 1H, CH=, cod), 4.36 (b, 2H, C*H*CH_2S, C*H*CHO), 4.44 (b, 2H, CH-O, CH= cod), 5.11 (b, 1H, CH= cod), 6.94-8.19 (m, 27H, CH= aromatic). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=0.1 (CH_3, $SiMe_3$), 1.4 (CH_3, $SiMe_3$), 14.8 (CH_3), 26.3 (CH_3), 26.7 (CH_3), 29.7 (CH_2, cod), 29.9 (CH_2, cod), 31.4 (CH_2, cod), 35.1 (CH_2, cod), 46.7 (CH_2-S), 69.8 (CH=, cod), 74.2 (CH=, cod), 74.9 (*C*HCH_2S), 79.4 (d, CH-O, $^2J_{C-P}$ =16.0 Hz), 80.2 (d, *C*HCHO, $^3J_{C-P}$ =9.2 Hz), 100.9 (d, CH=, cod, J_{C-P} =17.6 Hz), 102.8 (d, CH=, cod, J_{C-P} =15.3 Hz), 110.7 (CMe_2), 117.4-150.7 (aromatic carbons), 161.6 (q, C-B, BAr_F, $^1J_{C-B}$ =50.5 Hz). MS HR-ESI [found 1027.2993, $C_{48}H_{59}IrO_5PSSi_2$ $(M)^+$ requires 1027.2989].

[Ir(cod)(L19f)]BAr_F. Yield: 65 mg (94%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ=104.2 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.58 (s, 9H, CH_3, $SiMe_3$), 0.67 (s, 9H, CH_3, $SiMe_3$), 1.31 (s, 6H, CH_3), 1.79 (d, 3H, CH_3, $^3J_{H-H}$ =7.6 Hz), 1.88 (m, 2H, CH_2, cod), 1.98-1.93 (m, 3H, CH_2, cod), 2.17 (b, 3H, CH_2, cod), 3.53-3.62 (m, 1H, CH_2-O), 3.66 (b, 1H, CH=, cod), 3.95-4.02 (m, 1H, CH_2-O), 4.15-4.23 (m, 2H, C*H*CH_2O, CH_2-S), 4.46 (dd, 1H, C*H*CHS, $^3J_{H-H}$ =2.0, $^3J_{H-H}$ =8.0), 4.64-4.73 (b, 2H, CH=, cod), 4.96 (b, 1H, CH=, cod), 6.99-8.18 (m, 27H, CH= aromatic). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=0.3 (CH_3, $SiMe_3$), 1.3 (CH_3, $SiMe_3$), 19.0 (CH_3), 26.4 (CH_3), 26.7 (CH_3), 28.5 (CH_2, cod), 29.0 (CH_2, cod), 32.4 (d, CH_2, cod, J_{C-P} =4.1 Hz), 32.7 (d, CH_2, cod, J_{C-P} =3.5 Hz), 54.5 (CH-S), 67.2 (d, CH_2-O, $^2J_{C-P}$ =11.4 Hz), 68.8 (CH=, cod), 72.1 (*C*HCH_2O), 76.9 (CH=, cod), 80.9 (*C*HCHS), 104.0-104.3 (CH=, cod), 109.0 (CMe_2), 117.4-149.6 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^1J_{C-B}$ =49.7 Hz). MS HR-ESI [found 1027.2990, $C_{48}H_{59}IrO_5PSSi_2$ $(M)^+$ requires 1027.2989].

[Ir(cod)(L19g)]BAr_F. Yield: 61 mg (89%).^{31}P NMR (161.6 MHz, $CDCl_3$): δ=102.1 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.54 (s, 9H, CH_3, $SiMe_3$), 0.76 (s, 9H, CH_3, $SiMe_3$), 1.25 (s, 3H, CH_3), 1.32 (s, 3H, CH_3), 1.72 (d, 3H, CH_3, $^3J_{H-H}$ =6.8 Hz), 1.89 -2.40, (m, 2H, CH_2, cod), 2.07-2.15 (m, 2H, CH_2, cod), 2.22-2.26 (m, 4H, CH_2, cod), 3.33-3.37 (m, 1H, CH_2-O), 3.89 (b, 1H, CH=, cod), 3.97-4.17 (m, 3H, CH_2-O, C*H*CH_2O, CH-S), 4.32-4.38 (m, 1H, CH=, cod), 4.41 (d, 1H, C*H*CHS, $^3J_{H-H}$ =6.8 Hz), 4.8 (b, 1H, CH=, cod), 5.04 (b, 1H, CH=, cod), 7.03-8.21 (m, 27H, CH= aromatic). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=0.1 (CH_3, $SiMe_3$), 1.4 (CH_3, $SiMe_3$), 17.7 (CH_3), 26.5 (CH_3), 26.9 (CH_3), 29.7 (CH_2, cod), 30.4 (CH_2, cod), 30.9 (d, CH_2, cod, J_{C-P} =3.5 Hz), 34.5 (d, CH_2, cod, J_{C-P} =4.8 Hz), 56.2 (CH-S), 68.1 (d, CH_2O, $^2J_{C-P}$ =14.5 Hz), 69.3 (CH=, cod), 72.7 (d, *C*HCH_2O, $^3J_{C-P}$ =8.1 Hz), 74.8 (CH=, cod), 81.2 (*C*HCHS), 102.4 (d, CH=, cod, J_{C-P} =16.8 Hz), 104.7 (d, CH=, cod, J_{C-P} =15.3 Hz), 110.4 (CMe_2), 117.4-150.9 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^1J_{C-B}$ =49.7 Hz). MS HR-ESI [found 1027.2992, $C_{48}H_{59}IrO_5PSSi_2$ $(M)^+$ requires 1027.2989].

[Ir(cod)(L20a)]BAr_F. Yield: 64 mg (91%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ=101.2 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.27 (s, 3H, CH_3), 1.29 (s, 3H, CH_3), 1.36 (s, 9H, CH_3, ^{t}Bu), 1.37 (s, 9H, CH_3, ^{t}Bu), 1.51 (s, 9H, CH_3, ^{t}Bu), 1.73 (s, 9H, CH_3, ^{t}Bu), 1.76 (b, 1H, CH_2, cod), 1.86 (b, 1H, CH_2, cod), 1.95-2.19 (b, 6H, CH_2, cod), 3.64-3.76 (m, 3H, CH_2-O, CH_2-Se, CH= cod), 3.89 (b, 1H, CH_2-O), 3.95-4.01 (m, 1H, CH_2-Se), 4.13 (b, 1H, C*H*CH_2O), 4.30 (pt, 1H, C*H*CH_2Se, ^3J = 9.2 Hz), 4.61 (b, 2H, CH=, cod), 4.76 (b, 1H, CH=, cod), 7.19-7.71 (m, 21H, CH= aromatic). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 26.5 (CH_3), 28.1 (CH_2, cod), 29.4 (CH_2, cod), 31.2 (CH_3, ^{t}Bu), 31.3

(CH_3, ^{t}Bu), 31.8 (CH_2, cod), 32.0 (CH_3, ^{t}Bu), 33.2 (CH_2, cod), 34.9 (C, ^{t}Bu), 35.4 (C, ^{t}Bu), 35.5 (C, ^{t}Bu), 41.3 (CH_2-Se), 66.9 (b, CH=, cod), 69.2 (d, CH_2-O, $^2J_{C\text{-}P}$ =15.3 Hz), 75.1 (b, CH=, cod), 77.6 (*C*HCH$_2$O), 79.3 (*C*HCH$_2$S), 102.0 (d, CH=, cod, $J_{C\text{-}P}$ =16.0 Hz), 103.5 (d, CH=, cod, $J_{C\text{-}P}$ =16.1 Hz), 110.2 (CMe_2), 117.4-149.7 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^1J_{C\text{-}B}$ =49.7 Hz). MS HR-ESI [found 1041.3679, $C_{49}H_{69}IrO_5PSe$ $(M)^+$ requires 1041.3677].

[Ir(cod)(L20f)]BAr$_F$. Yield: 62 mg (88%).^{31}P NMR (161.9 MHz, $CDCl_3$): δ=100.4 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.53 (s, 9H, CH_3, $SiMe_3$), 0.72 (s, 9H, CH_3, $SiMe_3$), 1.26 (s, 3H, CH_3), 1.29 (s, 3H, CH_3), 1.69 (b, 1H, CH_2, cod), 1.82 (b, 1H, CH_2, cod), 1.91-2.13 (m, 6H, CH_2, cod), 3.51 (CH=, cod), 3.59-3.64 (m, 1H, CH_2-O), 3.69 (d, 2H, CH_2-Se, $^3J_{H\text{-}H}$ = 6.0), 3.89-3.97 (m, 1H, CH_2-O), 4.08-4.14 (m, 1H, C*H*CH$_2$O), 4.41-4.46 (m, 1H, C*H*CH$_2$Se), 4.57 (b, 1H, CH=, cod), 4.76 (b, 1H, CH=, cod), 4.86 (b, 1H, CH=, cod), 7.06-8.20 (m, 27H, CH= aromatic). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=0.0 (CH_3, $SiMe_3$), 1.1 (CH_3, $SiMe_3$), 26.4 (CH_3), 26.6 (CH_3), 27.7 (CH_2, cod), 30.0 (CH_2, cod), 31.1 (CH_2, cod), 33.8 (CH_2, cod), 41.2 (CH_2-Se), 68.1 (CH=, cod), 68.5 (d, CH_2O, $^2J_{C\text{-}P}$ =14.6 Hz), 76.1 (CH=, cod), 77.3 (*C*HCH$_2$O), 78.2 (*C*HCH$_2$S), 101.5 (d, CH=, cod, $J_{C\text{-}P}$ =16.9 Hz), 105.0 (d, CH=, cod, $J_{C\text{-}P}$ =15.0 Hz), 112.0 (CMe_2), 117.4-150.5 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^1J_{C\text{-}B}$ =50.5 Hz). MS HR-ESI [found 1061.2281, $C_{47}H_{57}IrO_5PSeSi_2$ $(M)^+$ requires 1061.2277].

[Ir(cod)(L20g)]BAr$_F$. Yield: 63 mg (89%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ=103.4 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.53 (s, 9H, CH_3, $SiMe_3$), 0.76 (s, 9H, CH_3, $SiMe_3$), 1.26 (s, 6H, CH_3), 1.59 (b, 1H, CH_2, cod), 1.74 (b, 1H, CH_2, cod), 2.00-2.23 (m, 6H, CH_2, cod), 3.39 (CH=, cod), 3.47-3.56 (m, 1H, CH_2-O), 3.60-3.66 (m, 2H, CH_2-O, CH_2-Se), 3.89-3.95 (m, 1H, CH_2-Se), 3.99-4.05 (m, 1H, C*H*CH$_2$O), 4.28 (pt, 1H, C*H*CH$_2$Se, $^3J_{H\text{-}H}$ =8.4), 4.52-4.59 (b, 2H, CH=, cod), 4.87 (b, 1H, CH=, cod), 7.08-8.22 (m, 27H, CH= aromatic). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=-0.2 (CH_3, $SiMe_3$), 1.4 (CH_3, $SiMe_3$), 26.4 (CH_3), 26.6 (CH_3), 26.8 (CH_2, cod), 30.4 (CH_2, cod), 30.7 (CH_2, cod), 34.7 (CH_2, cod), 42.1 (CH_2-Se), 67.0 (CH=, cod), 69.2 (d, CH_2-O, $^2J_{C\text{-}P}$ =13.8 Hz), 76.3 (CH=, cod), 78.0 (*C*HCH$_2$O), 80.4 (*C*HCH$_2$S), 102.9 (d, CH=, cod, $J_{C\text{-}P}$ =16.8 Hz), 103.4 (d, CH=, cod, $J_{C\text{-}P}$ =14.5 Hz), 110.2 (CMe_2), 117.4-150.1 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^1J_{C\text{-}B}$ =49.7 Hz). MS HR-ESI [found 1061.2282, $C_{47}H_{57}IrO_5PSeSi_2$ $(M)^+$ requires 1061.2277].

[Ir(cod)(L21f)]BAr$_F$. Yield: 66 mg (90%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ=103.6 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.55 (s, 9H, CH_3, $SiMe_3$), 0.81 (s, 9H, CH_3, $SiMe_3$), 1.26 (s, 3H, CH_3), 1.27 (s, 3H, CH_3), 1.70 (b, 1H, CH_2, cod), 1.99-2.22 (m, 7H, CH_2, cod), 3.43 (CH=, cod), 3.50-3.59 (m, 2H, CH_2-O), 3.62-3.72 (m, 2H, CH_2-O, CH_2-Se), 3.98-4.08 (m, 2H, CH_2-S, C*H*CH$_2$O), 4.32 (pt, 1H, C*H*CH$_2$S, $^3J_{H\text{-}H}$ =8.8 Hz), 4.55 (b, CH=, cod), 4.60-4.68 (m, 1H, CH=, cod), 4.95 (b, 1H, CH=, cod), 7.10-8.23 (m, 29H, CH= aromatic). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=0.0 (CH_3, $SiMe_3$), 1.4 (CH_3, $SiMe_3$), 26.4 (CH_3), 26.6 (CH_3), 26.9 (CH_2, cod), 30.4 (CH_2, cod), 30.7 (CH_2, cod), 34.6 (CH_2, cod), 42.1 (CH_2-Se), 67.2 (CH=, cod), 69.2 (d, CH_2-O, $^2J_{C\text{-}P}$ =14.6 Hz), 76.4 (CH=, cod), 78.0 (*C*HCH$_2$O), 79.6 (*C*HCH$_2$S), 102.7 (d, CH=, cod, $J_{C\text{-}P}$ =17.6 Hz), 103.8 (d, CH=, cod, $J_{C\text{-}P}$ =14.5 Hz), 110.2 (CMe_2), 117.4-150.1 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^1J_{C\text{-}B}$ =49.7 Hz). MS HR-ESI [found 1111.2438, $C_{51}H_{59}IrO_5PSeSi_2$ $(M)^+$ requires 1111.2433].

[Ir(cod)(L21g)]BAr$_F$. Yield: 68 mg (93%).^{31}P NMR (161.9 MHz, $CDCl_3$): δ=100.6 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.56 (s, 9H, CH_3, $SiMe_3$), 0.80 (s, 9H, CH_3, $SiMe_3$), 1.27 (s, 3H, CH_3), 1.29 (s, 3H, CH_3), 1.68 (b, 1H, CH_2, cod), 1.80 (b, 1H, CH_2, cod), 1.95 (b, 1H, CH_2, cod), 2.10 (b, 4H, CH_2, cod), 3.53 (CH=, cod), 3.66 (m, 1H, CH_2-O), 3.79 (m, 2H, CH_2-Se), 3.92-3.40 (m,

1H, CH_2-O), 4.13-4.18 (m, 1H, C*H*CH_2O), 4.49 (b, 1H, C*H*CH_2Se, $^3J_{H-H}$ =8.8 Hz), 4.60 (b, CH=, cod), 4.83 (b, 1H, CH=, cod), 4.95 (b, 1H, CH=, cod), 7.08-8.22 (m, 29H, CH= aromatic). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=0.0 (CH_3, $SiMe_3$), 1.1 (CH_3, $SiMe_3$), 26.4 (CH_3), 26.6 (CH_3), 27.7 (CH_2, cod), 30.1 (CH_2, cod), 31.1 (CH_2, cod), 33.9 (CH_2, cod), 41.4 (CH_2-Se), 68.2 (CH=, cod), 68.5 (d, CH_2-O, $^2J_{C-P}$ =14.6 Hz), 76.2 (CH=, cod), 77.2 (*C*HCH_2O), 78.1 (*C*HCH_2S), 101.5 (d, CH=, cod, J_{C-P} =17.6 Hz), 105.2 (d, CH=, cod, J_{C-P} =15.3 Hz), 112.1 (CMe_2), 117.4-150.5 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^1J_{C-B}$ =49.7 Hz). MS HR-ESI [found 1111.2437, $C_{51}H_{59}IrO_5PSeSi_2$ $(M)^+$ requires 1111.2433].

[Ir(cod)(L22a)]BAr_F. Yield: 65 mg (89%).^{31}P NMR (161.9 MHz, $CDCl_3$): δ=99.2 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.74 (s, 3H, CH_3), 1.25 (s, 3H, CH_3), 1.26 (s, 3H, CH_3), 1.34 (s, 9H, CH_3, ^{t}Bu), 1.37 (s, 9H, CH_3, ^{t}Bu), 1.39 (s, 3H, CH_3), 1.54 (s, 9H, CH_3, ^{t}Bu), 1.75 (b, 1H, CH_2, cod), 1.97 (m, 2H, CH_2, cod), 2.09-2.21 (b, 5H, CH_2, cod), 3.83 (b, 1H, CH=, cod), 4.04 (d, 1H, CH_2-S, $^2J_{H-H}$ =13.6 Hz), 4.22 (b, 1H, C*H*CMe_2O), 4.26-4.32 (m, 1H, CH_2-S), 4.37 (m, 1H, C*H*CH_2S), 4.50 (b, 1H, CH=, cod), 4.58 (b, 1H, CH=, cod), 4.73 (b, 1H, CH=, cod), 7.16-8.08 (m, 23H, CH= aromatic). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=22.7 (d, CH_3, $^3J_{H-H}$ =6.9 Hz), 26.4 (CH_3), 26.6 (CH_3), 27.5 (CH_2, cod), 29.7 (d, CH_2, cod, J_{C-P} =4.5 Hz), 30.0 (CH_2, cod), 31.3 (CH_3, ^{t}Bu), 31.6 (CH_3, ^{t}Bu), 32.0 (CH_3, ^{t}Bu), 33.9 (CH_2, cod), 34.8 (C, ^{t}Bu), 34.9 (C, ^{t}Bu), 35.4 (C, ^{t}Bu), 35.6 (C, ^{t}Bu), 47.9 (CH_2-S), 76.0 (CH=, cod), 77.2 (*C*HCH_2S), 83.8 (*C*$HCMe_2O$), 91.1 (d, CMe_2O, $^2J_{C-P}$ =35.1 Hz), 100.3 (d, CH=, cod, J_{C-P} =23.6 Hz), 101.1 (d, CH=, cod, J_{C-P} =16.9 Hz), 109.2 (CMe_2), 117.4-150.5 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^1J_{C-B}$ =49.7 Hz). MS HR-ESI [found 1105.3993, $C_{54}H_{73}IrO_5PSe$ $(M)^+$ requires 1105.3990].

[Ir(cod)(L22f)]BAr_F. Yield: 67 mg (91%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ=99.5 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.53 (s, 9H, CH_3, $SiMe_3$), 0.76 (s, 9H, CH_3, $SiMe_3$), 0.94 (s, 3H, CH_3), 0.99 (s, 3H, CH_3), 1.26 (s, 3H, CH_3), 1.32 (s, 3H, CH_3), 1.62-1.73 (b, 2H, CH_2, cod), 1.90-1.94 (m, 1H, CH_2, cod), 1.99-2.08 (m, 4H, CH_2, cod), 2.12-2.17 (m, 1H, CH_2, cod), 3.40 (b, 1H, CH=, cod), 3.76 (dd, 1H, CH_2-Se, $^2J_{H-H}$ =21.2 Hz, $^3J_{H-H}$ =8.0 Hz), 3.87 (dd, 1H, CH_2-Se, $^2J_{H-H}$ =11.2 Hz, $^3J_{H-H}$ =3.2 Hz) 4.00 (d, C*H*CMe_2O, $^3J_{H-H}$ =7.6 Hz), 4.58 (b, 1H, CH=, cod), 4.64-7.72 (b, 2H, C*H*CH_2Se, CH=, cod), 4.81 (b, 1H, CH=, cod), 6.97-8.21 (m, 29H, CH= aromatic). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=0.2 (CH_3, $SiMe_3$), 1.3 (CH_3, $SiMe_3$), 22.1 (CH_3), 26.7 (CH_3), 27.0 (CH_3), 27.5 (CH_2, cod), 29.0 (CH_3), 30.4 (CH_2, cod), 30.7 (CH_2, cod), 34.1 (CH_2, cod), 41.6 (CH_2-Se), 68.3 (CH=, cod), 75.5 (*C*HCH_2S), 77.2 (CH=, cod), 85.5 (d, *C*$HCMe_2O$, $^3J_{C-P}$ =8.3 Hz), 93.2 (d, CMe_2O, $^2J_{C-P}$ =21.4 Hz), 99.6 (d, CH=, cod, J_{C-P} =16.0 Hz), 101.9 (d, CH=, cod, J_{C-P} =15.3 Hz), 111.7 (CMe_2), 116.8-150.1 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^1J_{C-B}$ =49.7 Hz). MS HR-ESI [found 1139.2749, $C_{53}H_{63}IrO_5PSeSi_2$ $(M)^+$ requires 1139.2746].

[Ir(cod)(L22g)]BAr_F. Yield: 69 mg (93%).^{31}P NMR (161.9 MHz, $CDCl_3$): δ=101.4 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.38 (s, 3H, CH_3), 0.54 (s, 9H, CH_3, $SiMe_3$), 0.84 (s, 9H, CH_3, $SiMe_3$), 1.25 (s, 3H, CH_3), 1.29 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 1.48 (b, 1H, CH_2, cod), 1.61 (b, 1H, CH_2, cod), 1.97 (m, 2H, CH_2, cod), 2.05 (m, 3H, CH_2, cod), 2.17 (m, 1H, CH_2, cod), 3.36 (b, 1H, CH=, cod), 3.78 (d, 1H, CH_2-Se, $^2J_{H-H}$ =12.4 Hz), 4.01-4.08 (m, 2H, CH_2-Se, C*H*CMe_2O), 4.47 (pt, 1H, C*H*CH_2Se, $^3J_{H-H}$ =9.2 Hz), 4.62 (b, 2H, CH=, cod), 4.75 (b, 1H, CH=, cod), 6.99-8.22 (m, 29H, CH= aromatic). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=0.3 (CH_3, $SiMe_3$), 1.6 (CH_3, $SiMe_3$), 23.0 (d, CH_3, $^3J_{C-P}$ =6.1 Hz), 26.3(CH_3), 26.5 (CH_3), 26.6 (CH_2, cod), 26.8 (CH_3), 29.9 (CH_2, cod), 31.1 (CH_2, cod), 34.8 (CH_2, cod), 42.1 (CH_2-Se), 68.3 (CH=, cod), 75.6 (*C*HCH_2Se), 77.6 (CH=, cod),

84.9 (*C*HCMe$_2$O), 92.3 (d, CMe$_2$O, $^2J_{C\text{-}P}$ =21.4 Hz), 100.0 (d, CH=, cod, $J_{C\text{-}P}$ =17.6 Hz), 101.4 (d, CH=, cod, $J_{C\text{-}P}$ =14.5 Hz), 109.0 (CMe$_2$), 117.4-151.1 (aromatic carbons), 161.7 (q, C-B, BAr$_F$, $^1J_{C\text{-}B}$ =50.5 Hz). MS HR-ESI [found 1139.2750, $C_{53}H_{63}IrO_5PSeSi_2$ $(M)^+$ requires 1139.2746].

[Ir(cod)(L23f)]BAr$_F$. Yield: 65 mg (88%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ=101.8 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.47 (d, 3H, CH$_3$, $^3J_{H\text{-}H}$ =5.6 Hz), 0.56 (s, 9H, CH$_3$, SiMe$_3$), 0.84 (s, 9H, CH$_3$, SiMe$_3$), 1.27 (s, 3H, CH$_3$), 1.31 (s, 3H, CH$_3$), 1.49 (b, 1H, CH$_2$, cod), 1.65 (b, 1H, CH$_2$, cod), 1.99 (b, 5H, CH$_2$, cod), 2.18 (b, 1H, CH$_2$, cod), 3.09 (b, 1H, CH=, cod), 3.79 (d, 1H, CH$_2$-Se, $^2J_{H\text{-}H}$ =12.0 Hz), 3.93 (pt, 1H, C*H*CHO, $^3J_{H\text{-}H}$ =8.4 Hz), 4.04-4.09 (m, 1H, CH$_2$-Se), 4.33 (b, 1H, CH-O), 4.38 (m, 1H, C*H*CH$_2$Se), 4.57 (b, 1H, CH=, cod), 4.67 (b, 1H, CH=, cod), 4.77 (b, 1H, CH=, cod), 7.00-8.24 (m, 29H, CH= aromatic). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=-0.2 (CH$_3$, SiMe$_3$), 1.5 (CH$_3$, SiMe$_3$), 18.2 (CH$_3$), 26.5 (CH$_3$), 26.6 (CH$_3$), 26.9 (CH$_2$, cod), 30.3 (CH$_2$, cod), 30.7 (CH$_2$, cod), 34.5 (d, CH$_2$, cod, $J_{C\text{-}P}$ =4.6 Hz), 42.1 (CH$_2$S), 68.0 (CH=, cod), 77.8 (CH=, cod), 80.1 (*C*HCH$_2$S), 82.8 (*C*HCHO), 84.7 (d, CH-O, $^2J_{C\text{-}P}$ =19.9 Hz), 100.8 (d, CH=, cod, $J_{C\text{-}P}$ =17.6 Hz), 102.1 (d, CH=, cod, $J_{C\text{-}P}$ =15.3 Hz), 109.5 (CMe$_2$), 117.4-150.6 (aromatic carbons), 161.7 (q, C-B, BAr$_F$, $^1J_{C\text{-}B}$ =50.5 Hz). MS HR-ESI [found 1125.2593, $C_{52}H_{61}IrO_5PSeSi_2$ $(M)^+$ requires 1125.2590].

[Ir(cod)(L23g)]BAr$_F$. Yield: 66 mg (90%).^{31}P NMR (161.9 MHz, $CDCl_3$): δ= 98.9 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.55 (s, 9H, CH$_3$, SiMe$_3$), 0.69 (d, 3H, CH$_3$, $^3J_{H\text{-}H}$ =6.0 Hz), 0.75 (s, 9H, CH$_3$, SiMe$_3$), 1.30 (s, 3H, CH$_3$), 1.33 (s, 3H, CH$_3$), 1.67 (b, 1H, CH$_2$, cod), 1.89 (b, 3H, CH$_2$, cod), 2.05 (b, 3H, CH$_2$, cod), 2.18 (b, 1H, CH$_2$, cod), 3.45 (b, 1H, CH=, cod), 3.54-3.60 (m, 1H, CH$_2$-Se), 3.89-3.97 (m, 2H, CH$_2$-Se, C*H*CHO), 4.43 (b, 1H, CH-O), 4.64 (b, 2H, C*H*CH$_2$Se, CH=, cod), 4.76 (b, 1H, CH=, cod), 5.17 (b, 1H, CH=, cod), 7.00-8.21 (m, 29H, CH= aromatic). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=0.2 (CH$_3$, SiMe$_3$), 0.8 (CH$_3$, SiMe$_3$), 19.1 (CH$_3$), 26.4 (CH$_3$), 26.8 (CH$_3$), 28.5 (CH$_2$, cod), 29.5 (CH$_2$, cod), 31.8 (CH$_2$, cod), 33.1 (CH$_2$, cod), 41.4 (CH$_2$-Se), 68.1 (CH=, cod), 76.7 (*C*HCH$_2$Se), 78.1 (CH=, cod), 79.8 (CH-O, $^2J_{C\text{-}P}$ =14.5 Hz), 82.9 (d, *C*HCHO, $^3J_{C\text{-}P}$ =6.1 Hz), 101.3 (d, CH=, cod, $J_{C\text{-}P}$ =16.8 Hz), 104.5 (d, CH=, cod, $J_{C\text{-}P}$ =15.3 Hz), 112.4 (CMe$_2$), 117.4-152.9 (aromatic carbons), 161.7 (q, C-B, BAr$_F$, $^1J_{C\text{-}B}$ =49.7 Hz). MS HR-ESI [found 1125.2592, $C_{52}H_{61}IrO_5PSeSi_2$ $(M)^+$ requires 1125.2590].

3.3.4.3. Typical procedure for the hydrogenation of olefins

The alkene (0.5 mmol) and Ir complex (2 mol %) were dissolved in CH_2Cl_2 (2 mL) an placed in a high-pressure autoclave. The autoclave was purged 4 times with hydrogen. Then, it was pressurized at the desired pressure. After the desired reaction time, the autoclave was depressurized and the solvent evaporated off. The residue was dissolved in Et_2O (1.5 ml) and filtered through a short plug of celite. The enantiomeric excess was determined by chiral GC or chiral HPLC and conversions were determined by ^{1}H NMR. The enantiomeric excesses of hydrogenated products from **S1**,[9] **S2**,[22] **S3**-**S6**,[9] **S7**-**S10**,[8i] **S11**,[15a] **S12**,[9] **S13**-**S14**,[8l] **S15**,[18c] **S16**,[18a] **S17**-**S21**,[23] **S22**-**S23**,[19d] **S24**,[9] **S25**,[12c] **S26**,[9] **S27**-**S32**,[24] **S33**[9] and **S34**[16a] were determined using the conditions previously described.

3.3.5. Acknowledgements

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3.3.6. References

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UNIVERSITAT ROVIRA I VIRGILI
SCREENING OF MODULAR AND READILY AVAILABLE LIGAND LIBRARIES FOR C-X (X=H, C, N AND O) BOND FORMING REACTIONS. THE USE OF DFT STUDIES FOR CATALYSTS OPTIMIZATION
Jèssica Margalef Pallarès

3.4. A theoretically-guided optimization of a new family of modular P,S-ligands for iridium-catalyzed hydrogenation of minimally functionalized olefins

Jèssica Margalef, Xisco Caldentey, Erik A. Karlsson, Mercè Coll, Javier Mazuela, Oscar Pàmies, Montserrat Diéguez, and Miquel A. Pericàs in *Chem. Eur. J.* **2014**, *20*, 12201.

***Abstract**: A library of modular iridium complexes derived from thioether-phosphite/phosphinite ligands has been evaluated in the asymmetric iridium-catalyzed hydrogenation of minimally functionalized olefins. The modular ligand design has been shown to be crucial in finding highly selective catalysts for each substrate. A DFT study of the transition state responsible for the enantiocontrol in the Ir-catalyzed hydrogenation is also described and used for further optimization of the crucial stereodefining moieties. Excellent enantioselectivities (enantiomeric excess (ee) values up to 99%) have been obtained for a range of substrates, including (E)- and (Z)-trisubstituted and disubstituted olefins, α,β-unsaturated enones, tri- and disubstituted alkenylboronic esters and olefins with trifluoromethyl substitutents.*

3.4.1. Introduction

The growing demand for enantiomerically pure products, required in the preparation of both compounds of technological interest and compounds possessing biological activity, has stimulated the search for highly efficient asymmetric catalytic processes that display high selectivity and activity, minimal consumption of energy and minimal generation of byproducts.[1] Compared to other techniques, asymmetric catalysis is an attractive strategy, because it uses only a small amount of catalyst to produce an extensive amount of the requested target compound thus reducing the formation of byproducts. It also has the advantage of reducing the number of reaction steps and synthetic operations, thus bringing down the overall production cost.[1]

Asymmetric hydrogenation has become a highly useful tool for preparing enantiomerically pure compounds because of its high efficiency, low catalyst loadings, operational simplicity, and perfect atom economy.[1-2] Its uses have been largely accepted by the chemical community as illustrated by the commercial production of the Parkinson's drug L-3,4-dihydroxyphenylalanine (L-DOPA),[3] the broad-spectrum antibiotic levofloxacin (Daichii-Sankyo Co.)[4] and sitagliptin (Merck),[5] as well as the synthesis of the pesticide (*S*)-metolachlor.[6] Whereas today a notable series of chiral ligands (mostly phosphorus based) for the Ru- and Rh-catalyzed hydrogenation of olefins possessing polar functional groups is available to the chemical community,[2a,2b] the reduction of minimally functionalized substrates is by far less well-developed.[2d,7] The use of chiral analogues of Crabtree's catalyst[8] modified with phosphine-oxazoline (PHOX) ligands ([Ir(PHOX)(cod)]BAr_F) (cod=1,5-cyclooctadiene; [BAr_F]=[B{3,5-$(CF_3)_2C_6H_3$}$_4$]$^-$) represented the first breakthrough in the hydrogenation of this type of substrate.[9] Since then, mixed phosphorus-oxazoline ligands have been the most popular heterodonor ligands in this process. Many successful P-oxazoline ligands have been prepared by incorporating P-donor groups other than

phosphines and by modifying the chiral backbone.[10] Although these modifications have aided the development of new ligands that have considerably expanded the scope of Ir-catalyzed hydrogenation, most of the screened catalysts are still highly substrate-dependent, and their preparation involves long synthetic sequences. The development of efficient modular chiral ligands, readily available from simple starting materials, which tolerate a broad range of substrates, still remains a challenge. More recently, research has been expanded to design heterodonor P,X-ligands bearing more robust X-donor groups than oxazolines (pyridines,[11] amides,[12] thiazoles,[13] oxazoles,[14] etc.). In this respect, we have recently described the successful use of non-*N*-donor heterodonor ligands, sugar based thioether-phosphorus ligands, for enantioselective Ir-catalyzed reduction of minimally functionalized olefins.[15] Ir-complexes modified with these P-thioether ligands efficiently catalyzed the hydrogenation of a large range of (*E)*- and (*Z)*-trisubstituted olefins and the more difficult disubstituted olefins. The results are comparable to the best ones reported in the literature. A part from this, the use of other phosphorus-thioether ligands in the same process remains unexplored, and a systematic study of the scope of P,S-ligands is still needed. No mechanistic studies have been made using this type of ligands in order to enable *a priori* prediction of the right ligand needed to obtain high enantioselectivity. Therefore, more research is needed to discern the role of ligand parameters in the origin of enantioselectivity.

To address all these points, in this study we prepared and evaluated a new highly modular thioether-phosphite/phosphinite ligand library (Figure 3.4.1) in the Ir-catalyzed hydrogenation of a broad range of minimally functionalized olefins, including examples with neighboring polar groups. These ligands are easily prepared in few steps from readily available enantiopure arylglycidols. They also incorporate the advantages of the robustness of the thioether moiety[16] and the additional control provided by the flexibility of the chiral pocket through a highly modular ligand scaffold. In a simple three step procedure (Scheme 3.4.1), several ligand parameters could easily be tuned to maximize the catalyst performance. With this ligand library, we therefore investigated the effect of systematically changing the thioether (**L41**-**L46**) and alkoxy (**L41**, **L47** and **L49**) groups, the nature of the starting material arylglycidol (**L50**), the configuration of the biaryl phosphite moiety (**a**-**c**), and the consequences of replacing the phosphite moiety by a phosphinite group (**d**-**g**). In this paper we have also carried out DFT calculations in order to explain the origin of enantioselectivity. These DFT calculations have also been crucial in the optimization of the ligand design. Interestingly, we found that the catalytic performance of the new ligands is excellent and similar to the performance of the previous furanoside thioether-phosphorus counterparts,[15] which have recently emerged as some of the most successful catalysts designed for this process, with two added advantages. First, these new Ir-thioether-P catalytic systems are able to expand the scope to a larger range of olefins, which includes α,β-unsaturated enones, tri- and disubstituted alkenylboronic esters and olefins with trifluoromethyl substituents. Second, since the starting enantiopure epoxides are prepared through a catalytic Sharpless epoxidation, both enantiomeric series of the target P,S-ligands are equally available. The potential applicability of the Ir-thioether-

phosphite/phosphinite catalyst precursors ([Ir(cod)(**L41**-**L50a**-**g**)]BAr_F) was further proved using propylene carbonate as a green alternative solvent, which allows catalyst recycling.

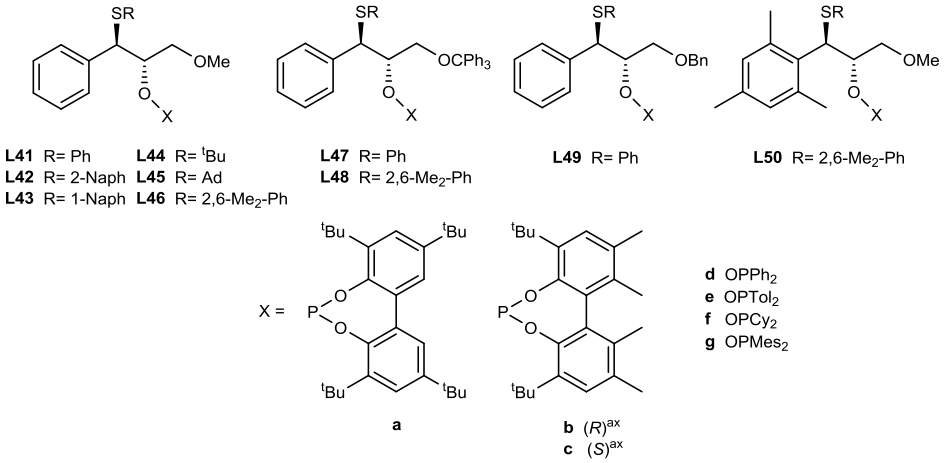


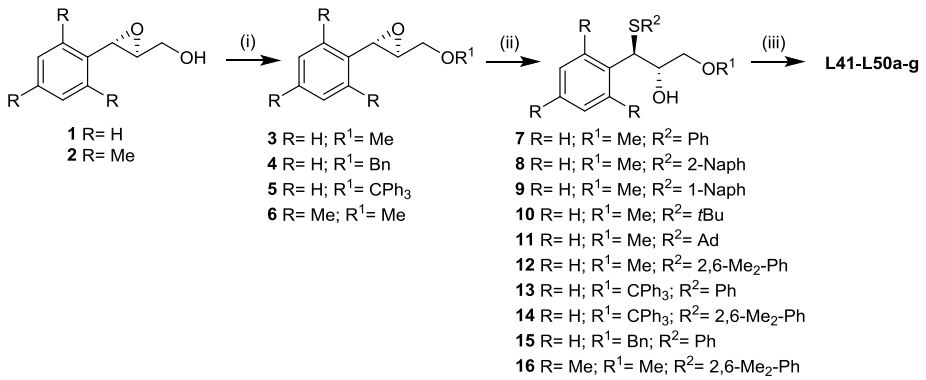
Figure 3.4.1. Thioether-phosphite/phosphinite ligand library **L41**-**L50a**-**g**.

3.4.2. Results and Discussion

3.4.2.1. Synthesis of ligands

The new thioether-phosphite **L41**-**L50a**-**c** and phosphinite **L41-L50d**-**g**[17] ligands were efficiently synthesized in one step from the corresponding readily accessible thioether-alcohols (**7**-**16**; Scheme 3.4.1). These compounds are easily prepared in two steps from enantiopure arylglycidols readily available in large scale (0.5-1.0 mol)[18] following previously reported procedures.[17] In the first step, the protection of the free hydroxyl group enables us to introduce the desired variety in the alkoxy group (Scheme 3.4.1, step (i)).[18c] In the second step, the regioselective and stereospecific ring-opening by thiolates produced the corresponding thioether-hydroxyls (**7**-**16**) (Scheme 3.4.1, step (ii)), thus giving room for additional diversity by performing the opening with different thiolates.[17] The last step of the ligand synthesis (Scheme 3.4.1, step (iii)) is the reaction of the corresponding thioether-hydroxyl in the presence of base with one equivalent of either the corresponding biaryl phosphorochloridite ($ClP(OR)_2$; $P(OR)_2$ = **a**-**c**) to provide thioether-phosphite ligands (**L41**-**L50a**-**c**) or the required chlorophosphine ($ClPR_2$; PR_2 = **d**-**g**) to achieve the new thioether-phosphinite ligands (**L41**-**L50d**-**g** (Scheme 3.4.1, step (iii)).

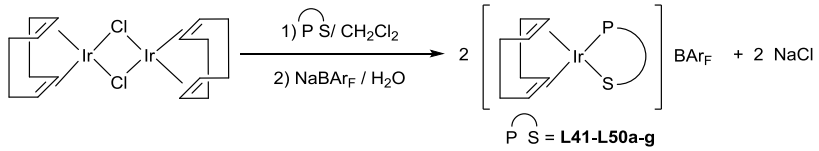
All of the ligands are stable in air at room temperature and to hydrolysis. They were isolated in good yields as white solids or colorless oils after purification on neutral alumina.



Scheme 3.4.1. Synthesis of new thioether-phosphite/phosphinite ligands **L41-L50a**-**g**. (i) R^1X/NaH/DMF;[18] (ii) R^2SH/NaOH/dioxane/H_2O;[17] (iii) $ClP(OR)_2$/pyridine/toluene/80 °C or $ClPR_2$/NEt_3/toluene.

3.4.2.2. Synthesis of the Ir-catalyst precursors

The catalyst precursors were prepared by treating 0.5 equivalent of $[Ir(\mu\text{-}Cl)(cod)]_2$ with an equimolar amount of the appropriate P,S-ligand (**L41**-**L50a**-**g**) in dichloromethane under reflux for 1 h. The Cl^-/BAr_F^- counterion exchange was then performed by reaction with sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate ($NaBAr_F$) (1 equiv) in water (Scheme 3.4.2). The catalyst precursors were obtained in pure form as air-stable red-orange solids. No further purification was thus needed. It should be mentioned that all attempts to prepare iridium complexes containing thioether-phosphinite ligands with the extremely bulky mesityl phosphinite (**f**) moiety were unsuccessful.



Scheme 3.4.2. Synthesis of Ir- precursors $[Ir(cod)(P\text{-}S)]BAr_F$ (P-S **= L41**-**L50a**-**g**).

The HRMS-ESI spectra show the heaviest ions at m/z which correspond to the loss of the BAr_F anion from the molecular species. The complexes were also characterized by ^1H, ^{13}C, and ^{31}P NMR spectroscopy. The spectral assignments, made using ^1H–^1H and ^{13}C–^1H correlation measurements, were as expected for these C_1-symmetric iridium complexes.

VT-NMR experiments in CD_2Cl_2 (+35 °C to -85 °C) indicate the presence of a single isomer in all cases except for [Ir(cod)(**L41**-**L49a**)][BAr_F] compounds. For these latter complexes, the ^{31}P VT-NMR spectra show that the signals become broader when the temperature is lowered. This behavior could indicate a rapid exchange of the possible diastereoisomers formed by conformational isomerism of the biphenyl moiety and/or when the thioether coordinates to the metal atom. The fact that the presence of different diastereoisomers in solution is only observed for complexes with ligands containing a conformationally labile biphenyl moiety (**a**) and not for related complexes with ligands

containing enantiopure biphenyl moieties (**b**,**c**), suggests that this behavior is due to the fast exchange of the biphenyl moiety on the NMR time scale. This hypothesis is further confirmed in the X-ray analysis of [Ir(cod)(**L46a**)][BAr_F] that shows the presence of the two diastereoisomers resulting from the conformational isomerism of the biphenyl phosphite moiety in the solid state (Figure 3.4.2). All this indicates that the ligand backbone is not able to control the conformational isomerism of the biaryl phosphite group. Therefore, it is not surprising that in catalytic studies the enantioselectivity obtained with [Ir(cod)(**L41**-**L49a**)][BAr_F] precursors was low (see below). It could thus be concluded from the VT-NMR experiments that the catalyst precursors are configurationally stable in solution at the sulphur centre, which, however, does not necessarily imply that the same holds true for the catalytically active Ir(III)/Ir(V)-complexes during the reaction conditions (see below).

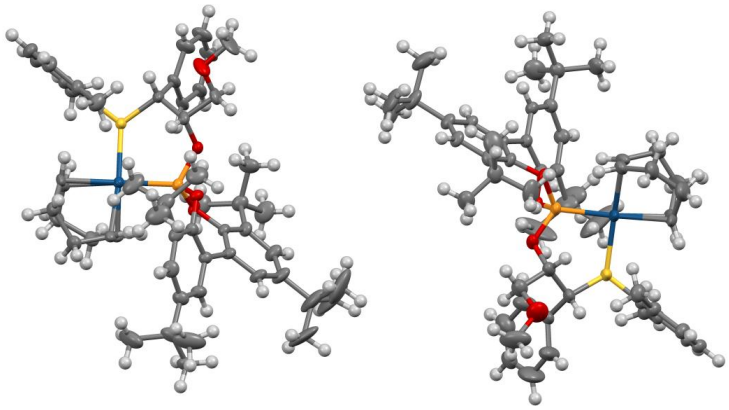


Figure 3.4.2. X-ray structure of [Ir(cod)(**L46a**)]BAr_F (CCDC 993596) that shows the presence of the two diastereoisomers resulting from the conformational isomerism of the biphenyl phosphite moiety (the BAr_F^- counterion and solvent molecules have been omitted for clarity).

Crystals suitable for X-ray diffraction analysis of [Ir(cod)(**L41d**)]BAr_F, [Ir(cod)(**L44a**)]BAr_F and [Ir(cod)(**L49a**)]BAr_F complexes were also obtained in order to determine the coordination mode of this new ligand class (Figure 3.4.3). In contrast to Ir-**L46a** complex, the solid-state structure of complexes containing **L44a** and **L49a** indicated that only one of the diastereoisomers crystallized.

In all cases, the six-membered chelate ring adopted a chair conformation, with the alkoxide group pointing in the opposite direction to the coordination sphere. However, while the crystal structures of [Ir(cod)(**L**)][BAr_F] (**L**= **L44a**, **L46a** and **L49a**), containing a phosphite moiety, showed the thioether substituent in an equatorial position, an axial disposition of the thioether substituent was observed for [Ir(cod)(**L41d**)]BAr_F, containing a phosphinite group.

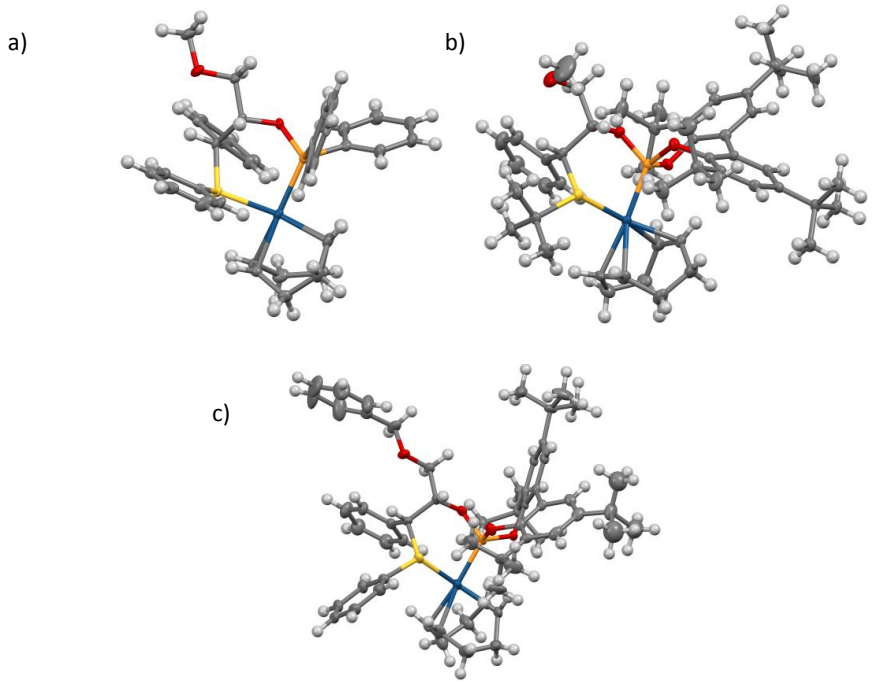


Figure 3.4.3. X-ray structures of (a) [Ir(cod)(**L41d**)]BAr_F (CCDC 993594), (b) [Ir(cod)(**L4a**)]BAr_F (CCDC 993595) and (c) [Ir(cod)(**L49a**)]BAr_F (CCDC 993597) (the BAr_F^- counterion and solvent molecules have been omitted for clarity).

3.4.2.3. Asymmetric hydrogenation

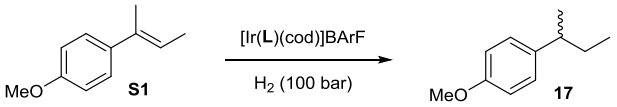
*Asymmetric hydrogenation of the minimally functionalized model olefin (E)-2-(4-methoxyphenyl)-2-butene (**S1**). A computational study for ligand optimization*

Initially, we applied phenylglycidol based ligands **L41**-**L49a**-**g** in the Ir-catalyzed hydrogenation of the model substrate (*E*)-2-(4-methoxyphenyl)-2-butene (**S1**). Model substrate **S1** has been successfully reduced by a large number of catalysts, thus enabling a direct comparison of the potential of the new ligands with the state of art.[2d,7] The results, which are summarized in Table 3.4.1, indicated that enantioselectivity is mainly affected by the thioether substituent and the type of P-donor group, while the effect of the alkoxy substituent is less pronounced. The small effect of the alkoxy substituent on enantioselectivity (i.e. Table 3.4.1; entries 1, 24 and 32) is not unexpected since this substituent is located far away from the coordination sphere as can be seen in the X-ray structures (see above) and the DFT-calculated transition states (TS) (see below).

We found that the correct choice of the thioether substituent is crucial to achieve the highest levels of enantioselectivity. The results showed that the presence of aryl substituents provided higher enantioselectivities than alkyl thioether substituents. Among the aryl substituents, enantioselectivities increase with increasing steric bulk of the

thioether substituent (2,6-Me_2-C_6H_3>1-Napth>2-Napth>Ph; Table 3.4.1, entries 23, 11, 7 and 4).

Table 3.4.1. Selected results for the Ir-catalyzed hydrogenation of **S1** using the P,S-ligand library **L41**-**L49a**-**g**.[a]



Entry	Ligand	% ee[b]	Entry	Ligand	% ee[b]
1	**L41a**	26 (*R*)	19	**L46a**	26 (*R*)
2	**L41b**	42 (*R*)	20	**L46b**	48 (*R*)
3	**L41c**	13 (*R*)	21	**L46c**	55 (*S*)
4	**L41d**	44 (*R*)	22	**L46d**	64 (*R*)
5	**L42b**	40 (*R*)	23	**L46e**	92 (*R*)
6	**L42c**	12 (*R*)	24	**L47a**	30 (*R*)
7	**L42e**	84 (*R*)	25	**L47b**	50 (*R*)
8	**L43a**	8 (*R*)	26	**L47c**	17 (*S*)
9	**L43b**	36 (*R*)	27	**L47d**	41 (*R*)
10	**L43c**	31 (*S*)	28	**L47e**	86 (*R*)
11	**L43e**	86 (*R*)	29	**L47f**	8 (*R*)
12	**L44a**	14 (*R*)	30	**L48a**	24 (*R*)
13	**L44b**	41 (*R*)	31	**L48e**	93 (*R*)
14	**L44c**	19 (*R*)	32	**L49a**	31 (*R*)
15	**L44d**	53 (*R*)	33	**L49b**	45 (*R*)
16	**L44e**	49 (*R*)	34	**L49c**	34 (*R*)
17	**L45a**	25 (*R*)	35	**L49d**	41 (*R*)
18	**L45e**	35 (*R*)	36[c]	**L48e**	93 (*R*)

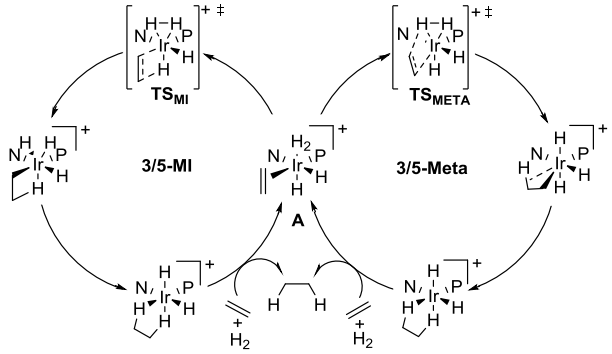
[a] Reactions carried out using 0.5 mmol of **S1**, 2 mol% of Ir-catalyst precursor, CH_2Cl_2 as solvent, 100 bar H_2, 4 h. [b] Conversion and enantiomeric excesses determined by chiral GC. [c] Reaction carried out using 0.25 mol% of Ir-catalyst precursor for 8 h.

Regarding the effect of the P-donor group on enantioselectivity, we found that the presence of a conformationally labile biaryl phosphite group (**a**) provided low enantioselectivities, because as observed in the VT-NMR spectra and X-ray structures of the [Ir(cod)(**L41**-**L49a**)][BAr_F] catalyst precursors, the ligand backbone is not able to control its conformational isomerization (Table 3.4.1, entries 1, 8, 12, 17, 19, 24, 30, and 32). Enantioselectivities therefore increased by using enantiopure biaryl phosphite groups (**b**,**c**; that is, Table 3.4.1, entries 13 and 14 vs. 12). We also found that there is a cooperative effect between the configuration of the ligand backbone and the configuration of the biaryl group that led to a matched combination for ligands containing an (*R*)-biaryl phosphite moiety (**b**; Table 3.4.1, entries 13 and 14). However, the best enantioselectivities were obtained with ligands containing a phosphinite group (ee's up to 93%, Table 3.4.1, entry 31). In particular, replacing the phosphite moiety by a bulky di-*o*-tolyl phosphinite group had a positive effect on enantioselectivity, whereas the use of a cyclohexyl phosphinite group led to poor enantioselectivities (Table 3.4.1, entry 29). This behavior is in contrast with the negative effect observed when replacing the phosphite group by a phosphinite

moiety in the previous furanoside-based thioether-P ligands.[15b] These results clearly show the importance of using a modular scaffold to build new ligand systems.

We also performed the reaction at low catalyst loading (0.25 mol%) using ligand **L48e**. High enantioselectivity (93% ee) and activity were maintained.

With the aim to find which ligand parameters should be further modified in order to increase enantioselectivity, we performed a DFT computational study of the transition states involved in the enantiocontrol of the iridium-catalyzed hydrogenation of substrate **S1**. Several DFT studies using P,N- and carbene-N ligands have indicated that the hydrogenation of minimally functionalized alkenes proceeds via Ir^{III}/Ir^{V} tetrahydride intermediates.[10p,19] Recent studies by Hopmann and coworkers using a phosphine-oxazoline (PHOX) based iridium catalyst,[19e] and by our group, in conjunction with Norrby's and Andersson's groups, using Ir-phosphite-oxazoline ligands,[10p] strongly support that the hydrogenation of minimally functionalized olefins using P,N-ligands follows a mechanism involving an Ir^{III}/Ir^{V} migratory-insertion/reductive-elimination pathway (labeled 3/5-MI in Scheme 3.4.3). In these studies, two catalytic pathways were contemplated. The already mentioned 3/5-MI pathway and the mechanism involving an Ir^{III}/Ir^{V} σ-metathesis/reductive-elimination pathway (labeled 3/5-Meta in Scheme 3.4.3). It has also been shown that the transition states for the migratory-insertion in the 3/5-MI pathway (**TS_{MI}**) and the σ-metathesis in the 3/5-Meta pathway (**TS_{META}**) are responsible for the selectivity in the Ir-catalyzed hydrogenation, and that the enantioselectivity therefore could be reliably calculated from the relative energies of these transition states.[19d]



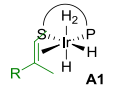
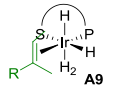
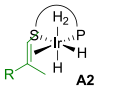
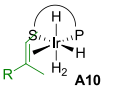
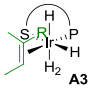
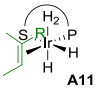
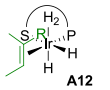
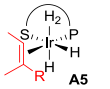
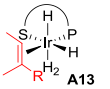
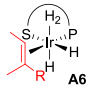
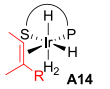
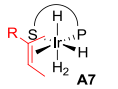
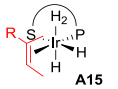
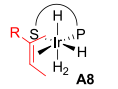
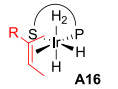
Scheme 3.4.3. 3/5-MI and 3/5-Meta catalytic cycles for the Ir-catalyzed hydrogenation.

On the basis of these previous studies we therefore performed a computational study of the **TS_{MI}** and **TS_{META}** transition states. In order to accelerate the DFT calculations, we initially studied ligands **L41d** and **L46d**, containing the simple unsubstituted diphenyl phosphinite moiety. In addition, these ligands contain two types of thioether groups that will help us to understand the already observed key role of introducing a bulky 2,6-dimethylphenyl thioether substituent on enantioselectivity. The transition states using **S1** as substrate for the stereochemistry determining migratory insertion (**TS_{MI}**) or σ-bond metathesis (**TS_{META}**) were calculated using the B3LYP functional,[20] the 6-31G*/LANL2DZ basis set,[21] and the PCM solvent model with parameters for CH_2Cl_2,[22] as implemented in

Gaussian 09.[23] The energies were further refined by performing single point calculations at the 6-311+G** level,[24] and by dispersion correction with the DFT-D3 model.[25]

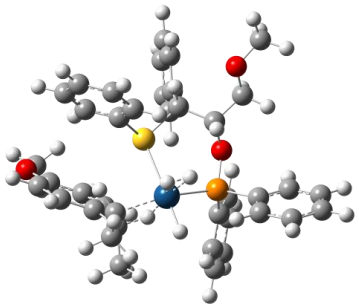
Table 3.4.2 shows the calculated energies for the most stable isomers of the transition states ($\mathbf{TS_{MI}}$ and $\mathbf{TS_{META}}$). These key isomers are the result of varying between the two possible configurations at the sulfur center, coordinating to the two enantiotopic faces (*re* and *si*) of the olefin, and changing the relative position of the hydride (up or down).[26] It should be mentioned that olefins coordinated through the *si* face are depicted in green and are reduced to the (*R*)-product, whereas those coordinated through the *re* face are depicted in red and give access to the (*S*)-product. The results in Table 3.4.2 show that the most stable transition state ($\mathbf{TSA1_{MI}}$) matches the major product obtained experimentally ((*R*)-product, Table 3.4.1, entries 4 and 22), while the most stable transition state with the *re* face coordinated ($\mathbf{TSA8_{MI}}$) is expected to be responsible for the formation of the minor (*S*)-product. The energy differences between the most stable transition states giving rise to the major and minor products are 4.5 and 8.5 kJ/mol, respectively, for **L41d** and **L46d.** We also found that the hydrogenation products are formed through the 3/5-MI mechanism, since the TS energies for the 3/5-Meta pathway, in both the major and minor configuration, are at least 13 kJ/mol higher than those for the 3/5-MI pathway (see Table 3.4.2). Nevertheless, since the energetic difference between the two pathways is relatively small, both have to be taken into consideration for further calculations. It should be pointed out that the fact that the calculations indicate that the minor (*S*)-product is formed through a transition state in which the configuration at the sulphur centre is (*S*), whereas the major (*R*)-product results from a transition state with (*R*)-configuration at the sulphur centre raised some concerns regarding the validity of the theoretical model. In general, a model of this kind, which only takes into account the relative energies of the transition states through which the various isomeric intermediates are transformed into their corresponding products, in order to calculate the product distribution, requires that the Curtin-Hammet principle be applicable, that is, that the interconversion of the said intermediates be faster than their evolution into the corresponding products. However, the VT-NMR studies, in combination with X-ray analysis of [Ir(cod)(**L41d**)][BAr_F], suggest that, at least at the level of the Ir^I catalyst precursors, the (*R*)-configuration is maintained at the sulphur centre in solution. In order to address these concerns, the transition states for the interconversion of the intermediates **A7** and **A8** were calculated. The results clearly show that the barrier for pyramidal inversion at the sulphur centre is considerably lower than the barriers leading to product formation, thus confirming the applicability of the Curtin-Hammet principle and the validity of the theoretical model (see Table SI.3 in the Supporting Information).

Table 3.4.2. Calculated energies for the transition states TS_{MI} and TS_{META} with substrate **S1** using ligands **L41d** and **L46d**.[a]

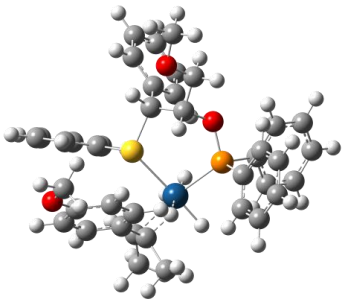
Starting geometry	TS_{MI}		Starting geometry	TS_{META}	
	L41d	**L46d**		**L41d**	**L46d**
 **A1** *R* config. on sulfur	0	0	 **A9** *R* config. on sulfur	17.0	20.2
 **A2** *S* config. on sulfur	20.0	30.5	 **A10** *S* config. on sulfur	20.2	26.0
 **A3** *R* config. on sulfur	25.5	36.7	 **A11** *R* config. on sulfur	31.8	34.3
 **A4** *S* config. on sulfur	19.1	30.3	 **A12** *S* config. on sulfur	32.7	44.1
 **A5** *R* config. on sulfur	9.8	19.0	 **A13** *R* config. on sulfur	31.7	36.3
 **A6** *S* config. on sulfur	22.6	35.1	 **A14** *S* config. on sulfur	34.6	42.9
 **A7** *R* config. on sulfur	18.2	20.5	 **A15** *R* config. on sulfur	13.1	21.1
 **A8** *S* config. on sulfur	4.5	8.5	 **A16** *S* config. on sulfur	26.2	31.0

[a] Energies in kJ/mol. R= 4-MeO-C_6H_4.

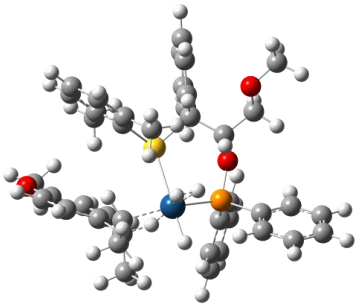
Figure 3.4.4 shows the most stable calculated transition states (TS) for the major and the minor pathway with both ligands. In these key transition states we can see, on the one hand, the proximity of the phenyl moiety in the ligand backbone group to the thioether substituent and, on the other hand, that the hydrogen at the *ortho* position of the phenyl group in the ligand skeleton is pointing towards the metal centre. All these findings indicate that the aromatic substituent in the ligand backbone could have an important influence on the enantioselectivity.



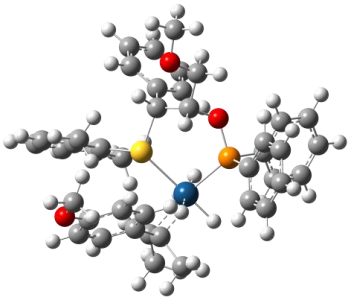
L41d, major pathway, 0 kJ/mol



L41d, minor pathway, 4.5 kJ/mol



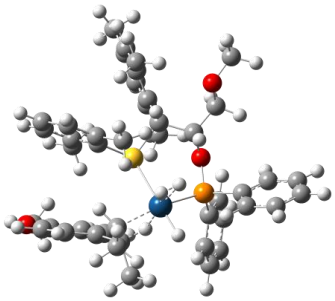
L46d, major pathway, 0 kJ/mol



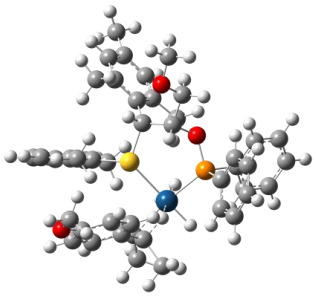
L46d, minor pathway, 8.5 kJ/mol

Figure 3.4.4. Calculated transition states (TS) for the major and the minor pathways with ligands **L41d** and **L46d**.

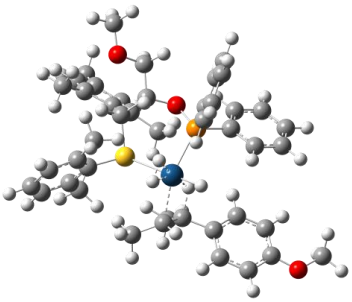
These features prompted us to recalculate the relevant transition states (from **A1** for the major pathway and **A8** for the minor pathway) by replacing the phenyl group by a mesityl group (ligand **L50d**; Figure 3.4.1). The results, which are summarized in Table 3.4.3 showed that the energy difference between the two transition states was unrealistically large (30.9 kJ/mol). In Figure 3.4.5, it can be seen that in the transition state giving the (*S*)-product there is a great steric interaction between the thioether substituent and the mesityl group, essentially locking the configuration at the sulphur centre to (*R*). We therefore switched from an (*S*)-configuration at the sulphur centre to an (*R*)-configuration choosing again the most stable isomers previously calculated for ligands **L41d** and **L46d** (TS from **A5**, **A7** and **A15**; Table 3.4.3). Thus, the obtained energy difference between the two most stable transition states responsible for the formation of both enantiomers of the hydrogenated product was 14.2 kJ/mol (ligand **L50d**) surpassing the $\Delta\Delta G^{+}_{cal}$ with ligands **L41d** and **L46d** (4.5 kJ/mol and 8.5 kJ/mol, respectively), indicating that this new modification should provide higher enantioselectivities than the Ir-**L41d** and Ir-**L46d** catalysts.



Major pathway, 0 kJ/mol



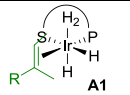
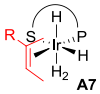
TS_{MI} from **A8**, 30.9 kJ/mol



Minor pathway, 14.2 kJ/mol

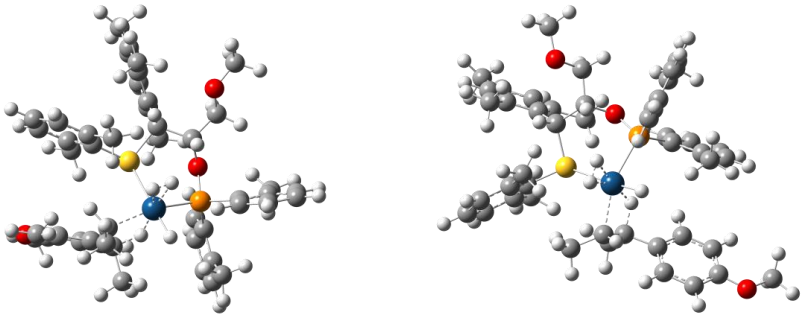
Figure 3.4.5. Calculated transition states (TS) for the major and the minor pathways with ligand **L50d**.

Table 3.4.3. Calculated energies for the relevant transition states with substrate **S1** using ligands **L50d** and **L50e**.[a]

Starting geometry	TS_{MI}		Starting geometry	TS_{META}	
	L50d	**L50e**		**L50d**	**L50e**
 **A1** *R* config. on sulfur	0	0	 **A5** *R* config. on sulfur	14.2	13.7
 **A8** *S* config. on sulfur	30.9	36.7	 **A7** *R* config. on sulfur	28.4	33.2
 **A15** *R* config. on sulfur	19.9	37.5			

[a] Energies in kJ/mol. R= 4-MeO-C_6H_4.

Encouraged by this result and having in mind that the catalytic experiments using phenyl glycidol-based ligands (**L41**-**L49**) showed that replacing the diphenyl phosphinite moiety by *o*-tolyl groups has a positive effect on enantioselectivity (i.e. Table 3.4.1, entries 27 and 28), we also performed the calculations of the relevant transition states with the mesityl-based ligand **L50e** (Figure 3.4.1), with tolyl groups at the phosphinite moiety. However, the calculated energy difference between the most stable transition states thus obtained was 13.7 kJ/mol, very similar to that achieved with ligand **L50d** (Table 3.4.3 and Figure 3.4.6). So, in contrast to that observed for ligands **L41**-**L49**, containing a phenyl group in the backbone (see above), the steric bulk of the phosphinite group should have little impact on enantioselectivity for the mesityl-based ligands.



Major pathway, 0 kJ/mol Minor pathway, 13.7 kJ/mol

Figure 3.4.6. Calculated transition states (TS) for the major and the minor pathways with ligand **L50e**.

With these latter theoretical results in hand, a decision was made to prepare and screen thioether-phosphinite ligands **L50d** and **L50e**, with a mesityl group, in the asymmetric hydrogenation of substrate **S1**. The experimental results are shown in Table 3.4.4 (entries 3 and 4). As predicted by the theoretical calculations, both mesityl-based ligands afforded similar higher enantioselectivities than ligands **L41**-**L49**. If we compare the calculated and experimental values (Table 3.4.4), we can conclude that, despite the fact that the calculated free energy differences are systematically higher than the experimental values, the general trend is reproduced well. The robustness of the theoretical model is demonstrated with the prediction of the new improved ligands **L50d**-**e** containing a mesityl group.

Table 3.4.4. Comparison between experimental and theoretical results.[a]

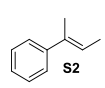
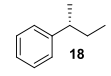
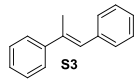
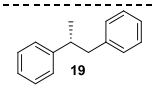
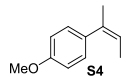
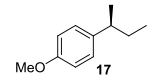
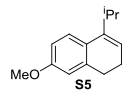
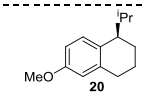
Entry	Ligand	ee%[a]	$\Delta\Delta G^{+}_{exp}$ [b]	$\Delta\Delta G^{+}_{calcd}$ [b]
1	**L41d**	44 (*R*)	2.3	4.5
2	**L46d**	64 (*R*)	3.8	8.5
3	**L50d**	94 (*R*)	8.6	14.2
4	**L50e**	95 (*R*)	9.1	13.7

[a] Reaction conditions: 0.5 mmol of **S1**, 2 mol % catalyst precursor, CH_2Cl_2 as solvent, 100 bar H_2, 4 h. Full conversions were achieved in all cases. Enantiomeric excesses measured by GC. [b] Energies in kJ/mol.

Asymmetric hydrogenation of other minimally functionalized olefins. Scope and limitations

To establish the scope of the new family of ligands in the Ir-catalyzed hydrogenation, we selected a representative family of substrates. We first studied the asymmetric hydrogenation of other (*E*)- and (*Z*)-trisubstituted olefins (**S2–S18**), including examples containing neighboring polar groups, by using the P,S-ligand library **L41**-**L50a**-**g**. The most noteworthy results are shown in Table 3.4.5, Table 3.4.6, and Table 3.4.7 (see Supporting information for a complete set of results). We found again that the correct choice of the ligand parameters is crucial to achieve the highest levels of enantioselectivity. We initially studied the hydrogenation of (*E*)-substrates **S2**-**S3**, related to **S1,** that differ in the substituents in both the aryl ring and the substituents *trans* to the aryl group. Excellent enantioselectivities, even higher than with the model substrate **S1**, were obtained (ee's between 98 to >99 %; Table 3.4.5 entries 2, 3, 5 and 6). The result followed the same trends as those observed for substrate **S1**. Enantioselectivities were thus best with the optimized ligands **L50d** and **L50e**.

Table 3.4.5. Selected results for the Ir-catalyzed hydrogenation of **S2**-**S5** using the P,S-ligand library **L41**-**L50a**-**g**.[a]

Entry	Substrate	Product	Ligand	ee%[b]
1			**L48e**	99 (*R*)
2			**L50d**	99 (*R*)
3			**L50e**	>99 (*R*)
4			**L48e**	97 (*R*)
5			**L50d**	98 (*R*)
6			**L50e**	99 (*R*)
7			**L46a**	62 (*S*)
8			**L46c**	62 (*S*)
9			**L50e**	58 (*S*)
10			**L48c**	36 (*R*)
11			**L48e**	78 (*R*)
12			**L50e**	82 (*R*)

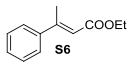
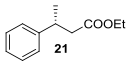
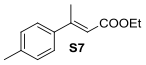
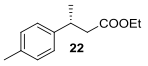
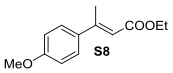
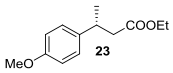
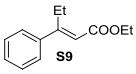
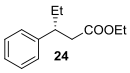
[a] Reactions carried out using 0.5 mmol of substrate, 2 mol% of Ir-catalyst precursor, CH_2Cl_2 as solvent, 100 bar H_2, 4 h. Full conversions were achieved in all cases. [b] Enantiomeric excesses determined by chiral GC or HPLC.

In order to assess the potential of the new ligand library for (*Z*)-trisubstituted isomers, which are usually hydrogenated less enantioselectively than the corresponding (*E*)-isomers, we chose substrates **S4** and **S5** (Table 3.4.5, entries 7-12). The reduction of the model (*Z*)-substrate **S4** proceeded with moderate enantiocontrol and followed a different trend than that observed with (*E*)-substrates **S1**-**S3**. The enantioselectivities were thus best with ligands **L46a** and **c** (Table 3.4.5, entries 7 and 8). The moderate enantioselectivity can be explained by a competition between direct hydrogenation versus (*Z*)/(*E*)-isomerization of the substrate. The hydrogenation of the (*E*)-isomer produces the opposite configuration of the hydrogenated product than when (*Z*)-isomer is hydrogenated, which results in low enantioselectivity.[2d] Accordingly, the reduction of dehydronaphthalene **S5**, which has a (*Z*)-

configuration and for which (*Z*)/(*E*)-isomerization is not possible, produces higher enantioselectivities (ee's up to 82 %; Table 3.4.5, entry 12). Moreover in contrast to **S4**, the best enantioselectivities were achieved with the optimized mesityl-based ligands **L50d** and **L50e**.

We next studied the reduction of a wide range of trisubstituted olefins containing several types of neighboring polar groups **S6**-**S9** (Table 3.4.6) and **S10**-**S18** (Table 3.4.7). The hydrogenation of this type of substrates is especially relevant, because they allow for further functionalization and could therefore be important intermediates for the synthesis of more complex chiral molecules. We were pleased to find that enantioselectivities are among the best observed in most of the examples. A range of α,β-unsaturated esters (**S6**-**S9**) were thus efficiently hydrogenated (ee's ranging from 98 % to >99 %; Table 3.4.6). It should be noted that ee's are highly independent of the nature of the alkyl substituent and the electronic nature of the substrate phenyl ring. Although enantioselectivities follow the same trend regarding the effect of the thioether, alkoxy and the P-donor group, the nature of the aryl group in the ligand backbone is less pronounced. Enantioselectivities were thus best with ligands **L46e**, **L48e**, **L50d** and **L41e**.

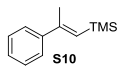
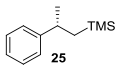
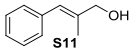
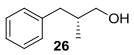
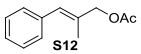
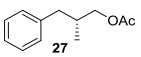
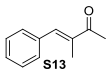
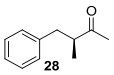
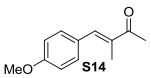
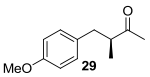
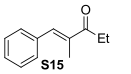
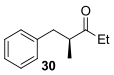
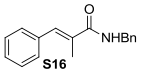
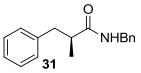
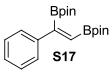
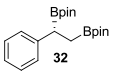
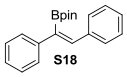
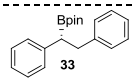
Table 3.4.6. Selected results for the Ir-catalyzed hydrogenation of **S6**-**S9** using the P,S-ligand library **L41**-**L50a**-**g**.[a]

Entry	Substrate	Product	Ligand	ee%[b]
1	 **S6**	 **21**	**L48e**	>99 (*R*)
2			**L50d**	99 (*R*)
3			**L50e**	>99 (*R*)
4	 **S7**	 **22**	**L48e**	99 (*R*)
5			**L50d**	99 (*R*)
6			**L50e**	99 (*R*)
7	 **S8**	 **23**	**L48e**	98 (*R*)
8			**L50d**	98 (*R*)
9			**L50e**	99 (*R*)
10	 **S9**	 **24**	**L48e**	99 (*R*)
11			**L50d**	99 (*R*)
12			**L50e**	99 (*R*)

[a] Reactions carried out using 0.5 mmol of substrate, 2 mol% of Ir-catalyst precursor, CH_2Cl_2 as solvent, 100 bar H_2, 4 h. Full conversions were achieved in all cases. [b] Enantiomeric excesses determined by chiral GC or HPLC.

On the other hand, the presence of a trimethylsilyl group in the substrate (**S10**) has a negative effect on enantioselectivity (Table 3.4.7, entries 1-3), whereas the reduction of allylic alcohol and acetate **S11**-**S12** provided higher enantioselectivities (ee's up to 85 %, Table 3.4.7, entry 9). The use of the optimized mesityl-based ligands **L50d** and **L50e** was essential to achieve the highest levels of enantioselectivity in the reduction of several α,β-unsaturated ketones **S13**-**S15** (ee's ranging from 98 % to 99 %, Table 3.4.7, entries 10-18), for which the previous furanoside P-S ligands proved to be unsuccessful.[27] This represents an important entry point to the formation of ketones with stereogenic centers in the α-position to the carbonyl group. Despite this, they have been less studied than other trisubstituted olefins with a neighboring polar group.[2d]

Table 3.4.7. Selected results for the Ir-catalyzed hydrogenation of **S10**-**S18** using the P,S-ligand library **L41**-**L50a**-**g**.[a]

Entry	Substrate	Product	Ligand	ee%[b]
1			**L47e**	60 (*R*)
2			**L48e**	61 (*R*)
3			**L50e**	68 (*R*)
4			**L47e**	78 (*R*)
5			**L48e**	79 (*R*)
6			**L50e**	81 (*R*)
7			**L47e**	81 (*R*)
8			**L48e**	80 (*R*)
9			**L50e**	85 (*R*)
10			**L46d**	94 (*S*)
11			**L50d**	98 (*S*)
12			**L50e**	99 (*S*)
13			**L46d**	96 (*S*)
14			**L50d**	97 (*S*)
15			**L50e**	99 (*S*)
16			**L46d**	95 (*S*)
17			**L50d**	98 (*S*)
18			**L50e**	98 (*S*)
19			**L48e**	70 (*S*)
20			**L50d**	69 (*S*)
21			**L50e**	72 (*S*)
22			**L49d**	43 (*R*)
23			**L50d**	44 (*R*)
24			**L50e**	45 (*R*)
25			**L47a**	94 (+)
26			**L47c**	93 (+)
27			**L50e**	83 (+)

[a] Reactions carried out using 0.5 mmol of substrate, 2 mol% of Ir-catalyst precursor, CH_2Cl_2 as solvent, 100 bar H_2, 4 h. Full conversions were achieved in all cases. [b] Enantiomeric excesses determined by chiral GC or HPLC.

Other challenging substrate types that have been less investigated are the α,β-unsaturated amides (**S16**)[28] and alkenylboronic esters (**S17**-**S18**).[29] Amides with stereogenic centers in the α-position are an important class of compounds since this motif is present in several natural products and they can be easily transformed into other useful compounds (i.e. amines).[30] The hydrogenation of alkenylboronic esters provides easy access to chiral borane compounds, which are valuable organic intermediates since the C-B bond can be easily transformed to C-O, C-N and C-C bonds with retention of the chirality.[31] The hydrogenation of α,β-unsaturated amide **S16** followed the same trend as substrate **S1** (Table 3.4.7). Enantioselectivities up to 72 % were thus achieved with ligand **L50e**. The reduction of alkenylboronic esters followed a different trend than **S1** (Table 3.4.7). Whereas for the more studied substrate **S17** moderate enantioselectivities were achieved, for the less studied substrate **S18** high enantioselectivities up to 94 % were reached using

phosphite-thioether ligands **L47a** and **L47c**. These results again showed the importance of having a modular ligand design.

The stereochemical outcome in the reduction of these trisubstituted olefins can be easily rationalized by a quadrant diagram based on the optimized DFT calculated structures of the transition states (Figure 3.4.7). In this quadrant model we found that the thioether substituent blocks the upper left quadrant and one of the P-aryl groups partly occupies the lower right quadrant making it semi-hindered. The other two quadrants, which are free from bulky groups, are open. The DFT structures thus show that the Ir-PS catalysts generate a pocket that is well suited to olefins with large *trans* substituents ((*E*)-olefins; Figure 3.4.7a). This fully explains the high enantioselectivities obtained with the DFT-optimized thioether-phosphinite ligands in the reductions of olefins **S1**-**S3**, **S6**-**S9** and **S11**-**S12**. However, the reduction of substrates **S13**-**S16** gives products with the opposite absolute configuration to what is suggested by the quadrant model as previously observed for α-substituted-α,β-unsaturated esters.[2d,32] On the other hand, in the reduction of alkenylboronic ester **S18**, the bulky pinacolato boron group (Bpin) faces the steric bulk of the ligand in the semihindered lower right quadrant. Thus the need to switch to phosphite ligands **L47a** and **L47c** to obtain high enantioselectivity could be justified by the flexibility of the biphenyl phosphite moiety,[33] which could tune the steric hindrance of this lower right quadrant so that it can accommodate the pinacolato boron substituent of the substrate.

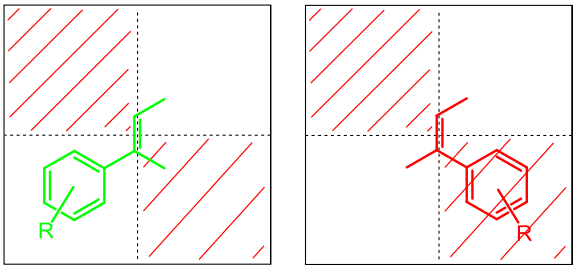


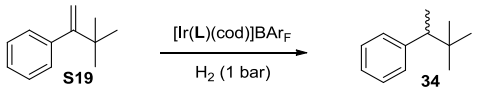
Figure 3.4.7. Quadrant diagram describing the substrate-ligand interactions.

By using this quadrant model, we can also explain the change in the sense of enantioselectivity observed experimentally when using (*Z*)-trisubstituted olefins instead to (*E*)-olefins. The (*Z*)-olefin must coordinate preferentially through the *re* face, with the aryl substituent in the semihindered lower right quadrant and the hydrogen atom positioned in the hindered upper left quadrant (Figure 3.4.7b). This model also explains the lower enantioselectivities when the optimized ligands were used in the reduction of (*Z*)-olefins. The favorable chiral pocket for (*E*)-olefins generated by our Ir-PS catalysts, which can accommodate large *trans* substituents, fails to perfectly control the face coordination preference of the (*Z*)-olefins.

To assess the potential of the ligand library **L41**-**L50a**-**g** for the more challenging 1,1-disubstitued olefins, which generally are hydrogenated less enantioselectively than the corresponding trisubstituted ones, we next chose to hydrogenate substrate **S19** as a model. The lower enantioselectivity obtained with 1,1-disubstituted terminal olefins than that

obtained with trisubstituted olefins has been attributed to two main motives.[2d,7a,7e] The first is that enantioface olefin coordination is difficult to control due to the comparable steric size of the alkyl and aryl substituent at the olefinic C atom. The second reason is that the terminal double bond can undergo isomerization under hydrogenation conditions to produce the more stable internal *trans*-alkene, whose hydrogenation leads to the predominant formation of the opposite enantiomer of the product. The results under optimized conditions are shown in Table 3.4.8.

Table 3.4.8. Ir-catalyzed hydrogenation of **S19** using the P,S-ligand library **L41**-**L50a**-**g**.[a]



Entry	Ligand	ee%[b]	Entry	Ligand	ee%[b]
1	**L41a**	46 (*S*)	20	**L46b**	95 (*S*)
2	**L41b**	70 (*S*)	21	**L46c**	94 (*R*)
3	**L41c**	82 (*R*)	22	**L46d**	93 (*S*)
4	**L41d**	64 (*S*)	23	**L46e**	96 (*S*)
5	**L42b**	88 (*S*)	24	**L47a**	30 (*S*)
6	**L42c**	74 (*R*)	25	**L47b**	78 (*S*)
7	**L42e**	81 (*S*)	26	**L47c**	82 (*R*)
8	**L43a**	31 (*S*)	27	**L47d**	76 (*S*)
9	**L43b**	93 (*S*)	28	**L47e**	72 (*S*)
10	**L43c**	93 (*R*)	29	**L47f**	54 (*S*)
11	**L43e**	75 (*S*)	30	**L48a**	66 (*S*)
12	**L44a**	62 (*S*)	31	**L48e**	90 (*S*)
13	**L44b**	60 (*S*)	32	**L49a**	30 (*S*)
14	**L44c**	92 (*S*)	33	**L49b**	64 (*S*)
15	**L44d**	87 (*S*)	34	**L49c**	76 (*R*)
16	**L44e**	80 (*S*)	35	**L49d**	69 (*S*)
17	**L45a**	64 (*S*)	36	**L50d**	97 (*S*)
18	**L45e**	76 (*S*)	37	**L50e**	97 (*S*)
19	**L46a**	94 (*S*)	38[c]	**L50e**	97 (*S*)

[a] Reactions carried out using 0.5 mmol of **S19**, 2 mol% of Ir-catalyst precursor, CH_2Cl_2 as solvent, 1 bar H_2, 4 h. Full conversions were achieved in all cases except for entries 9 and 10 (86% and 96% conversion, respectively). [b] Enantiomeric excesses determined by chiral GC. [c] Reaction carried out using 0.25 mol% of Ir-catalyst precursor for 8 h.

We were again able to fine-tune the ligand parameters to achieve high activities and enantioselectivities (ee's up to 97 %) in the reduction of this substrate at low catalyst loadings (0.25 mol%) and hydrogen pressures (1 bar).

The results showed that the effect on enantioselectivity of the thioether and the alkoxy substituents and the aryl-glycidol group follow the same trend as for **S1**. However, in contrast to **S1**, enantioselectivities for substrate **S19** are similar for ligands containing either an enantiopure biaryl phosphite moiety (**b**,**c**) or a diaryl phosphinite group (**d**,**e**) (i.e. Table 3.4.8, entries 20-23). Interestingly, we found that the sense of enantioselectivity is controlled by the configuration of the biaryl phosphite group (Table 3.4.8, entries 20 and 21), and this represents an additional possibility for the control of the absolute configuration of the products through ligand modification.[34] As observed for **S1**, the

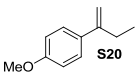
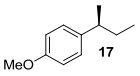
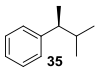
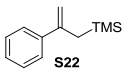
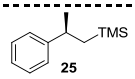
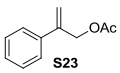
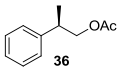
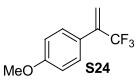
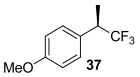
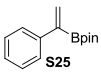
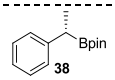
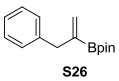
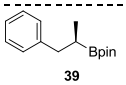
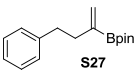
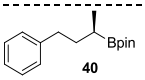
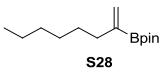
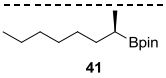
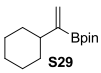
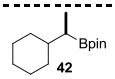
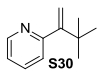
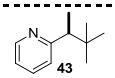
tropoisomerism in the fluxional biaryl phosphite group **a** is not controlled by the ligand backbone, except for ligand backbone **L46**, containing an 2,6-dimethylphenyl thioether substituent, which provided similar high enantioselectivities as the enantiopure phosphite counterparts (Table 3.4.8, entries 19 vs 20 and 21).

We then investigated the scope of the new ligand library in the asymmetric hydrogenation of other 1,1-disubstituted substrates (Table 3.4.9). The results with substrates **S19**-**S21** indicated that enantioselectivity is affected by the alkyl chain substituent (ee's ranging from 27 % to 97 %; Table 3.4.8, entries 36 and 37; and Table 3.4.9, entries 3 and 6). This can be explained by the competition between isomerization *vs* direct hydrogenation for substrates **S20** and **S21**. Accordingly, high amounts of isomerized internal olefins were observed as byproducts in the hydrogenation of **S20** and **S21**.

We next turned our attention to study substrates with neighbouring polar groups (**S22**-**S29**), due to their importance in the preparation of chiral synthons (see Supporting information for a complete set of results). The reduction of substrates **S22** and **S23**, containing trimethylsilyl and acetate groups respectively, provided moderate enantioselectivities (ee's up to 71 %; Table 3.4.9, entries 7-12). To study whether these enantioselectivities can be due again to their isomerization to the trisubstituted internal olefins under reaction conditions, a decision was made to hydrogenate olefins containing trifluoromethyl and boronate neighboring groups which cannot undergo isomerization (substrates **S24** and **S25**). The hydrogenation of substrate **S24** proceeded with excellent enantiocontrol (ee's up to 99 %; Table 3.4.9, entries 13-15).[35] These results are of interest since enantioenriched α-trifluoromethyl chiral molecules are relevant building blocks for the development of agrochemicals, pharmaceuticals, and materials owing to the unique properties of the fluorine atom.[36] Interestingly, the reduction of alkenylboronic ester **S25** also provided high enantioselectivities (ee's up to 91 %, Table 3.4.9, entry 18). Encouraged by this latter result we also tested other challenging terminal boronic esters **S26**-**S29** (Table 3.4.9, entries 19-30). Although these substrates are also prone to isomerization they can be reduced with acceptable values of enantioselectivity (ee's up to 84 %). If we compare these latter results, with those achieved by the only successful report on this substrate class using Ir-phosphinite-imidazoline ligands,[29b] we can conclude that the new P,S catalytic systems overcome the limitation of the Pfaltz ligands in the hydrogenation of **S25** and **S29**, for which poor enantioselectivities were reported (ee's up to 4 % for **S25** and 33 % for **S29** at -20 °C).[29b]

Finally, we could also obtain excellent enantioselectivity in the hydrogenation of heteroaromatic alkene **S30** (ee's up to 96 %, Table 3.4.9, entry 33). Substrates containing heteroaraomatic groups are popular in fine-chemistry industries since the heterocyclic part allows for further functionalization.

Table 3.4.9. Selected results for the Ir-catalyzed hydrogenation of **S20**-**S30** using the P,S-ligand library **L41**-**L50a**-**g**.[a]

Entry	Substrate	Product	Ligand	ee%[b]
1	 **S20**	 **17**	**L46a**	34 (*S*)[c]
2			**L46e**	54 (*S*)[d]
3			**L50e**	62 (*S*)[e]
4	 **S21**	 **35**	**L46a**	16 (*S*)[f]
5			**L46e**	21 (*S*)[g]
6			**L50e**	27 (*S*)[h]
7	 **S22**	 **25**	**L47a**	29 (*R*)
8			**L47c**	58 (*R*)
9			**L50e**	71 (*R*)
10	 **S23**	 **36**	**L47a**	43 (*R*)
11			**L47c**	52 (*R*)
12			**L50e**	68 (*R*)
13	 **S24**	 **37**	**L41a**	99 (-)
14			**L41c**	99 (-)
15			**L48e**	99 (-)
16	 **S25**	 **38**	**L43c**	74 (*S*)
17			**L50d**	55 (*S*)
18			**L43c**	91 (*S*)[i]
19	 **S26**	 **39**	**L41c**	72 (*R*)
20			**L43c**	74 (*R*)
21			**L50d**	28 (*R*)
22	 **S27**	 **40**	**L41c**	76 (*R*)
23			**L43c**	81 (*R*)
24			**L50d**	19 (*R*)
25	 **S28**	 **41**	**L41c**	76 (*R*)
26			**L46c**	77 (*R*)
27			**L50e**	62 (*R*)
28	 **S29**	 **42**	**L41c**	76 (*S*)
29			**L50d**	75 (*R*)
30			**L50e**	84 (*R*)
31	 **S30**	 **43**	**L46b**	95 (+)
32			**L46c**	94 (-)
33			**L50e**	96 (+)

[a] Reactions carried out using 0.5 mmol of substrate, 2 mol% of Ir-catalyst precursor, CH_2Cl_2 as solvent, 1 bar H_2, 4 h. Full conversions were achieved in all cases. [b] Enantiomeric excesses determined by chiral GC or HPLC. [c] 38% of isomerized **S1** and 2% of **S2**. d 32% of isomerized **S1**. [e] 35% of isomerized **S1**. [f] 41% of tetrasubstituted olefin. [g] 32% of tetrasubstituted olefin. [h] 29% of tetrasubstituted olefin. [i] Reaction carried out at -20 °C.

Asymmetric hydrogenation using propylene carbonate as environmentally benign solvent. Recycling experiments

Finally, we focused our attention to replace the widely used dichloromethane solvent with propylene carbonate (PC) as an environmentally benign solvent.[37] The use of PC as solvent not only allows the hydrogenation to be performed in a more sustainable way but

also makes possible the recycling of the Ir catalysts by a simple two-phase extraction.[38] Catalyst recycling is desirable in large scale processes due to the high cost of iridium.

To assess whether the new Ir-P,S catalysts could be employed using PC as solvent, we screened the Ir-**L50e** catalytic system in the hydrogenation of model substrates **S1** and **S19** (Table 3.4.10). Although the reaction rates are lower in PC than in dichloromethane, similar high enantioselectivities were achieved (ee's up to 94% for **S1** and 96% for **S19**). In addition, we were able to recycle the Ir-catalysts up to 3 times without any drop of enantioselectivity. As previously observed, the reaction times necessary to achieve high conversions increased.[38] This drop in activity could be attributed to the loss of iridium catalyst to the hexane phase,[10k,38a] to the formation of inactive iridium clusters,[39] or to both.

Another important feature of using PC as a solvent in the asymmetric hydrogenation using Ir-P/N catalytic systems, observed by Börner et al., is that the rate of isomerization of terminal olefins to the corresponding trisubstituted ones diminishes compared to when dichloromethane is used. This behavior was exploited in order to improve enantioselectivity in the reduction of 1-methylene-1,2,3,4-tetrahydronaphthalene, which easily isomerizes to form the trisubstituted olefin.[10k, 38a] We therefore also performed the asymmetric hydrogenation of substrate **S20** with Ir-**L50e** using PC as solvent. We were pleased to find that the amount of isomerized trisubstituted substrate substantially diminished, and that the enantioselectivity consequently improved (ee's up to 72%, compared with 62% in dichloromethane).

Table 3.4.10. Asymmetric hydrogenation using propylene carbonate using catalyst precursor [Ir(cod)(**L50e**)]BAr_F. Recycling experiments.[a]

Cycle	Substrate	% Conv (Time / h)[b]	% ee[c]
1[d]	**S1**	98 (6)	94 (*R*)
2[d]		84 (10)	94 (*R*)
3[d]		89 (15)	93 (*R*)
1[e]	**S19**	97 (4)	95 (*S*)
2[e]		96 (8)	96 (*S*)
3[e]		81 (10)	95 (*S*)
1[e]	**S20**	99 (6)[f]	72 (*S*)

[a] Reactions carried out using 0.5 mmol of substrate and 2 mol% of Ir-catalyst precursor. [b] Conversion measured by ^{1}H-NMR for substrate **S1** or by GC for substrates **S19** and **S20**. [c] Enantiomeric excesses determined by chiral HPLC (substrate **S1**) or GC (substrates **S19** and **S20**). [d] Reaction carried out at 125 bar. [e] Reaction carried out at 50 bar. [f] 18% of **S1** observed.

3.4.3. Conclusion

A modular ligand design, with the help of DFT studies, has been shown to be highly successful in the identification and tuning of the crucial stereodefining groups in order to generate more selective catalysts. Following this approach, a library of modularly constructed thioether-phosphinite/phosphite ligands derived from the ring opening of enantiopure epoxides has been evaluated in the asymmetric iridium-catalyzed hydrogenation of a wide range of olefins. An extensive study on the influence of the different structural parameters has been done, demonstrating the highly modular nature of these ligands. Computations gave an understanding of the enantiocontrol in the reaction

allowing rationalization of the modifications required for improving selectivity. The computations moreover indicated that the diastereoisomers resulting from coordination of the thioether to the metal centre interconvert rapidly under the reaction conditions through pyramidal inversion, thus allowing for the use of the Curtin-Hammet principle in predicting the outcome of the reaction. In general, enantioselectivities are mainly controlled by the nature of the thioether, the aryl moieties and the type of P-donor group. However, the effect of changing these modules depends on the substrate class. The degree of activity and stereoinduction achieved with the lead ligands were amongst the highest with respect to the ones reported in the literature. The asymmetric hydrogenations were also performed using propylene carbonate as solvent, which allowed the Ir catalyst to be reused.

3.4.4. Experimental Section

3.4.4.1. General considerations

All reactions were carried out using standard Schlenk techniques under an argon atmosphere. Solvents were purified and dried by standard procedures. Phosphorochloridites were easily prepared in one step from the corresponding biphenols.[40] Intermediate compounds **1**-**2**,[18] **3**-**8**,[17] **10**-**13**[17] and **15**[17]; and thioether-phosphinite ligands **L41d**,[17] **L44d**,[17] **L46**-**L47d**[17] and **L49d**[17] were prepared as previously reported. ^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded using a 400 MHz spectrometer. Chemical shifts are relative to that of $SiMe_4$ (^{1}H and ^{13}C) as internal standard or H_3PO_4 (^{31}P) as external standard. ^{1}H, ^{13}C and ^{31}P assignments were made on the basis of ^{1}H-^{1}H gCOSY, ^{1}H-^{13}C gHSQC and ^{1}H-^{31}P gHMBC experiments.

3.4.4.2. Computational details

Geometries of all transition states were optimized using the Gaussian 09 program,[23] employing the B3LYP[20] density functional and the LANL2DZ[21d] basis set for iridium and the 6-31G*[21a-c] basis set for all other elements. Solvation correction was applied in the course of the optimizations using the PCM model with the default parameters for dichloromethane.[22] The complexes were treated with charge +1 and in the singlet state. No symmetry constraints were applied. Normal mode analysis of all transition states revealed a single imaginary mode corresponding to the expected hydride transfer or σ-bond metathesis. In the case of hydride transfer concomitant cleavage of the dihydrogen ligand was observed. The energies were further refined by performing single point calculations using the abovementioned parameters, with the exception that the 6-311+G**[24] basis set was used for all elements except iridium, and by applying dispersion correction using the DFT-D3[25] model. All energies reported are Gibbs free energies at 298.15 K and calculated as $G_{reported} = G_{6\text{-}31G^*} + E_{6\text{-}311+G^{**}} - E_{6\text{-}31G^*} + E_{DFT\text{-}D3}$.

3.4.4.3. General procedure for the preparation of tioether-alcohols 9, 14 and 16

To a suspension of the desired chiral epoxide (1.34 mmol) and sodium hydroxide (107 mg, 2.68 mmol, 2 equiv) in 6.6 mL of dioxane:water (10:1 v/v) was added the corresponding thiol (2.68 mmol, 2 equiv). The mixture was heated for 4 h at 90 °C. The

reaction was monitored by TLC until disappearance of the starting epoxide. The mixture was left to reach rt; and then water (15 mL) was added. The mixture was extracted with DCM (3 x 15 mL). The combined organic extracts were washed with brine, dried with Na_2SO_4 and filtered. The solvent was removed under vacuum and the crude was purified by flash chromatography on SiO_2 to produce the desired thioether-alcohol as a white solid.

(1*R*,2*S*)-3-methoxy-1-(naphthalen-1-ylthio)-1-phenylpropan-2-ol (9). Yield: 330 mg (84%). Reaction carried out using 1.34 mmol of starting epoxide. Column eluted with cyclohexane: ethyl acetate (95:5 to 2:1). ^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS): δ= 8.32-8.70 (m, 1 H; CH=), 7.70-7.98 (m, 2 H; CH=), 7.45-7.67 (m, 3 H; CH=), 7.21-7.39 (m, 6 H; CH=), 4.34 (d, ^3J (H,H) = 6.1 Hz, 1 H; CH-S), 4.14-4.22 (m, 1 H; CH-O), 3.38-2.55 (m, 2 H; CH_2), 3.30 (s, 3 H; CH_3-O), 2.54 ppm (d, ^3J(H,H) = 3.9 Hz, 1 H; OH). ^{13}C NMR (126 MHz, $CDCl_3$, 25°C, TMS): δ= 125.4-138.2 (aromatic carbons) 74.0 (s; CH_2), 72.0 (s; CH-O), 59.0 (s; CH-S), 56.2 ppm (s; CH_3). MS HR-ESI [found 347.1076, $C_{20}H_{20}O_2S$ $(M\text{-}Na)^+$ requires 347.1076].

(1*R*,2*S*)-1-((2,6-dimethylphenyl)thio)-1-phenyl-3-(trityloxy)propan-2-ol (14). Yield: 251 mg (84% yield). Reaction carried out using 0.56 mmol of starting epoxide Column eluted with hexane: ethyl acetate (95:5 to 4:1). ^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS): δ= 7.65-6.74 (m, 23 H; CH=), 4.07 (b, 2 H; CH-S, CH-O), 3.22 (b, 2 H; CH_2), 2.35 ppm (s, 6 H; CH_3). ^{13}C NMR (126 MHz, $CDCl_3$, 25°C, TMS): δ= 127.0-143.7 (aromatic carbons), 86.9 (s; C), 72.3 (s; CH-O), 65.2 (s; CH_2), 55.8 (s; CH-S), 22.0 ppm (s; CH_3). MS HR-ESI [found 553.2169, $C_{36}H_{34}O_2S$ $(M\text{-}Na)^+$ requires 553.2172].

(1*R*,2*S*)-1-((2,6-dimethylphenyl)thio)-1-mesityl-3-methoxypropan-2-ol (16). Yield: 255 mg (83%). Reaction carried out using 0.9 mmol of starting epoxide. Column eluted with hexane: ethyl acetate (95:5 to 2:1). ^{1}H NMR (500 MHz, $CDCl_3$, 25°C, TMS): δ= 7.14 - 7.05 (m, 1 H; CH=), 7.00 (d, ^3J(H,H) = 8.0 Hz, 2 H; CH=), 6.84 (s, 1 H; CH=), 6.60 (s, 1 H; CH=), 4.59 (d, ^3J(H,H) = 10.5 Hz, 1 H; CH-S), 4.42 - 4.32 (m, 1 H; CH-O), 3.91 (dd, ^3J(H,H) = 9.6 Hz, ^2J(H,H) = 2.5 Hz, 1 H; CH_2), 3.85 (dd, ^3J(H,H) = 9.6 Hz, ^2J(H,H) = 4.5 Hz, 1 H; CH_2), 3.46 (s, 3H; CH_3-O), 2.69 (s, 3 H; CH_3), 2.24 (s, 6 H; CH_3), 2.22 (s, 3 H; CH_3), 2.00 (d, ^3J(H,H) = 4.6 Hz, 1 H; OH,), 1.62 ppm (s, 3 H; CH_3). ^{13}C NMR (126 MHz, $CDCl_3$, 25°C, TMS): δ= 127.9-144.2 (aromatic carbons), 74.2 (s; CH_2), 71.1 (s; CH-O), 59.1 (s; CH_3-O), 49.6 (s; CH-S), 21.5 (s; CH_3), 20.9 (s; CH_3), 20.8 (s; CH_3), 20.2 ppm (s; CH_3). MS HR-ESI [found 367.1713, $C_{21}H_{28}O_2S$ $(M\text{-}Na)^+$ requires 367.1702].

3.4.4.4. General procedure for the preparation of the thioether-phosphite ligands L41-L49a-c

The corresponding phosphorochloridite (0.55 mmol) produced *in situ* was dissolved in toluene (2.5 mL), and pyridine (0.15 mL, 2.9 mmol) was added. The corresponding thioether-hydroxyl compound (0.5 mmol) was azeotropically dried with toluene (3 x 2 mL) and then dissolved in toluene (2.5 mL) to which pyridine (0.15 mL, 2.9 mmol) was added. The alcohol solution was then transferred slowly to the phosphorochloridite solution. The reaction mixture was stirred at 80 °C for 90 min, after which the pyridine salts were removed by filtration. Evaporation of the solvent gave a white foam, which was purified by flash chromatography on alumina (toluene/NEt_3 = 100/1) to produce the corresponding ligand as a white solid.

L41a. Yield: 256 mg (72%). ^{31}P NMR (162 MHz, C_6D_6, 25°C, H_3PO_4): δ= 144.1 ppm (s). ^{1}H NMR (400 MHz, C_6D_6, 25°C, TMS): δ=7.60 (d, ^4J(H,H) = 2.4 Hz, 1 H; CH=), 7.55 (d, ^4J(H,H) = 2.4 Hz, 1 H; CH=), 7.28-7.43 (m, 6 H; CH=), 7.00-7.16 (m, 4 H; CH=), 6.81-6.89 (m, 2 H; CH=), 5.29 (m, 1 H; CH-O), 4.70 (d, ^3J(H,H) = 4.0 Hz,1 H; CH-S), 3.19 (dd, ^2J(H,H) = 10.0 Hz, ^3J(H,H) = 6.0 Hz, 1 H; CH_2), 3.04 (dd, ^2J(H,H) = 9.2 Hz, ^3J(H,H) = 7.6 Hz, 1 H; CH_2), 2.91 (s, 3 H; CH_3-O), 1.55 (s, 9 H; CH_3, ^{t}Bu), 1.53 (s, 9 H; CH_3, ^{t}Bu), 1.30 (s, 9 H; CH_3, ^{t}Bu), 1.27 ppm (s, 9 H, CH_3, ^{t}Bu). ^{13}C NMR (126 MHz, C_6D_6, 25°C, TMS): δ= 124.7-147.0 (aromatic carbons), 76.6 (s; CH-O), 73.1 (s; CH_2), 58.9 (s; CH_3-O), 55.5 (d, ^3J(C,P) = 3.9 Hz; CH-S), 36.1 (s; C, ^{t}Bu), 36.0 (s; C, ^{t}Bu), 35.1 (s; C, ^{t}Bu), 35.0 (s; C, ^{t}Bu), 32.0 (s; CH_3, ^{t}Bu), 31.9 (d, J(C,P) = 1.6 Hz; CH_3, ^{t}Bu,), 31.8 ppm (d, J(C,P)=3.1 Hz; CH_3, ^{t}Bu). MS HR-ESI [found 735.3623, $C_{44}H_{57}O_4PS$ (M-Na)$^+$ requires 735.3607].

L41b. Yield: 200 mg (61%). ^{31}P NMR (162 MHz, C_6D_6, 25°C, H_3PO_4): δ= 133.6 ppm (s). ^{1}H NMR (400 MHz, C_6D_6, 25°C, TMS): δ= 7.53 (d, ^3J(H,H) = 8.4 Hz, 1 H; CH=), 7.33 (d, ^3J(H,H) = 8.4 Hz, 1 H; CH=), 7.01-7.21 (m, 7 H; CH=), 6.80-6.92 (m, 3 H; CH=), 5.26 (m, 1 H; CH-O), 1.38 (s, 9 H; CH_3, ^{t}Bu), 1.57 (s, 9 H; CH_3, ^{t}Bu), 1.67 (s, 3 H; CH_3), 4.86 (d, ^3J(H,H) = 4.4 Hz, 1 H; CH-S), 2.85 (dd, ^2J(H,H) = 9.2 Hz, ^3J(H,H) = 8.0 Hz, 1 H; CH_2), 2.83 (s, 3 H; CH_3-O), 2.66 (dd, ^2J(H,H) = 9.2 Hz, ^3J(H,H) = 4.0 Hz, 1 H; CH_2), 2.06 (s, 3 H; CH_3), 2.05 (s, 3 H; CH_3), 1.78 ppm (s, 3 H; CH_3). ^{13}C NMR (126 MHz, C_6D_6, 25°C, TMS): δ= 125.3-145.4 (aromatic carbons), 75.3 (d, ^2J(C,P) = 7.7 Hz; CH-O,),16.1 (s; CH_3), 71.7 (s; CH_2), 57.9 (s; CH_3-O), 54.4 (d, ^3J(C,P) = 5.4 Hz; CH-S), 34.5 (s; C, ^{t}Bu), 31.4 (s; CH_3, ^{t}Bu), 31.3 (d, J(C,P) = 5.4 Hz; CH_3, ^{t}Bu,), 20.1 (s; CH_3), 19.9 (s; CH_3), 16.4 ppm (s; CH_3). MS HR-ESI [found 679.2992, $C_{40}H_{49}O_4PS$ (M-Na)$^+$ requires 679.2981].

L41c. Yield: 187 mg (57%). ^{31}P NMR (162 MHz, C_6D_6, 25°C, H_3PO_4): δ= 141.0 ppm (s). ^{1}H NMR (400 MHz, C_6D_6, 25°C, TMS): δ= 7.11-7.27 (m, 6 H; CH=), 6.96-7.04 (m, 3 H; CH=), 6.80-6.88 (m, 3 H; CH=), 5.13 (m, 1 H; CH-O), 4.39 (d, ^3J(H,H) = 3.6 Hz, 1 H; CH-S), 3.47 (dd, ^3J(H,H) = 7.6 Hz, ^2J(H,H) = 10.0 Hz, 1 H; CH_2), 3.32 (dd, ^2J(H,H) = 9.6 Hz, ^3J(H,H) = 4.8 Hz, 1 H; CH_2), 2.98 (s, 3 H; CH_3-O), 2.16 (s, 3 H; CH_3), 2.08 (s, 3 H; CH_3), 1.82 (s, 3 H; CH_3), 1.73 (s, 3 H; CH_3), 1.67 (s, 9 H; CH_3, ^{t}Bu), 1.47 ppm (s, 9 H; CH_3, ^{t}Bu). ^{13}C NMR (126 MHz, C_6D_6, 25°C, TMS): δ= 126.0-146.5 (aromatic carbons), 77.4 (d, ^2J(C,P) = 10.9 Hz; CH-O), 73.4 (d, ^3J(C,P) = 2.9 Hz; CH_2), 56.2 (d, ^3J(C,P) = 1.6 Hz; CH-S), 58.9 (s; CH_3-O), 35.4 (s; C, ^{t}Bu), 32.1 (s; CH_3, ^{t}Bu), 32.0 (d, J(C,P) = 4.7 Hz; CH_3, ^{t}Bu), 20.9 (s; CH_3), 20.8 (s; CH_3), 17.3 (s; CH_3), 17.0 ppm (s; CH_3). MS HR-ESI [found 679.3014, $C_{40}H_{49}O_4PS$ (M-Na)$^+$ requires 679.2981].

L42b. Yield: 190 mg (54%). ^{31}P NMR (162 MHz, C_6D_6, 25°C, H_3PO_4): δ= 133.8 ppm (s). ^{1}H NMR (400 MHz, C_6D_6, 25°C, TMS): δ= 7.84 (d, ^4J(H,H) = 1.6 Hz, 1 H; CH=), 7.58-7.60 (m, 2 H; CH=), 7.35-7.45 (m, 4 H; CH=), 7.00-7.19 (m, 7 H; CH=), 5.34 (m, 1 H; CH-O), 5.03 (d, ^3J(H,H) = 4.4 Hz, 1 H; CH-S), 2.91 (dd, ^2J(H,H) = 9.6 Hz, ^3J(H,H) = 8.0 Hz, 1 H; CH_2), 2.84 (s, 3 H; CH_3-O), 2.72 (dd, ^2J(H,H) = 9.2 Hz, ^3J(H,H) = 4.0 Hz, 1 H; CH_2), 2.06 (s, 3 H; CH_3), 2.04 (s, 3 H; CH_3), 1.79 (s, 3 H; CH_3), 1.68 (s, 3 H; CH_3), 1.51 (s, 9 H; CH_3, ^{t}Bu), 1.41 ppm (s, 9 H; CH_3, ^{t}Bu). ^{13}C NMR (126 MHz, C_6D_6, 25°C, TMS): δ= 125.3-145.0 (aromatic carbons), 75.2 (d, ^2J(C,P) = 7.6 Hz; CH-O), 71.8 (s; CH_2), 58.0 (s; CH_3-O), 54.2 (d, ^3J(C,P) = 4.6 Hz; CH-S), 34.6 (s; C, ^{t}Bu), 34.5 (s; C, ^{t}Bu), 31.4 (s; CH_3, ^{t}Bu), 31.2 (d, J(C,P) = 5.3 Hz; CH_3, ^{t}Bu), 20.0 (s; CH_3), 19.9 (s; CH_3), 16.4 (s; CH_3), 16.1 ppm (s; CH_3). MS HR-ESI [found 729.3123, $C_{44}H_{51}O_4PS$ (M-Na)$^+$ requires 729.3138].

L42c. Yield: 222 mg (63%). ^{31}P NMR (162 MHz, C_6D_6, 25°C, H_3PO_4): δ= 141.2 ppm (s). ^{1}H NMR (400 MHz, C_6D_6, 25°C, TMS): δ= 7.64 (d, ^{4}J(H,H) = 0.8 Hz, 1 H; CH=), 7.25-7.44 (m, 8 H; CH=), 6.96-7.16 (m, 5 H; CH=), 5.21 (m, 1 H; CH-O), 4.56 (d, ^{3}J(H,H) = 3.6 Hz, 1 H; CH-S), 3.53 (dd, ^{2}J(H,H) = 10.0 Hz, ^{3}J(H,H) = 7.2 Hz, 1 H; CH_2), 3.37 (dd, ^{2}J(H,H) = 9.6 Hz, ^{3}J(H,H) = 5.2 Hz, 1 H; CH_2), 3.00 (s, 3 H; CH_3-O), 2.18 (s, 3 H; CH_3), 2.08 (s, 3 H; CH_3), 1.84 (s, 3 H; CH_3), 1.74 (s, 3 H; CH_3), 1.69 (s, 9 H; CH_3, ^{t}Bu), 1.47 ppm (s, 9 H; CH_3, ^{t}Bu). ^{13}C NMR (126 MHz, C_6D_6, 25°C, TMS): δ= 125.3-145.7 (aromatic carbons), 76.7 (d, ^{2}J(C,P) = 10.8 Hz; CH-O), 72.8 (s; CH_2), 58.2 (s; CH_3-O), 55.4 (s; CH-S), 34.7 (s; C, ^{t}Bu), 34.6 (s; C, ^{t}Bu), 31.4 (s; CH_3, ^{t}Bu), 31.3 (s; CH_3, ^{t}Bu), 20.2 (s; CH_3), 20.1 (s; CH_3), 16.6 (s; CH_3), 16.3 ppm (s; CH_3). MS HR-ESI [found 729.3130, $C_{44}H_{51}O_4PS$ (M-Na)$^{+}$ requires 729.3138].

L43a. Yield: 215 mg (59%). ^{31}P NMR (162 MHz, C_6D_6, 25°C, H_3PO_4): δ= 144.0 ppm (s). ^{1}H NMR (400 MHz, C_6D_6, 25°C, TMS): δ= 8.70 (dd, ^{3}J(H,H) = 8.4 Hz, ^{4}J(H,H) = 0.8 Hz, 1 H; CH=), 7.50-7.61 (m, 4 H; CH=), 7.35-7.39 (m, 5 H; CH=), 7.27-7.31 (m, 1 H; CH=), 6.93-7.21 (m, 5 H; CH=), 5.41 (m, 1 H; CH-O), 4.70 (d, ^{3}J(H,H) = 4.0 Hz, 1 H; CH-S), 3.19 (dd, ^{2}J(H,H) = 9.6 Hz, ^{3}J(H,H) = 5.4 Hz, 1 H; CH_2), 3.03 (dd, ^{2}J(H,H) = 9.2 Hz, ^{3}J(H,H) = 6.4 Hz, 1 H; CH_2), 2.88 (s, 3 H; CH_3-O), 1.55 (s, 9 H; CH_3, ^{t}Bu), 1.52 (s, 9 H; CH_3, ^{t}Bu), 1.30 (s, 9 H; CH_3, ^{t}Bu), 1.27 ppm (s, 9 H; CH_3, ^{t}Bu). ^{13}C NMR (126 MHz, C_6D_6, 25°C, TMS): δ= 124.7-147.0 (aromatic carbons), 76.9 (s; CH-O), 73.2 (s; CH_2), 58.8 (s; CH_3-O), 55.9 (d, ^{3}J(C,P) = 4.7 Hz; CH-S), 36.1 (s; C, ^{t}Bu), 36.0 (s; C, ^{t}Bu), 35.0 (s; C, ^{t}Bu), 32.0 (s; CH_3, ^{t}Bu), 31.9 (d, J(C,P) = 1.1 Hz; CH_3, ^{t}Bu,), 31.7 ppm (d, J(C,P) = 3.1 Hz; CH_3, ^{t}Bu). MS HR-ESI [found 785.3763, $C_{48}H_{59}O_4PS$ (M-Na)$^{+}$ requires 785.3770].

L43b. Yield: 211 mg (60%). ^{31}P NMR (162 MHz, C_6D_6, 25°C, H_3PO_4): δ= 133.5 ppm (s). ^{1}H NMR (400 MHz, C_6D_6, 25°C, TMS): δ= 8.72 (d, ^{3}J(H,H) = 8.0 Hz 1 H; CH=), 7.48-7.58 (m, 4 H; CH=), 7.38 (d, ^{3}J(H,H) = 8.0 Hz, 1 H; CH=), 7.29 (m, 1 H; CH=), 6.94-7.22 (m, 7 H; CH=), 5.39 (m, 1 H; CH-O), 4.86 (d, ^{3}J(H,H) = 4.4 Hz, 1 H; CH-S), 2.87 (dd, ^{2}J(H,H) = 9.6 Hz, ^{3}J(H,H) = 8.4 Hz, 1 H; CH_2), 2.79 (s, 3 H; CH_3-O), 2.66 (dd, ^{2}J(H,H) = 9.2 Hz, ^{3}J(H,H) = 4.0 Hz, 1 H; CH_2), 2.37 (s, 3 H; CH_3), 2.05 (s, 3 H; CH_3), 1.79 (s, 3 H; CH_3), 1.67 (s, 3 H; CH_3), 1.54 (s, 9 H; CH_3, ^{t}Bu), 2.16 (s, 3 H, CH_3),1.40 ppm (s, 9 H; CH_3, ^{t}Bu). ^{13}C NMR (126 MHz, C_6D_6, 25°C, TMS): δ= 126.0-146.2 (aromatic carbons), 76.2 (d, J(C,P) = 7.7 Hz; CH-O), 72.6 (s; CH_2), 58.7 (s; CH_3-O), 55.4 (d, J(C,P) = 5.4 Hz; CH-S), 35.3 (s; C, ^{t}Bu), 32.1 (s; CH_3, ^{t}Bu), 32.0 (d, J(C,P) = 5.4 Hz; CH_3, ^{t}Bu), 20.8 (s; CH_3), 20.6 (s; CH_3), 17.1 (s; CH_3), 16.9 ppm (s; CH_3). MS HR-ESI [found 729.3129, $C_{44}H_{51}O_4PS$ (M-Na)$^{+}$ requires 729.3138].

L43c. Yield: 201 mg (56%). ^{31}P NMR (162 MHz, C_6D_6, 25°C, H_3PO_4): δ= 141.4 ppm (s). ^{1}H NMR (400 MHz, C_6D_6, 25°C, TMS): δ= 8.61 (d, ^{3}J(H,H) = 8.8 Hz, 1 H; CH=), 7.50 (d, ^{3}J(H,H) = 8.4 Hz, 2 H; CH=), 6.89-7.36 (m, 11 H; CH=), 5.28 (m, 1 H; CH-O), 4.42 (d, ^{3}J(H,H) = 4.0 Hz, 1 H; CH-S), 3.50 (dd, ^{2}J(H,H) = 10.0 Hz, ^{3}J(H,H) = 7.6 Hz, 1 H; CH_2), 3.28 (dd, ^{2}J(H,H) = 9.6 Hz, ^{3}J(H,H) = 5.2 Hz, 1 H; CH_2), 2.96 (s, 3 H; CH_3-O), 2.08 (s, 3 H; CH_3), 1.83 (s, 3 H; CH_3), 1.74 (s, 3 H; CH_3), 1.65 (s, 9 H; CH_3, ^{t}Bu), 1.46 ppm (s, 9 H; CH_3, ^{t}Bu). ^{13}C NMR (126 MHz, C_6D_6, 25°C, TMS): δ= 126.0-146.5 (aromatic carbons), 77.7 (d, ^{2}J(C,P) = 12.3 Hz; CH-O), 73.6 (s; CH_2), 58.9 (s; CH_3-O), 56.3 (d, ^{3}J(C,P) = 2.3 Hz; CH-S), 35.5 (s; C, ^{t}Bu), 35.4 (s; C, ^{t}Bu), 32.1 (s; CH_3, ^{t}Bu), 32.0 (d, J(C,P) = 5.4 Hz; CH_3, ^{t}Bu), 20.9 (s; CH_3), 20.8 (s; CH_3), 17.3 (s; CH_3), 17.0 ppm (s; CH_3). MS HR-ESI [found 729.3137, $C_{44}H_{51}O_4PS$ (M-Na)$^{+}$ requires 729.3138].

L44a. Yield: 169 mg (49%). ^{31}P NMR (162 MHz, C_6D_6, 25°C, H_3PO_4): δ= 144.6 ppm (s). ^{1}H NMR (400 MHz, C_6D_6, 25°C, TMS): δ= 7.53-7.61 (m, 4 H; CH=), 7.33 (d, ^{4}J(H,H) = 2.4 Hz, 1 H; CH=), 7.30 (d, ^{4}J(H,H) = 2.4 Hz, 1 H; CH=), 7.00-7.16 (m, 3 H; CH=), 5.16 (m, 1 H; CH-O), 4.35 (d, ^{3}J(H,H) = 3.6 Hz, 1 H; CH-S), 3.06 (m, 1 H; CH_2), 2.94 (m, 1 H; CH_2), 2.96 (s, 3 H; CH_3-O), 1.58 (s, 9 H; CH_3, ^{t}Bu), 1.54 (s, 9 H; CH_3, ^{t}Bu), 1.30 (s, 9 H; CH_3, ^{t}Bu), 1.27 (s, 9 H; CH_3, ^{t}Bu), 1.16 ppm (s, 9 H; CH_3, ^{t}Bu). ^{13}C NMR (126 MHz, C_6D_6, 25°C, TMS): δ= 124.5-147.3 (aromatic carbons), 78.7 (s; CH-O), 73.1 (s; CH_2), 58.8 (s; CH_3-O), 49.5 (d, ^{3}J(C,P) = 4.6 Hz; CH-S), 44.3 (s; C, ^{t}Bu), 36.1 (s; C, ^{t}Bu), 35.0 (s; C, ^{t}Bu), 32.0 (s; CH_3, ^{t}Bu), 31.9 (s; CH_3, ^{t}Bu), 31.7 ppm (s; CH_3, ^{t}Bu). MS HR-ESI [found 715.3919, $C_{42}H_{61}O_4PS$ $(M\text{-}Na)^+$ requires 715.3924].

L44b. Yield: 137 mg (43%). ^{31}P NMR (162 MHz, C_6D_6, 25°C, H_3PO_4): δ= 133.2 ppm (s). ^{1}H NMR (400 MHz, C_6D_6, 25°C, TMS): δ= 7.61-7.63 (m, 2 H; CH=), 7.00-7.23 (m, 5 H; CH=), 5.17 (m, 1 H; CH-O), 4.37 (d, ^{3}J(H,H) = 4.0 Hz, 1 H; CH-S), 2.88 (s, 3 H; CH_3-O), 2.75 (m, 1 H; CH_2), 2.46 (dd, ^{2}J(C,H) = 9.6 Hz, ^{3}J(C,H) = 4.4 Hz, 1 H; CH_2), 2.07 (s, 3 H; CH_3), 2.06 (s, 3 H; CH_3), 1.80 (s, 3 H; CH_3), 1.68 (s, 3 H; CH_3), 1.66 (s, 9 H; CH_3, ^{t}Bu), 1.38 (s, 9 H; CH_3, ^{t}Bu), 1.20 ppm (s, 9 H; CH_3, ^{t}Bu). ^{13}C NMR (126 MHz, C_6D_6, 25°C, TMS): δ= 125.3-145.5 (aromatic carbons), 77.7 (d, ^{2}J(C,P) = 10.2 Hz; CH-O), 71.8 (s; CH_2), 58.0 (s; CH_3-O), 48.5 (d, ^{3}J(C,P) = 5.4 Hz; CH-S), 43.6 (s; C, ^{t}Bu), 34.7 (s; C, ^{t}Bu), 31.5 (d, J(C,P) = 5.4 Hz; CH_3, ^{t}Bu), 34.5 (s; C, ^{t}Bu), 31.4 (s; CH_3, ^{t}Bu), 30.1 (s; CH_3, ^{t}Bu), 20.1 (s; CH_3), 19.9 (s; CH_3), 16.4 (s; CH_3), 16.1 ppm (s; CH_3). MS HR-ESI [found 659.3291, $C_{38}H_{53}O_4PS$ $(M\text{-}Na)^+$ requires 659.3294].

L44c. Yield: 162 mg (51%). ^{31}P NMR (162 MHz, C_6D_6, 25°C, H_3PO_4): δ= 143.7 ppm (s). ^{1}H NMR (400 MHz, C_6D_6, 25°C, TMS): δ= 7.39-7.42 (m, 2 H; CH=), 7.30 (s, 1 H; CH=), 7.25 (s, 1 H; CH=), 7.00-7.16 (m, 4 H; CH=), 4.06 (m, 1 H; CH-O), 4.25 (d, ^{3}J(H,H) = 3.2 Hz, 1 H; CH-S), 3.45 (dd, ^{2}J(C,H) = 9.6 Hz, ^{3}J(C,H) = 6.8 Hz, 1 H; CH_2), 3.29 (dd, ^{2}J(C,H) = 9.2 Hz, ^{3}J(C,H) = 6.0 Hz, 1 H; CH_2), 3.01 (s, 3 H; CH_3-O), 2.09 (s, 3 H; CH_3), 2.07 (s, 3 H; CH_3), 1.75 (s, 3 H; CH_3), 1.74 (s, 3 H; CH_3), 1.73 (s, 9 H; CH_3, ^{t}Bu), 1.50 (s, 9 H; CH_3, ^{t}Bu), 1.08 ppm (s, 9 H; CH_3, ^{t}Bu). ^{13}C NMR (126 MHz, C_6D_6, 25°C, TMS): δ= 125.3-147.2 (aromatic carbons), 78.3 (d, ^{2}J(C,P) = 18.4 Hz; CH-O), 72.9 (s; CH_2), 58.1 (s; CH_3-O), 49.4 (s; CH-S), 43.3 (s; C, ^{t}Bu), 34.8 (s; C, ^{t}Bu), 34.7 (s; C, ^{t}Bu), 31.6 (s; CH_3, ^{t}Bu), 31.5 (d, J(C,P) = 4.6 Hz; CH_3, ^{t}Bu), 30.8 (s; CH_3, ^{t}Bu), 20.1 (s; CH_3), 20.0 (s; CH_3), 16.5 (s; CH_3), 16.3 ppm (s; CH_3). MS HR-ESI [found 659.3300, $C_{38}H_{53}O_4PS$ $(M\text{-}Na)^+$ requires 659.3294].

L45a. Yield: 177mg (46%). ^{31}P NMR (162 MHz, C_6D_6, 25°C, H_3PO_4): δ= 144.4 ppm (s). ^{1}H NMR (400 MHz, C_6D_6, 25°C, TMS): δ= 7.58-7.61 (m, 4 H; CH=), 7.54 (d, ^{4}J(H,H) = 2.4 Hz, 1 H; CH=), 7.32 (d, ^{4}J(H,H) = 2.4 Hz, 1 H; CH=), 7.31 (d, ^{4}J(C,P) = 2.8 Hz, 1 H; CH=), 6.99-7.16 (m, 3 H; CH=), 5.17 (m, 1 H; CH-O), 4.50 (d, ^{3}J(H,H) = 3.6 Hz, 1 H; CH-S), 3.08 (dd, ^{2}J(H,H) = 9.2 Hz, ^{3}J(H,H) = 5.6 Hz, 1 H; CH_2), 2.98 (s, 3 H; CH_3-O), 2.95-3.00 (m, 1 H; CH_2), 1.81-1.91 (m, 6 H; CH_2, Ad), 1.74 (m, 3 H; CH, Ad), 1.60 (s, 9 H; CH_3, ^{t}Bu), 1.55 (s, 9 H; CH_3, ^{t}Bu), 1.43 (m, 6 H; CH_2, Ad), 1.30 (s, 9 H; CH_3, ^{t}Bu), 1.27 ppm (s, 9 H; CH_3, ^{t}Bu). ^{13}C NMR (126 MHz, C_6D_6, 25°C, TMS): δ= 124.5-146.9 (aromatic carbons), 79.0 (s; CH-O), 73.2 (s; CH_2), 58.8 (s; CH_3-O), 46.7 (d, ^{3}J(C,P) = 3.9 Hz; CH-S), 46.6 (s; C, Ad), 44.5 (s; CH_2, Ad), 36.8 (s; CH_2, Ad), 36.1 (s; CH_2, Ad), 35.0 (s; C, ^{t}Bu), 32.0 (s; CH_3, ^{t}Bu), 31.9 (s; CH_3, ^{t}Bu), 30.4 ppm (s; CH, Ad). MS HR-ESI [found 793.4380, $C_{48}H_{67}O_4PS$ $(M\text{-}Na)^+$ requires 793.4390].

L46a. Yield: 174 mg (47%). ^{31}P NMR (162 MHz, C_6D_6, 25°C, H_3PO_4): δ= 144.2 ppm (s). ^{1}H NMR (400 MHz, C_6D_6, 25°C, H_3PO_4): δ= 7.63 (d, ^{4}J(H,H) = 2.4 Hz, 1 H; CH=), 7.54 (d, ^{4}J(H,H) =

2.8 Hz, 1 H; CH=), 7.34 (d, ^4J(H,H) = 2.8 Hz, 2 H; CH=), 7.27-7.29 (m, 1 H; CH=), 7.00-7.15 (m, 2 H; CH=), 6.83-6.88 (m, 3 H; CH=), 5.41 (m, 1 H; CH-O), 4.24 (d, ^3J(H,H) = 4.4 Hz, 1 H; CH-S), 3.15 (dd, ^2J(H,H) = 10.0 Hz, ^3J(H,H) = 5.2 Hz, 1 H; CH_2), 3.01 (dd, ^2J(H,H) = 9.2 Hz, ^3J(H,H) = 6.8 Hz, 1 H; CH_2), 2.86 (s, 3 H; CH_3-O), 2.31 (s, 6 H; CH_3), 1.60 (s, 9 H; CH_3, ^{t}Bu), 1.54 (s, 9 H; CH_3, ^{t}Bu), 1.31 (s, 9 H; CH_3, ^{t}Bu), 1.26 ppm (s, 9 H; CH_3, ^{t}Bu). ^{13}C NMR (126 MHz, C_6D_6, 25°C, H_3PO_4): δ= 124.6-147.3 (aromatic carbons), 77.5 (s; CH-O), 73.4 (s; CH_2), 58.8 (s; CH_3-O), 56.8 (d, ^3J(C,P) = 4.6 Hz; CH-S), 36.1 (s; C, ^{t}Bu), 35.1 (s; C, ^{t}Bu), 35.0 (s; C, ^{t}Bu), 32.0 (s; CH_3, ^{t}Bu), 31.9 (s; CH_3, ^{t}Bu), 31.8 (s; CH_3, ^{t}Bu), 22.6 ppm (s; CH_3). MS HR-ESI [found 763.3911, $C_{46}H_{61}O_4PS$ $(M\text{-}Na)^+$ requires 763.3920].

L46b. Yield: 212 mg (62%). ^{31}P NMR (162 MHz, C_6D_6, 25°C, H_3PO_4): δ= 133.7 ppm (s). ^{1}H NMR (400 MHz, C_6D_6, 25°C, TMS): δ= 7.36-7.39 (m, 2 H; CH=), 7.24 (s, 1 H; CH=), 7.07-7.16 (m, 2 H; CH=), 6.99-7.07 (m, 2 H; CH=), 6.84-6.91 (m, 3 H; CH=), 5.42 (m, 1 H; CH-O), 4.36 (d, ^3J(H,H) = 5.2 Hz, 1 H; CH-S), 2.87 (dd, ^2J(H,H) = 9.2 Hz, $^3J_{(H,H)}$ =8.0 Hz, 1 H; CH_2), 2.79 (s, 3 H; CH_3-O), 2.69 (dd, ^2J(H,H) = 9.2 Hz, ^3J(H,H) = 3.6 Hz 1 H; CH_2), 2.37 (s, 6 H; CH_3), 2.07 (s, 3 H; CH_3), 2 .06 (s, 3 H; CH_3), 1.80 (s, 3 H; CH_3), 1.69 (s, 3 H; CH_3), 1.67 (s, 9 H; CH_3, ^{t}Bu), 1.42 ppm (s, 9 H; CH_3, ^{t}Bu). ^{13}C NMR (126 MHz, C_6D_6, 25°C, TMS): δ= 125.3-145.5 (aromatic carbons), 76.3 (d, ^{2}(C,P) = 6,9 Hz; CH-O), 72.0 (s; CH_2), 57.9 (s; CH_3-O), 55.8 (d, ^3J(C,P) = 5.3 Hz; CH-S), 34.6 (s; C, ^{t}Bu), 31.4 (s; CH_3, ^{t}Bu), 31.4 (s; CH_3, ^{t}Bu), 22.0 (s; CH_3), 20.0 (s; CH_3), 19.9 (s; CH_3), 16.4 (s; CH_3), 16.1 ppm (s; CH_3). MS HR-ESI [found 707.3295, $C_{42}H_{53}O_4PS$ $(M\text{-}Na)^+$ requires 707.3294].

L46c. Yield: 219 mg (64%). ^{31}P NMR (162 MHz, C_6D_6, 25°C, H_3PO_4): δ= 143.2 ppm (s). ^{1}H NMR (400 MHz, C_6D_6, 25°C, TMS): δ= 7.30 (s, 1 H; CH=), 7.25 (s, 1 H; CH=), 6.79-7.16 (m, 8 H; CH=), 5.23 (m, 1 H; CH-O), 4.08 (d, ^3J(H,H) = 4.0 Hz, 1 H; CH-S), 3.48 (dd, ^2J(H,H) = 9.2 Hz, ^3J(H,H) = 6.8 Hz, 1 H; CH_2), 3.29 (dd, ^2J(H,H) = 9.6 Hz, ^3J(H,H) = 5.6 Hz, 1 H; CH_2), 2.96 (s, 3 H; CH_3-O), 2.22 (s, 6 H; CH_3), 2.17 (s, 3 H; CH_3), 2.07 (s, 3 H; CH_3), 1.77 (s, 3 H; CH_3), 1.74 (s, 3 H; CH_3), 1.70 (s, 9 H; CH_3, ^{t}Bu), 1.52 ppm (s, 9 H; CH_3, ^{t}Bu). ^{13}C NMR (126 MHz, C_6D_6, 25°C, TMS): δ= 126.8-143.5 (aromatic carbons), 77.7 (d, ^2J(C,P) = 17.4 Hz; CH-O), 73.3 (s; CH_2), 58.1 (s; CH_3-O), 56.6 (s; CH-S), 34.7 (s; C, ^{t}Bu), 31.5 (s; CH_3, ^{t}Bu), 31.4 (s; CH_3, ^{t}Bu), 21.8 (s; CH_3), 20.0 (s; CH_3), 16.5 (s; CH_3), 16.3 ppm (s; CH_3). MS HR-ESI [found 707.3296, $C_{42}H_{53}O_4PS$ $(M\text{-}Na)^+$ requires 707.3294].

L47a. Yield: 301 mg (64%). ^{31}P NMR (162 MHz, C_6D_6, 25°C, H_3PO_4): δ= 143.6 ppm (s). ^{1}H NMR (400 MHz, C_6D_6, 25°C, TMS): δ= 7.57 (d, ^4J(H,H) = 2.4 Hz 1 H; CH=), 7.55 (d, ^4J(H,H) = 2.4 Hz, 1 H; CH=), 7.41-7.47 (m, 8 H; CH=), 7.29-7.33 (m, 2 H; CH=), 7.11-7.21 (m, 3 H; CH=), 6.87-7.06 (m, 14 H; CH=), 5.28 (m, 1 H; CH-O), 4.97 (d, ^3J(H,H) = 4.0 Hz, 1 H; CH-S), 3.56 (dd, ^2J(H,H) = 9.6 Hz, ^3J(H,H) = 4.8 Hz, 1 H; CH_2), 3.19 (m, 1 H; CH_2), 1.48 (s, 9 H; CH_3, ^{t}Bu), 1.47 (s, 9 H; CH_3, ^{t}Bu), 1.31 (s, 9 H; CH_3, ^{t}Bu), 1.29 ppm (s, 9 H; CH_3, ^{t}Bu). ^{13}C NMR (126 MHz, C_6D_6, 25°C, TMS): δ= 123.9-146.3 (aromatic carbons), 87.2 (s; C-O), 76.5 (s; CH-O), 64.5 (s; CH_2), 55.0 (s; CH-S), 35.4 (s; C, ^{t}Bu), 35.3 (s; C, ^{t}Bu), 34.3 (s; C, ^{t}Bu), 31.3 (s; CH_3, ^{t}Bu), 31.2 (d, J(C,P) = 2.1 Hz; CH_3, ^{t}Bu), 31.1 ppm (d, J(C,P) = 2.0 Hz; CH_3, ^{t}Bu). MS HR-ESI [found 963.4587, $C_{62}H_{69}O_4PS$ $(M\text{-}Na)^+$ requires 963.4546].

L47b. Yield: 269 mg (61%). ^{31}P NMR (162 MHz, C_6D_6, 25°C, H_3PO_4): δ= 133.1 ppm (s). ^{1}H NMR (400 MHz, C_6D_6, 25°C, TMS): δ= 7.58 (d, ^3J(H,H) = 8.0 Hz, 2 H; CH=), 7.43-7,45 (m, 2 H; CH=), 7.34 (d, ^3J(H,H) = 7.2 Hz, 6 H; CH=), 7.11-7.21 (m, 3 H; CH=), 6.87-7.05 (m, 14 H; CH=),

5.55 (m, 1 H; CH-O), 5.24 (d, ^3J(H,H) = 2.4 Hz, 1 H; CH-S), 2.72 (dd, ^2J(H,H) = 8.8 Hz, ^3J(H,H) = 4.8 Hz, 1 H; CH_2), 2.42 (m, 1 H; CH_2), 2.06 (s, 3 H; CH_3), 2.00 (s, 3 H; CH_3), 1.68 (s, 3 H; CH_3), 1.61 (s, 9 H; CH_3, ^{t}Bu), 1.52 (s, 3 H; CH_3), 1.14 ppm (s, 9 H; CH_3, ^{t}Bu). ^{13}C NMR (126 MHz, C_6D_6, 25°C, TMS): δ= 126.0-145.8 (aromatic carbons), 87.5 (s; C-O), 76.5 (d, ^2J(C,P) = 10.7 Hz; CH-O), 64.4 (s; CH_2), 54.5 (d, ^3J(C,P) = 6.1 Hz; CH-S), 35.2 (s; C, ^{t}Bu), 32.2 (s; CH_3, ^{t}Bu), 31.9 (d, J(C,P) = 5.3 Hz; CH_3, ^{t}Bu), 20.7 (s; CH_3), 17.3 (s; CH_3), 16.9 ppm (s; CH_3). MS HR-ESI [found 907.3913, $C_{58}H_{61}O_4PS$ (M-Na)$^+$ requires 907.3920].

L47c. Yield: 256 mg (58%). ^{31}P NMR (162 MHz, C_6D_6, 25°C, H_3PO_4): δ= 141.8 ppm (s). ^{1}H NMR (400 MHz, C_6D_6, 25°C, TMS): δ= 7.56 (d, ^3J(H,H) = 8.4 Hz, 6 H; CH=), 6.98-7.25 (m, 15 H; CH=), 6.80-6.90 (m, 6 H; CH=), 5.08 (m, 1 H; CH-O), 4.60 (d, ^3J(H,H) = 3.6 Hz, 1 H; CH-S), 3.72 (dd, ^{2}J(H,H) = 9.6 Hz, ^3J(H,H) = 6.0 Hz, 1 H; CH_2), 3.50 (dd, ^2J(H,H) = 10.4 Hz, ^3J(H,H) = 5.6 Hz, 1 H; CH_2), 2.11 (s, 3 H; CH_3), 2.08 (s, 3 H; CH_3), 1.78 (s, 3 H; CH_3), 1.72 (s, 3 H; CH_3), 1.67 (s, 9 H; CH_3, ^{t}Bu), 1.40 ppm (s, 9 H; CH_3, ^{t}Bu). ^{13}C NMR (126 MHz, C_6D_6, 25°C, TMS): δ= 126.0-146.3 (aromatic carbons), 88.4 (s; C-O), 78.1 (d, ^2J(C,P) = 11.5 Hz; CH-O), 65.4 (s; CH_2), 56.5 (s; CH-S), 35.5 (s; C, ^{t}Bu), 35.3 (s; C, ^{t}Bu), 32.2 (s; CH_3, ^{t}Bu), 20.9 (s; CH_3), 20.8 (s; CH_3), 17.2 (s; CH_3), 17.0 ppm (s; CH_3). MS HR-ESI [found 907.3953, $C_{58}H_{61}O_4PS$ (M-Na)$^+$ requires 907.3920].

L48a. Yield: 285 mg (59%). ^{31}P NMR (162 MHz, C_6D_6, 25°C, H_3PO_4): δ= 143.7 ppm (s). ^{1}H NMR (400 MHz, C_6D_6, 25°C, TMS): δ= 7.61 (d, ^4J(H,H) = 2.4 Hz, 1 H; CH=), 7.54 (d, ^4J(H,H) = 2.4 Hz, 2 H; CH=), 7.43-7.46 (m, 6 H; CH=), 7.35 (d, ^4J(H,H) = 2.4 Hz, 1 H; CH=), 6.86-7.24 (m, 17 H; CH=), 5.34 (m, 1 H; CH-O), 4.52 (d, ^3J(H,H) = 4.0 Hz, 1 H; CH-S), 3.60 (dd, ^2J(H,H) = 10.0 Hz, ^3J(H,H) = 5.2 Hz 1 H; CH_2), 3.19 (m, 1 H; CH_2), 2.40 (s, 6 H; CH_3), 1.57 (s, 9 H; CH_3, ^{t}Bu), 1.49 (s, 9 H; CH_3, ^{t}Bu), 1.31 (s, 9 H; CH_3, ^{t}Bu),1.29 ppm (s, 9 H; CH_3, ^{t}Bu). ^{13}C NMR (126 MHz, C_6D_6, 25°C, TMS): δ= 123.9-146.3 (aromatic carbons), 87.1 (s; C-O), 77.6 (s; CH-O), 64.7 (s; CH_2), 56.1 (s; CH-S), 35.3 (s; C, ^{t}Bu), 34.3 (s; C, ^{t}Bu), 31.3 (s; CH_3, ^{t}Bu), 31.2 (s; CH_3, ^{t}Bu), 30.1 (s; CH_3, ^{t}Bu), 26.9 (s; CH_3, ^{t}Bu), 22.1 ppm (s; CH_3). MS HR-ESI [found 991.4862, $C_{64}H_{73}O_4PS$ (M-Na)$^+$ requires 991.4864].

L49a. Yield: 240 mg (61%). ^{31}P NMR (162 MHz, C_6D_6, 25°C, H_3PO_4): δ= 144.0 ppm (s). ^{1}H NMR (400 MHz, C_6D_6, 25°C, TMS): δ= 7.60 (d, ^4J(H,H) = 2.4 Hz, 1 H; CH=), 7.58 (d, ^4J(H,H) = 2.0 Hz, 1 H; CH=), 7.35-7.40 (m, 4 H; CH=),6.99-7.29 (m, 10 H; CH=),6.81-6.88 (m, 3 H; CH=), 5.34 (m, 1 H; CH-O), 4.72 (d, ^3J(H,H) = 4.0 Hz, 1 H; CH-S), 4.20 (d, ^2J(H,H) = 11.6 Hz, 1 H; CH_2-O), 4.12 (d, ^2J(H,H) = 12.4 Hz, 1 H; CH_2-O), 3.39 (dd, ^2J(H,H) = 10.0 Hz, ^3J(H,H) = 8.6 Hz, 1 H; CH_2), 3.27 (dd, ^2J(H,H) = 10.0 Hz, ^3J(H,H) = 6.8 Hz, 1 H; CH_2), 1.55 (s, 9H; CH_3, ^{t}Bu), 1.51 (s, 9 H; CH_3, ^{t}Bu), 1.30 (s, 9 H; CH_3, ^{t}Bu), 1.27 ppm (s, 9 H; CH_3, ^{t}Bu). ^{13}C NMR (126 MHz, C_6D_6, 25°C, TMS): δ= 124.7-147.2 (aromatic carbons), 76.7 (s; CH-O), 73.8 (s; CH_2-O), 71.2 (s; CH_2), 55.6 (d, ^3J(C,P) = 3.9 Hz; CH-S), 36.1 (s; C, ^{t}Bu), 36.0 (s; C, ^{t}Bu), 35.0 (s; C, ^{t}Bu), 32.0 (s; CH_3, ^{t}Bu), 31.8 ppm (s; CH_3, ^{t}Bu). MS HR-ESI [found 811.3948, $C_{50}H_{61}O_4PS$ (M-Na)$^+$ requires 811.3920].

L49b. Yield: 212 mg (58%). ^{31}P NMR (162 MHz, C_6D_6, 25°C, H_3PO_4): δ= 133.5 ppm (s). ^{1}H NMR (400 MHz, C_6D_6, 25°C, TMS): δ= 7.50 (d, ^3J(H,H) = 7.6 Hz, 1 H; CH=), 7.32 (d, ^3J(H,H) = 8.8 Hz, 1 H; CH=), 7.02-7.21 (m, 12 H; CH=), 6.80-6.90 (m, 3 H; CH=), 5.32 (m, 1 H; CH-O), 4.90 (d, ^3J(H,H) = 4.0 Hz, 1 H; CH-S), 4.09 (d, ^2J(H,H) = 12.0 Hz, 1 H; CH_2-O), 4.04 (d, ^2J(H,H) = 12.4 Hz, 1 H; CH_2-O), 3.09 (dd, ^2J(H,H) = 9.6 Hz, ^3J(H,H) = 8.0 Hz, 1 H; CH_2), 2.88 (dd, ^2J(H,H) =

9.6 Hz, ^{3}J(H,H) = 4.4 Hz, 1 H; CH_2), 2.06 (s; 3 H, CH_3), 2.05 (s, 3 H; CH_3), 1.76 (s, 3 H; CH_3), 1.67 (s, 3 H; CH_3), 1.57 (s, 9 H; CH_3, ^{t}Bu), 1.37 ppm (s, 9 H; CH_3, ^{t}Bu). ^{13}C NMR (126 MHz, C_6D_6, 25°C, TMS): δ= 126.0-146.0 (aromatic carbons), 76.2 (d, ^{2}J(C,P) = 7.0 Hz; CH-O), 73.7 (s; CH_2-O), 70.8 (s; CH_2), 55.1 (d, ^{3}J(C,P) = 4.7 Hz; CH-S), 35.3 (s; C, ^{t}Bu), 32.1 (s; CH_3, ^{t}Bu), 32.0 (d, J(C,P) = 5.4 Hz; CH_3, ^{t}Bu), 20.8 (s; CH_3), 20.7 (s; CH_3), 17.1 (s; CH_3), 16.8 ppm (s; CH_3). MS HR-ESI [found 755.3321, $C_{46}H_{53}O_4PS$ $(M\text{-}Na)^+$ requires 755.3294].

L49c. Yield: 219 mg (60%). ^{31}P NMR (162 MHz, C_6D_6, 25°C, H_3PO_4): δ= 140.9 ppm (s). ^{1}H NMR (400 MHz, C_6D_6, 25°C, TMS): δ= 7.95-7.26 (m, 14 H; CH=), 6.80-6.87 (m, 3 H; CH=), 5.21 (m, 1 H; CH-O), 4.90 (d, ^{3}J(H,H) = 4.0 Hz, 1 H; CH-S), 4.26 (d, ^{3}J(H,H) = 12.4 Hz, 1 H; CH_2-O), 4.17 (d, ^{2}J(H,H) = 12.4 Hz, 1 H; CH_2-O), 3.62 (dd, ^{2}J(H,H) = 10.0 Hz, ^{3}J(H,H) = 7.6 Hz, 1 H; CH_2), 3.49 (dd, ^{2}J(H,H) = 10.0 Hz, ^{3}J(H,H) = 4.8 Hz, 1 H; CH_2), 2.15 (s, 3 H; CH_3), 2.08 (s, 3 H; CH_3), 1.82 (s, 3 H; CH_3), 1.72 (s, 3 H; CH_3), 1.65 (s, 9 H; CH_3, ^{t}Bu), 1.46 ppm (s, 9 H; CH_3, ^{t}Bu). ^{13}C NMR (126 MHz, C_6D_6, 25°C, TMS): δ= 126.0-146.4 (aromatic carbons), 77.6 (d, ^{2}J(C,P) = 10.2 Hz; CH-O), 73.7 (s; CH_2-O), 71.3 (s; CH_2), 56.2 (s; CH-S), 35.4 (s; C, ^{t}Bu), 32.1 (s; CH_3, ^{t}Bu), 32.0 (s; CH_3, ^{t}Bu), 20.9 (s; CH_3), 20.8 (s; CH_3), 17.3 (s; CH_3), 17.0 ppm (s; CH_3). MS HR-ESI [found 755.3326, $C_{46}H_{53}O_4PS$ $(M\text{-}Na)^+$ requires 755.3294].

3.4.4.5. General procedure for the preparation of the thioether-phosphinite ligands L41-L50d-g

The corresponding thioether-hydroxyl compound (0.5 mmol) and DMAP (6.7 mg, 0.055 mmol) were dissolved in toluene (1 ml), and triethylamine was added (0.09 ml, 0.65 mmol) at r.t, followed by the addition of the corresponding chlorophosphine (0.55 mmol) via syringe. The reaction was stirred for 20 min at r.t. The solvent was removed *in vacuo*, and the product was purified by flash chromatography on alumina (toluene/NEt_3 = 100/1) to produce the corresponding ligand as an oil.

L42e. Yield: 203 mg (76%). ^{31}P NMR (162 MHz, C_6D_6, 25°C, H_3PO_4): δ= 102.5 ppm (s). ^{1}H NMR (400 MHz, C_6D_6, 25°C, TMS): δ= 7.77-7.85 (m, 3 H; CH=), 7.34-7.48 (s, 6 H; CH=), 6.88-7.16 (s, 11 H; CH=), 4.86 (d, ^{3}J(H,H) = 4.8 Hz, 1 H; CH-S), 4.79 (m, 1 H; CH-O), 3.36 (dd, ^{2}J(H,H) = 9.6 Hz, ^{3}J(H,H) = 6.0 Hz, 1 H; CH_2), 3.50 (dd, ^{2}J(H,H) = 10.0 Hz, ^{3}J(H,H) = 5.2 Hz, 1H; CH_2), 2.81 (s, 3 H; CH_3-O), 2.47 (s, 3 H; CH_3), 2.31 ppm (s, 3 H; CH_3). ^{13}C NMR (126 MHz, C_6D_6, 25°C, TMS): δ= 126.0-141.5 (aromatic carbons), 82.7 (d, ^{2}J(H,H) = 22.2 Hz; CH-O), 73.6 (d, ^{3}J(H,H) = 4.6 Hz; CH_2), 58.7 (CH_3-O), 56.4 (d, ^{3}J(H,H) = 5.3 Hz; CH-S), 21.1 (s; CH_3), 21.3 (d, ^{3}J(H,H) = 19.8 Hz; CH_3), 20.8 ppm (d, ^{3}J(H,H) = 19.9 Hz; CH_3). MS HR-ESI [found 559.1827, $C_{34}H_{33}O_2PS$ $(M\text{-}Na)^+$ requires 559.1831].

L43e. Yield: 190 mg (71%). ^{31}P NMR (162 MHz, C_6D_6, 25°C, H_3PO_4): δ= 102.6 ppm (s). ^{1}H NMR (400 MHz, C_6D_6, 25°C, TMS): δ= 8.64 (d, ^{3}J(H,H) = 7.6 Hz, 1 H; CH=), 7.75-7.85 (m, 2 H; CH=), 7.50-7.55 (m, 2 H; CH=), 7.27-7.40 (m, 4 H; CH=), 6.89-7.21 (m, 9 H; CH=),4.82 (m, 1 H; CH-O), 4.70 (d, ^{3}J(H,H) = 5.2 Hz, 1 H; CH-S), 3.49 (dd, ^{2}J(H,H) = 10.0 Hz, ^{3}J(H,H) = 5.6 Hz, 1 H; CH_2), 3.32 (dd, ^{2}J(H,H) = 9.2 Hz, ^{3}J(H,H) = 5.2 Hz, 1 H; CH_2), 2.78 (s, 3 H; CH_3-O), 2.47 (d, ^{4}J(H,P) = 1.2 Hz, 3 H; CH_3), 2.31 ppm (d, ^{4}J(H,P) = 1.2 Hz, 3 H; CH_3). ^{13}C NMR (126 MHz, C_6D_6, 25°C, TMS): δ= 125.3-141.1 (aromatic carbons), 82.3 (d, ^{2}J(C,P) =21.8 Hz; CH-O), 73.1 (d, ^{3}J(C,P) =3.8 Hz; CH_2), 57.9 (s; CH_3-O), 55.9 (d, ^{3}J(C,P) = 6.2 Hz; CH-S), 20.6 (d, ^{3}J(C,P) = 20.2 Hz; CH_3), 20.1 ppm (d, ^{3}J(C,P) = 21.3 Hz; CH_3). MS HR-ESI [found 559.1828, $C_{34}H_{33}O_2PS$ $(M\text{-}Na)^+$ requires 559.1831].

L44e. Yield: 158 mg (68%). ^{31}P NMR (162 MHz, C_6D_6, 25°C, H_3PO_4): δ= 101.4 ppm (s). ^{1}H NMR (400 MHz, C_6D_6, 25°C, TMS): δ= 7.82 (m, 1 H; CH=), 7.62 (m, 1 H; CH=), 7.43 (m, 2 H; CH=), 6.8-7.2 (m, 9 H; CH=), 4.61 (m, 1 H; CH-O), 4.37 (d, ^{3}J(H,H) = 4.8 Hz, 1 H; CH-S), 3.49 (dd, ^{2}J(H,H) = 10.2 Hz, ^{3}J(H,H) = 4.4 Hz 1 H; CH_2), 3.36 (dd, ^{2}J(H,H) = 10.2 Hz, ^{3}J(H,H) = 6.0 Hz, 1 H; CH_2), 2.91 (s, 3 H; CH_3-O), 2.43 (s, 3 H; CH_3), 2.28 (s, 3 H; CH_3), 1.10 ppm (s, 9 H; CH_3, ^{t}Bu). ^{13}C NMR (126 MHz, C_6D_6, 25°C, TMS): δ= 126.0-142.5 (aromatic carbons), 84.9 (d, ^{2}J(C,P) = 21.0 Hz; CH-O), 73.6 (d, ^{3}J(C,P) =4,7 Hz; CH_2), 58.7 (s; CH_3-O), 50.1 (d, ^{3}J(C,P) = 6.2 Hz; CH-S), 44.2 (s; C, ^{t}Bu), 31.7 (s; CH_3, ^{t}Bu), 21.4 (d, ^{3}J(C,P) = 20.2 Hz; CH_3), 20.8 ppm (d, ^{3}J(C,P) = 20.3 Hz; CH_3). MS HR-ESI [found 489.1984, $C_{28}H_{35}O_2PS$ (M-Na)$^+$ requires 489.1992].

L45e. Yield: 141 mg (52%). ^{31}P NMR (162 MHz, C_6D_6, 25°C, H_3PO_4): δ= 101.4 ppm (s). ^{1}H NMR (400 MHz, C_6D_6, 25°C, TMS): δ= 7.82-7.86 (m, 1 H; CH=), 7.68-7.71 (m, 1 H; CH=), 7.52-7.55 (m, 2 H; CH=), 7.10-7.16 (m, 3 H; CH=), 7.00-7.08 (m, 4 H; CH=), 6.94-6.96 (m, 1 H; CH=), 6.87-6.90 (m, 1 H; CH=), 4.65 (m, 1 H; CH-O), 4.49 (d, ^{3}J(H,H) = 5.2 Hz, 1 H; CH-S), 3.58 (dd, ^{2}J(H,H) = 9.6 Hz, ^{3}J(H,H) = 4.8 Hz, 1 H; CH_2), 3.37 (dd, ^{2}J(H,H) = 9.2 Hz, ^{3}J(H,H) = 5.6 Hz, 1 H; CH_2), 2.92 (s, 3 H; CH_3-O), 2.50 (s, 3 H; CH_3), 2.30 (s, 3 H; CH_3), 1.77-1.84 (m, 6 H; CH_2, Ad), 1.71-1.73 (m, 3 H, CH; Ad), 1.41 ppm (m, 6 H; CH_2, Ad). ^{13}C NMR (126 MHz, C_6D_6, 25°C, TMS): δ= 126.0-143.0 (aromatic carbons), 85.2 (d, ^{2}J(C,P) = 21.8 Hz; CH-O), 73.7 (d, ^{3}J(C,P) = 3.9 Hz; CH_2), 58.7 (s; CH_3-O), 47.5 (d, ^{3}J(C,P) = 5.4 Hz; CH-S), 46.6 (s; C, Ad), 44.5 (s; CH_2, Ad), 36.8 (s; CH_2, Ad), 30.4 (s; CH, Ad), 21.6 (d, ^{3}J(C,P) = 22.6 Hz; CH_3), 20.8 ppm (d, ^{3}J(C,P) = 20.2 Hz; CH_3). MS HR-ESI [found 567.2458, $C_{34}H_{41}O_2PS$ (M-Na)$^+$ requires 567.2463].

L46e. Yield: 172 mg (67%). ^{31}P NMR (162 MHz, C_6D_6, 25°C, H_3PO_4): δ= 102.4 ppm (s). ^{1}H NMR (400 MHz, C_6D_6, 25°C, TMS): δ= 7.81-7.84 (m, 1 H; CH=), 7.62-7.66 (m, 1 H; CH=), 7.24-7.26 (m, 2 H; CH=), 6.82-7.26 (m, 12 H; CH=), 4.83 (m, 1 H; CH-O), 4.32 (d, ^{2}J(H,H) = 6.4 Hz, 1 H; CH-S), 3.52 (dd, ^{2}J(H,H) = 9.60 Hz, ^{3}J(H,H) = 4.8 Hz, 1 H; CH_2), 3.36 (dd, ^{2}J(H,H) = 9.6 Hz, ^{3}J(H,H) = 5.2 Hz, 1 H; CH_2), 2.70 (s, 3 H; CH_3-O), 2.42 (d, ^{4}J(H,P) = 0.8 Hz, 3 H; CH_3), 2.34 (s, 3 H; CH_3), 2.32 ppm (s, 6 H; CH_3). ^{13}C NMR (126 MHz, C_6D_6, 25°C, TMS): δ= 126.0-144.2 (aromatic carbons), 83.7 (d, ^{2}J(C,P) = 22.2 Hz; CH-O), 74.0 (d, ^{3}J(C,P) = 3.8 Hz; CH_2), 58.6 (s; CH_3-O), 56.8 (d, ^{3}J(C;P) = 6.4 Hz; CH-S), 22.6 (s; CH_3), 21.8 (s; CH_3), 21.3 (d, ^{3}J(C,P) = 19.2 Hz; CH_3), 20.8 ppm (d, ^{3}J(C,P) = 19.2 Hz; CH_3). MS HR-ESI [found 537.1991, $C_{32}H_{35}O_2PS$ (M-Na)$^+$ requires 537.1994].

L47e. Yield: 228 mg (64%). ^{31}P NMR (162 MHz, C_6D_6, 25°C, H_3PO_4): δ= 101.7 ppm (s). ^{1}H NMR (400 MHz, C_6D_6, 25°C, TMS): δ= 7.45 (m, 1 H; CH=), 7.32 (m, 1 H; CH=), 6.98-7.40 (m, 6 H; CH=), 6.86-6.92 (m, 4 H; CH=), 6.70-6.78 (m, 6 H; CH=), 6.40-6.66 (m, 15 H; CH=), 4.44 (m, 1 H; CH-S), 4.40 (m, 1 H; CH-O), 3.18 (dd, ^{2}J(H,H) = 10.0 Hz, ^{3}J(H,H) = 6.0 Hz, 1 H; CH_2), 2.96 (dd, ^{2}J(H,H) = 10.0 Hz, ^{3}J(H,H) = 6.0 Hz, 1 H; CH_2), 2.11 (s, 3 H; CH_3), 2.08 (s, 3 H; CH_3), 1.83 (s, 3 H; CH_3),1.71 ppm (s, 3 H; CH_3). ^{13}C NMR (126 MHz, C_6D_6, 25°C, TMS): δ= 125.7-143.9 (aromatic carbons), 87.2 (s; C-O), 82.5 (d, ^{2}J(C,P) = 20.6 Hz; CH-O), 64.6 (d, ^{3}J(C,P) = 4,6 Hz; CH_2), 56.3 (d, ^{3}J(C,P) = 5,4 Hz; CH-S), 20.6 (d, ^{3}J(C,P) = 19.9 Hz; CH_3), 20.2 ppm (d, ^{3}J(C,P) = 20.6 Hz; CH_3). MS HR-ESI [found 737.2610, $C_{48}H_{43}O_2PS$ (M-Na)$^+$ requires 737.2614].

L47f. Yield: 130 mg (34%). ^{31}P NMR (162 MHz, C_6D_6, 25°C, H_3PO_4): δ= 118.5 ppm (s). ^{1}H NMR (400 MHz, C6D6, 25°C, TMS): δ= 7.22 (d, 3J(H,H) =7.6 Hz, 1 H; CH=), 6.97 (m, 2 H; CH=), 6.88 (m, 11 H; CH=), 6.63 (m, 3 H; CH=), 6.53 (m, 3 H; CH=), 6.38 (d, 4J(H,H) = 2.0 Hz, 2 H; CH=), 6.30 (d, 4J(H,H) = 2.8 Hz, 2 H; CH=), 4.63 (d, 3J(H,H) = 4.8 Hz, 1 H; CH-S), 4.34 (m, 1

H; CH-O), 3.55 (dd, 2J(H,H) = 9.2 Hz, 3J(H,H) = 5.2 Hz, 1 H; CH2), 3.30 (dd, 2J(H,H) = 9.6 Hz, 3J(H,H) = 6.0 Hz, 1 H; CH_2), 2.27 (s, 3 H; CH_3), 2.01 (s, 3 H; CH_3), 1.81 (s, 6 H; CH_3), 1.73 (s, 3 H; CH_3), 1.75 ppm (s, 3 H; CH_3). ^{13}C NMR (126 MHz, C_6D_6, 25°C, TMS): δ= 125.3-144.0 (aromatic carbons), 87.3 (s; C-O), 82.2 (d, ^2J(C,P) = 21.8 Hz; CH-O), 63.4 (d, ^3J(C,P) = 6.2 Hz; CH_2), 56.0 (d, ^3J(C,P) = 5.4 Hz; CH-S), 22.2 (d, ^3J(C,P) = 17.5 Hz; CH_3), 22.0 (d, ^3J(C,P) = 21.0 Hz; CH_3), 21.1 (s; CH_3), 20.5 ppm (d, ^3J(C,P) = 21.8 Hz; CH_3). MS HR-ESI [found 793.3237, $C_{52}H_{51}O_2PS$ (M-Na)$^+$ requires 793.3241].

L47g. Yield: 199 mg (57%). ^{31}P NMR (162 MHz, C_6D_6, 25°C, H_3PO_4): δ= 113.9 ppm (s). ^{1}H NMR (400 MHz, C_6D_6, 25°C, TMS): δ= 7.50-7.54 (m, 8 H; CH=), 7.39-7.41 (m, 2 H; CH=), 6.82-7.16 (m, 15 H; CH=), 5.09 (d, ^3J(H,H) = 2.8 Hz, 1 H; CH-S), 4.60 (m, 1 H; CH-O), 3.76 (m, 1 H; CH_2), 3.09 (dd, ^2J(H,H) = 9.6 Hz, ^3J(H,H) = 7.6 Hz, 1 H; CH_2), 2.20 (m, 1 H; CH_2, Cy), 1.00-1.85 ppm (m, 21 H; CH, CH_2, Cy),. ^{13}C NMR (126 MHz, C_6D_6, 25°C, TMS): δ= 125.3-144.1 (aromatic carbons). 87.4 (s; C-O), 81.9 (d, ^2J(C,P) = 16.9 Hz; CH-O), 64.3 (d, ^3J(C,P) = 6.8 Hz; CH_2), 56.3 (d, ^3J(C,P) = 5.3 Hz; CH-S), 38.4 (d, ^1J(C,P) = 19.1 Hz; CH, Cy), 37.6 (d, ^1J(C,P) = 17.6 Hz; CH, Cy), 28.1 (d, ^2J(C,P) = 16.2 Hz; CH_2, Cy), 27.8 (d, ^2J(C,P) = 21.8 Hz; CH_2, Cy), 27.3 (s; CH_2, Cy), 26.9 (s; CH_2, Cy), 26.8 (s; CH_2, Cy), 26.7-27.2 (m; CH_2, Cy), 26.6 (s; CH_2, Cy), 26.4 ppm (s; CH_2, Cy). MS HR-ESI [found 699.3450, $C_{46}H_{51}O_2PS$ (M-H)$^+$ requires 699.3420].

L48e. Yield: 237 mg (64%). ^{31}P NMR (162 MHz, C_6D_6, 25°C, H_3PO_4): δ= 102.8 ppm (s). ^{1}H NMR (400 MHz, C_6D_6, 25°C, TMS): δ= 6.92-7.94 (m, 31 H; CH=), 4.89 (m, 1 H; CH-O), 4.46 (d, ^3J(H,H) = 3.6 Hz, 1 H; CH-S), 3.60 (m, 1 H; CH_2), 3.36 (dd, ^2J(H,H) = 9.2 Hz, ^3J(H,H) = 6.4 Hz, 1 H; CH_2), 2.36 (s, 6 H; CH_3), 2.30 ppm (s, 6 H; CH_3),. ^{13}C NMR (126 MHz, C_6D_6, 25°C, TMS): δ= 124.0-144.0 (aromatic carbons), 85.4 (s; C-O), 82.5 (d, ^2J(C,P) = 20.4 Hz; CH-O), 63.2 (s; CH_2), 56.4 (d, ^3J(C,P) = 3.2 Hz; CH-S), 21.7 (s; CH_3), 21.3 (d, ^3J(C,P) = 19.2 Hz; CH_3), 20.8 (d, ^3J(C,P) = 19.2 Hz; CH_3),19.2 ppm (s; CH_3),. MS HR-ESI [found 765.2924, $C_{50}H_{47}O_2PS$ (M-Na)$^+$ requires 765.2930].

L50d. Yield: 117 mg (47%). ^{31}P NMR (162 MHz, C_6D_6, 25°C, H_3PO_4): δ= 113.8 ppm (s). ^{1}H NMR (400 MHz, C_6D_6, 25°C, TMS): δ= 7.51-7.55 (m, 2 H; CH=), 7.00-7.16 (m, 4 H; CH=), 6.83-6.93 (m, 7 H; CH=), 6.57 (d, ^4J(H,H) = 0.8 Hz, 1 H; CH=), 6.44 (d, ^4J(H,H) = 0.8 Hz, 1 H; CH=), 5.11 (d, ^3J(H,H) = 10.8 Hz, 1 H; CH-S), 4.88 (m, 1 H; CH-O), 3.93 (dd, ^2J(H,H) = 10.4 Hz, ^3J(H,H) = 4.0 Hz, 1 H; CH_2), 3.78 (dd, ^2J(H,H) = 10.4 Hz, ^3J(H,H) = 2.4 Hz, 1 H; CH_2), 2.94 (s, 3 H; CH_3-O), 2.75 (s, 3 H; CH_3), 2.34 (s, 6 H; CH_3), 2.05 (s, 3 H; CH_3), 1.81 ppm (s, 3 H; CH_3). ^{13}C NMR (126 MHz, C_6D_6, 25°C, TMS): δ= 126.0-145.0 (aromatic carbons), 81.3 (d, ^2J(C,P) = 19.9 Hz; CH-O), 74.1 (s; CH_2), 58.5 (s; CH_3-O), 49.9 (d, ^3J(C,P) = 6.1 Hz; CH-S), 22.2 (s; CH_3), 21.9 (s; CH_3), 21.8 (s; CH_3), 21.2 (s; CH_3), 21.1 ppm (s; CH_3). MS HR-ESI [found 551.2143, $C_{33}H_{37}O_2PS$ (M-Na)$^+$ requires 551.2147].

L50e. Yield: 113 mg (43%). ^{31}P NMR (162 MHz, C_6D_6, 25°C, H_3PO_4): δ= 101.8 ppm (s). ^{1}H NMR (400 MHz, C_6D_6, 25°C, TMS): δ= 7.79-7.82 (m, 1 H; CH=), 7.11-7.16 (m, 1 H; CH=), 6.96-7.06 (m, 2 H; CH=), 6.70-6.94 (m, 7 H; CH=),6.51 (s, 1 H; CH=), 6.40 (s, 1 H; CH=), 5.05 (d, ^3J(H,H) = 10.8 Hz, 1 H; CH-S), 4.80 (m, 1 H; CH-O), 3.89 (dd, ^2J(H,H) = 10.4 Hz, ^3J(H,H) = 3.6 Hz, 1 H; CH_2), 3.77 (dd, ^2J(H,H) = 10.4 Hz, ^3J(H,H) = 2.0 Hz, 1 H; CH_2), 2.91 (s, 3 H; CH_3-O), 2.71 (s, 3 H; CH_3), 2.34 (s, 6 H; CH_3), 2.30 (s, 3 H; CH_3), 2.10 (s, 3 H; CH_3), 2.03 (s, 3 H; CH_3), 1.79 ppm (s, 3 H; CH_3). ^{13}C NMR (126 MHz, C_6D_6, 25°C, TMS): δ= 125.8-145.0 (aromatic carbons), 81.9 (d, ^2J(C,P) = 22.2 Hz; CH-O), 74.2 (s; CH_2), 58.6 (s; CH_3-O), 50.1 (d, ^3J(C,P) = 6.1 Hz; CH-

S), 22.3 (s; CH_3), 21.8 (s; CH_3), 21.2 (s; CH_3), 21.1 (s; CH_3), 20.9 (d, ^3J(C,P) = 6.1 Hz; CH_3), 20.7 ppm (d, ^3J(C,P) = 6.9 Hz; CH_3). MS HR-ESI [found 579.2454, $C_{35}H_{41}O_2PS$ $(M\text{-}Na)^+$ requires 579.2459].

3.4.4.6. General procedure for the preparation of [Ir(cod)(L)]BAr_F (L=L41-L50a-g)

The corresponding ligand (0.074 mmol) was dissolved in CH_2Cl_2 (5 mL) and [Ir(μ-Cl)(cod)]$_2$ (25.0 mg, 0.037 mmol) was added. The reaction mixture was refluxed at 50 °C for 1 hour. After 5 min at room temperature, NaBArF (77.2 mg, 0.080 mmol) and water (5 mL) were added and the reaction mixture was stirred vigorously for 30 min at room temperature. The phases were separated and the aqueous phase was extracted twice with CH_2Cl_2. The combined organic phases were dried with $MgSO_4$, filtered through a plug of celite and the solvent was evaporated to give the product as a red-orange solid.

[Ir(cod)(L41a)]BAr_F. Yield: 128 mg (92%). ^{31}P NMR (162 MHz, $CDCl_3$, 25°C, H_3PO_4): δ= 90.8 ppm (s). ^{1}H NMR (400 MHz, $CDCl_3$, 25°C, TMS): δ= 7.0-7.9 (m, 26 H; CH= aromatic), 5.21 (b, 1 H; CH-O), 5.11 (s, 1 H; CH-S), 4.79 (b, 1 H; CH=, cod), 4.52 (b, 1 H; CH=, cod), 4.46 (b, 1 H; CH=, cod), 3.65 (b, 1 H; CH=, cod), 3.20 (m, 1 H; CH_2), 3.13 (s, 1 H; CH_3-O), 2.85 (m, 1 H; CH_2), 2.2-2.3 (b, 2 H; CH_2, cod), 1.9-2.15 (b, 5 H; CH_2, cod), 1.7-1.8 (b, 1 H; CH_2, cod), 1.72 (s, 9 H; CH_3, ^{t}Bu), 1.41 (s, 9 H; CH_3, ^{t}Bu), 1.36 (s, 9 H; CH_3, ^{t}Bu), 1.31 ppm (s, 9 H; CH_3, ^{t}Bu),. ^{13}C NMR (126 MHz, $CDCl_3$, 25°C, TMS): δ= 161.9 (q, ^1J(C,B) = 49.9 Hz; C-B, BArF), 117.6-149.4 (aromatic carbons), 103.8 (d, J(C,P) = 12.2 Hz; CH=, cod), 100.8 (d, J(C,P) = 14.7 Hz; CH=, cod), 75.6 (s; CH=, cod), 75.3 (s; CH_2), 71.1 (s; CH=, cod), 59.1 (s; CH_3-O), 53.6 (s; CH-S), 36.2 (s; C, ^{t}Bu), 35.7 (s; C, ^{t}Bu), 35.0 (s; C, ^{t}Bu), 34.9 (s; C, ^{t}Bu), 33.8 (d, J(C,P) = 4.2 Hz; CH_2, cod), 32.7 (s; CH_3, ^{t}Bu), 32.1 (s; CH_2, cod), 31.6 (s; CH_3, ^{t}Bu), 31.5 (s; CH_3, ^{t}Bu), 29.6 (s; CH_2, cod), 27.9 ppm (b; CH_2, cod). MS HR-ESI [found 1011.4237, $C_{52}H_{69}IrO_4PS$ (M)+ requires 1011.4255].

[Ir(cod)(L41b)]BAr_F. Yield: 126 mg (94%). ^{31}P NMR (162 MHz, $CDCl_3$, 25°C, H_3PO_4): δ= 90.8 ppm (s). ^{1}H NMR (400 MHz, $CDCl_3$, 25°C, TMS): δ= 6.86-7.96 (m, 24 H; CH= aromatic), 5.19 (s, 1 H; CH-S), 5.06 (b, 1 H; CH-O), 4.73 (b, 1 H; CH= cod), 4.56 (b, 1 H; CH= cod), 4.40 (b, 1 H; CH=, cod), 3.19 (b, 1 H; CH=, cod), 3.15 (s, 1 H; CH_3-O), 3.10 (dd, ^2J(H,H) = 9.6 Hz, ^3J(H,H) = 5.6 Hz, 1 H; CH_2), 2.75 (m, 1 H; CH_2), 2.30 (s, 3 H; CH_3), 2.22 (s, 3 H; CH_3), 2.19-2.31 (b, 3 H; CH_2, cod), 1.82 (s, 3 H; CH_3), 1.75-2.01 (b, 5 H; CH_2, cod), 1.72 (s, 12 H; CH_3, CH_3, ^{t}Bu), 1.28 ppm (s, 9 H; CH_3, ^{t}Bu). ^{13}C NMR (126 MHz, $CDCl_3$, 25°C, TMS): δ= 161.7 (q, ^1J(C,B) = 49.9 Hz; C-B, BArF), 117.4-144.4 (aromatic carbons), 103.3 (d, J(C,P) = 14.8 Hz; CH=, cod), 99.9 (d, J(C,P) = 15.6 Hz; CH=, cod), 77.2 (s; CH-O), 75.6 (s; CH=, cod), 70.8 (d, ^3J(C,P) = 8.6 Hz; CH_2), 70.0 (s; CH=, cod), 58.9 (s; CH_3-O), 56.1 (s; CH-S), 35.5 (s; C, ^{t}Bu), 34.8 (s; C, ^{t}Bu), 34.1 (d, J(C,P) = 6.7 Hz; CH_2, cod),133.1 (s; CH_3, ^{t}Bu), 31.6 (s; CH_3, ^{t}Bu), 31.5 (b; CH_2, cod), 29.9 (CH_2, cod), 27.3 (b; CH_2, cod), 20.4 (s; CH_3), 20.2 (s; CH_3), 16.6 (s; CH_3), 6.4 ppm (s; CH_3). MS HR-ESI [found 955.3617, $C_{48}H_{61}IrO_4PS$ $(M)^+$ requires 955.3629].

[Ir(cod)(L41c)]BAr_F. Yield: 124 mg (92%). ^{31}P NMR (162 MHz, $CDCl_3$, 25°C, H_3PO_4): δ= 97.7 ppm (s). ^{1}H NMR (400 MHz, $CDCl_3$, 25°C, TMS): δ= 7.20-7.72 (m, 24 H; CH= aromatic), 5.50 (b, 1 H; CH-O), 4.80 (b, 2 H; CH= cod, CH-S), 4.64 (b, 2 H; CH=, cod), 3.50 (dd, ^2J(H,H) = 9.6 Hz, ^3J(H,H) = 4.4 Hz, 1 H; CH_2), 3.36 (m, 1 H; CH=, cod), 3.14 (s, 1 H; CH_3-O), 2.97 (m, 1 H; CH_2), 2.28 (s, 3 H; CH_3), 2.26 (s, 3 H; CH_3), 2.13-2.36 (b, 4 H; CH_2, cod), 1.90-2.03 (b, 4 H; CH_2,

cod), 1.80 (s, 3 H; CH_3), 1.76 (s, 3 H; CH_3), 1.68 (s, 9 H; CH_3, ^{t}Bu), 1.47 ppm (s, 9 H; CH_3, ^{t}Bu). ^{13}C NMR (126 MHz, $CDCl_3$, 25°C, TMS): δ= 161.8 (q, ^1J(C,B) = 49.9 Hz; C-B, BArF), 117.6-144.3 (aromatic carbons), 106.3 (d, J(C,P) = 14.8 Hz; CH=, cod), 103.0 (d, J(C,P) = 14.8 Hz; CH=, cod), 81.2 (d, ^2J(H,H) = 7.0 Hz; CH-O), 77.8 (s; CH=, cod), 70.9 (d, ^3J(C,P) = 10.9 Hz; CH_2), 70.3 (s; CH=, cod), 61.4 (s; CH-S), 59.3 (s; CH_3-O), 35.3 (s; C, ^{t}Bu), 35.2 (s; C, ^{t}Bu), 33.1 (s; CH_2, cod), 32.7 (s; CH_3, ^{t}Bu), 32.6 (s; CH_2, cod), 31.6 (s; CH_3, ^{t}Bu), 28.8 (b; CH_2, cod), 28.6 (b; CH_2, cod), 20.5 (s; CH_3), 16.6 (s; CH_3), 16.5 ppm (s; CH_3). MS HR-ESI [found 955.3629, $C_{48}H_{61}IrO_4PS$ $(M)^+$ requires 955.3629].

[Ir(cod)(L41d)]BAr$_F$. Yield: 115 mg (96%). ^{31}P NMR (162 MHz, $CDCl_3$, 25°C, H_3PO_4): δ= 99.9 ppm (s). ^{1}H NMR (400 MHz, $CDCl_3$, 25°C, TMS): δ= 7.00-7.90 (m, 32 H; CH= aromatic), 4.81 (s, 1 H; CH-S), 4.51 (b, 1 H; CH-O), 4.51 (b, 2 H; CH=, cod), 3.62 (b, 1 H; CH=, cod), 3.16 (m, 1 H; CH_2), 3.09 (s, 1 H; CH_3-O), 2.91 (m, 1 H; CH_2), 2.24 (b, 2 H; CH_2, cod), 2.11 (b, 4 H; CH_2, cod), 1.88 ppm (b, 2 H; CH_2, cod). ^{13}C NMR (126 MHz, $CDCl_3$, 25°C, TMS): δ= 161.7 (q, ^1J(C,B) = 49.6 Hz; C-B, BArF), 117.5-134.8 (aromatic carbons), 98.6 (d, J(C,P) = 11.6 Hz; CH=, cod), 97.4 (d, J(C,P) = 10.8 Hz; CH=, cod), 77.9 (s; CH-O), 75.1 (s; CH=, cod), 72.0 (d, ^3J(C,P) = 7.6 Hz; CH_2), 70.2 (s; CH=, cod), 58.9 (s; CH_3-O), 56.7 (s; CH-S), 32.9 (s; CH_2, cod), 31.9 (s; CH_2, cod), 29.6 (s; CH_2, cod), 28.8 ppm (s; CH_2, cod),. MS HR-ESI [found 985.2934, $C_{36}H_{39}IrO_2PS$ $(M)^+$ requires 985.2948]. Suitable crystals for X-ray diffraction were achieved by slow diffusion of petrolium ether to an isopropanol solution

[Ir(cod)(L42b)]BAr$_F$. Yield: 127 mg (92%). ^{31}P NMR (162 MHz, $CDCl_3$, 25°C, H_3PO_4): δ= 91.0 ppm (s). ^{1}H NMR (400 MHz, $CDCl_3$, 25°C, TMS): δ= 6.73-8.02 (m, 26 H; CH= aromatic), 5.25 (s, 1 H; CH-S), 5.14 (m, 1 H; CH-O), 4.83 (b, 1 H; CH=, cod), 4.61 (m, 1 H; CH=, cod), 4.47 (m, 1 H; CH=, cod), 3.18 (b, 2 H; CH_2, CH= cod), 3.16 (s, 3 H; CH_3-O), 2.81 (m, 1 H; CH_2), 2.32 (s, 3 H; CH_3), 2.24 (s, 3 H; CH_3), 2.12-2.29 (b, 4 H; CH_2, cod), 1.85 (s, 3 H; CH_3), 1.78 (s, 9 H; CH_3, ^{t}Bu), 1.73-2.00 (b, 4 H; CH_2, cod), 1.76 (s, 3 H; CH_3), 1.33 ppm (s, 9 H; CH_3, ^{t}Bu). ^{13}C NMR (126 MHz, $CDCl_3$, 25°C, TMS): δ= 161.7 (q, ^1J(C,B) = 49.7 Hz; C-B, BArF), 117.4-143.5 (aromatic carbons), 103.3 (d, J(C,P) = 14.5 Hz; CH=, cod), 100.2 (d, J(C,P) = 15.3 Hz; CH=, cod), 77.2 (d, ^2J(C,P) = 4.0 Hz; CH-O), 75.8 (CH=; cod), 70.8 (d, ^3J(C,P) = 8.3 Hz; CH_2), 69.9 (s; CH=, cod), 58.8 (s; CH_3-O), 56.4 (s; CH-S), 35.5 (s; C, ^{t}Bu), 34.9 (s; CH_2, cod), 33.9 (d, J(C,P) = 4.5 Hz; CH_2, cod), 33.1 (s; CH_3, ^{t}Bu), 31.7 (s; CH_3, ^{t}Bu), 29.8 (b; CH_2, cod), 27.4 (d, J(C,P) = 2.3 Hz; CH_2, cod), 20.4 (s; CH_3), 20.2 (s; CH_3), 16.6 (s; CH_3), 16.4 ppm (s; CH_3), MS HR-ESI [found 1005.3743, $C_{52}H_{63}IrO_4PS$ $(M)^+$ requires 1005.3785].

[Ir(cod)(L42c)]BAr$_F$. Yield: 131 mg (95%). ^{31}P NMR (162 MHz, $CDCl_3$, 25°C, H_3PO_4): δ= 97.9 ppm (s). ^{1}H NMR (400 MHz, $CDCl_3$, 25°C, TMS): δ= 7.22-8.05 (m, 26 H; CH= aromatic), 5.56 (b, 1 H; CH-O), 4.90 (d, ^3J(H,H) = 2.4 Hz, 1 H; CH-S), 4.86 (b, 1 H; CH=, cod), 4.67 (b, 2 H; CH=, cod), 3.54 (dd, ^2J(H,H) = 9.2 Hz, ^3J(H,H) = 3.6 Hz, 1 H; CH_2), 3.35 (b, 1 H; CH= cod), 3.15 (s, 3 H; CH_3-O), 3.00 (m, 1 H; CH_2), 2.34 (b, 1 H; CH_2, cod), 2.30 (s, 3 H; CH_3), 2.27 (s, 3 H; CH_3), 2.13 (b, 2 H; CH_2, cod), 1.88-2.04 (b, 5 H; CH_2, cod), 1.81 (s, 3 H; CH_3), 1.77 (s, 3 H; CH_3), 1.72 (s, 9 H; CH_3, ^{t}Bu), 1.50 ppm (s, 9 H; CH_3, ^{t}Bu),. ^{13}C NMR (126 MHz, $CDCl_3$, 25°C, TMS): δ= 161.7 (q, ^1J(C,B) = 49.7 Hz; C-B, BArF), 117.4-144.3 (aromatic carbons), 106.1 (d, J(C,P) = 14.6 Hz; CH=, cod), 103.1 (d, J(C,P) = 14.5 Hz; CH=, cod), 81.2 (d, ^2J(C,P) = 6.8 Hz; CH-O), 77.6 (s; CH=, cod), 70.8 (d, ^3J(C,P) = 11.5 Hz; CH_2), 70.0 (s; CH=, cod), 61.1 (s; CH-S), 59.1 (s; CH_3-O), 35.1 (s; C, ^{t}Bu), 35.0 (s; C, ^{t}Bu), 33.3 (s; CH_2, cod), 32.5 (s; CH_3, ^{t}Bu), 32.4 (s; CH_2,

cod), 31.5 (s; CH_3, ^{t}Bu), 28.6 (s; CH_2, cod), 28.3 (s; CH_2, cod), 20.3 (s; CH_3), 16.4 (s; CH_3), 16.3 ppm (s; CH_3). MS HR-ESI [found 1005.3768, $C_{52}H_{63}IrO_4PS$ $(M)^+$ requires 1005.3785].

[Ir(cod)(L42e)]BAr$_F$. Yield: 116 mg (93%).^{31}P NMR (162 MHz, $CDCl_3$, 25°C, H_3PO_4): δ= 106.8 ppm (s). ^{1}H NMR (400 MHz, $CDCl_3$, 25°C, TMS): δ= 7.1-8.9 (m, 32 H; CH= aromatic), 5.49 (b, 1 H; CH-O), 5.03 (s, CH-S; 1 H), 4.92 (b, 1 H; CH=, cod), 4.64 (b, 2 H; CH=, cod), 3.54 (m, 1 H; CH= cod), 3.24 (b, 1 H; CH_2), 3.17 (s, 3 H; CH_3-O), 3.03 (m, 1 H; CH_2), 2.87 (s, 3 H; CH_3), 2.2-2.4 (b, 4 H; CH_2, cod), 2.09 (s, 3 H; CH_3), 1.8-2.1 ppm (b, 4 H; CH_2, cod). ^{13}C NMR (126 MHz, $CDCl_3$, 25°C, TMS): δ= 161.7 (q, ^1J(C,B) = 49.8 Hz; C-B, BArF), 117.4-145.2 (aromatic carbons), 97.4 (d, J(C,P) = 14.4 Hz; CH=, cod), 96.3 (d, J(C,P) = 12.6 Hz; CH=, cod), 85.6 (d, ^2J(C,P) =4.2 Hz; CH-O), 77.2 (s; CH=, cod), 72.2 (b; CH_2), 71.6 (s; CH=, cod), 63.9 (s; CH-S), 58.8 (s; CH_3-O), 34.2 (b; CH_2, cod), 30.5 (s; CH_2, cod), 29.7 (s; CH_2, cod), 27.5 (b; CH_2, cod), 22.3 (s; CH_3), 21.3 ppm (s; CH_3). MS HR-ESI [found 835.2472, $C_{42}H_{45}IrO_2PS$ $(M)^+$ requires 835.2478].

[Ir(cod)(L43a)]BAr$_F$. Yield: 134 mg (94%). ^{31}P NMR (162 MHz, $CDCl_3$, 25°C, H_3PO_4): δ= 93.8 ppm (s). ^{1}H NMR (400 MHz, $CDCl_3$, 25°C, TMS): δ= 7.14-8.40 (m, 28 H; CH= aromatic), 5.40 (b, 1 H; CH-O), 4.98 (b, 1 H; CH-S), 4.87 (b, 1 H; CH=, cod), 4.39 (b, 2 H; CH=, cod), 3.80 (b, 1 H; CH=, cod), 3.23 (b, 1 H; CH_2), 3.08 (s, 3 H; CH_3-O), 2.89 (m, 1 H; CH_2), 2.01-2.29 (b, 4 H; CH_2, cod), 1.85 (s, 9 H; CH_3, ^{t}Bu), 1.63-1.84 (b, 4 H; CH_2, cod), 1.50 (s, 9 H; CH_3, ^{t}Bu), 1.37 (s, 9 H; CH_3, ^{t}Bu), 1.33 ppm (s, 9 H; CH_3, ^{t}Bu). ^{13}C NMR (126 MHz, $CDCl_3$, 25°C, TMS): δ= 161.7 (q, ^1J(C,B) = 49.9 Hz; C-B, BArF), 117.4-149.3 (aromatic carbons), 105.0 (m; 2CH=, cod), 78.8 (s; CH-O), 77.2 (b; CH=, cod), 74.2 (b; CH=, cod), 71.1 (d, ^3J(C,P) = 8.7 Hz; CH_2), 59.0 (s; CH_3-O), 57.8 (s; CH-S), 36.0 (s; C, ^{t}Bu), 35.6 (s; C, ^{t}Bu), 34.8 (s; C, ^{t}Bu), 34.7 (s; C, ^{t}Bu), 33.3 (s; CH_2, cod), 32.3 (s; CH_3, ^{t}Bu), 31.5 (s; CH_3, ^{t}Bu), 31.3 (s; CH_3, ^{t}Bu), 29.1 (s; CH_2, cod), 27.9 ppm (s; CH_2, cod). MS HR-ESI [found 1061.4376, $C_{56}H_{71}IrO_4PS$ $(M-)^+$ requires 1061.4411].

[Ir(cod)(L43b)]BAr$_F$. Yield**:** 131 mg (95%). ^{31}P NMR (162 MHz, $CDCl_3$, 25°C, H_3PO_4): δ= 90.7 ppm (s). ^{1}H NMR (400 MHz, $CDCl_3$, 25°C, TMS): δ= 6.65-8.43 (m, 26 H; CH= aromatic), 5.22 (b, 1 H; CH-O), 5.15 (b, 1 H; CH-S), 4.82 (b, 1 H; CH=, cod), 4.62 (m, 1 H; CH=, cod), 4.24 (m, 1 H; CH=, cod), 3.16 (m, 2 H; CH_2, CH= cod), 3.12 (s, 3 H; CH_3-O), 2.78 (m, 1 H; CH_2), 2.32 (s, 3 H; CH_3), 2.24 (s, 3 H; CH_3), 2.05-2.33 (b, 4 H; CH_2, cod), 1.86 (s, 9 H; CH_3, ^{t}Bu), 1.85 (s, 3 H; CH_3), 1.77 (s, 3 H; CH_3), 1.70-1.92 (b, 4 H; CH_2, cod), 1.34 ppm (s, 9 H; CH_3, ^{t}Bu),. ^{13}C NMR (126 MHz, $CDCl_3$, 25°C, TMS): δ= 161.8 (q, ^1J(C,B) = 49.8 Hz; C-B, BArF), 117.6-147.9 (aromatic carbons), 105.1 (d, J(C,P) = 15.2 Hz; CH=, cod), 100.4 (d, J(C,P) = 11.8 Hz; CH=, cod), 78.0 (s; CH-O), 76.0 (b; CH=, cod), 71.2 (s; CH_2), 70.0 (b; CH=, cod), 59.1 (s; CH_3-O), 56.6 (s; CH-S), 35.9 (s; C, ^{t}Bu), 35.1 (s; C, ^{t}Bu), 33.8 (b; CH_2, cod), 33.3 (s; CH_3, ^{t}Bu), 32.3 (b; CH_2, cod), 31.9 (s; CH_3, ^{t}Bu), 29.6 (b; CH_2, cod), 28.0 (b; CH_2, cod), 20.6 (s; CH_3), 20.5 (s; CH_3), 16.8 (s; CH_3), 16.7 ppm (s; CH_3). MS HR-ESI [found 1005.3768, $C_{52}H_{63}IrO_4PS$ $(M)^+$ requires 1005.3785].

[Ir(cod)(L43c)]BAr$_F$. Yield: 134 mg (97%). ^{31}P NMR (162 MHz, $CDCl_3$, 25°C, H_3PO_4): δ= 97.7 ppm (s). ^{1}H NMR (400 MHz, $CDCl_3$, 25°C, TMS): δ= 6.65-8.43 (m, 26 H; CH= aromatic), 5.62 (b, 1 H; CH-O), 4.90 (d, ^3J(H,H) = 2.4 Hz, 1 H; CH-S), 4.65 (m, 2 H; CH=, cod), 4.20 (m, 1 H; CH=, cod), 3.51 (m, 1 H; CH_2), 3.15 (m, 1 H; CH= cod), 3.11 (s, 3 H; CH_3-O), 2.98 (dd, ^2J(H,H) = 12.0 Hz, ^3J(H,H) = 6.8 Hz, 1 H; CH_2), 2.3-2.4 (b, 3 H; CH_2), 2.29 (s, 3 H; CH_3), 2.26 (s,

3 H; CH_3), 2.0-2.2 (b, 5 H; CH_2, cod), 1.80 (s, 3 H; CH_3), 1.77 (s, 3 H; CH_3), 1.71 (s, 9 H; CH_3, ^{t}Bu), 1.53 ppm (s, 9 H; CH_3, ^{t}Bu). ^{13}C NMR (126 MHz, $CDCl_3$, 25°C, TMS): δ= 161.7 (q, ^1J(C,B) = 49.8 Hz; C-B, BArF), 117.4-144.6 (aromatic carbons), 107.3 (d, J(C,P) = 15.2 Hz; CH=, cod), 103.1 (d, J(C,P) = 14.7 Hz; CH=, cod), 80.5 (d, J(C,P) = 5.4 Hz; CH-O), 77.6 (s; CH=, cod), 70.7 (d, J(C,P) = 10.8 Hz; CH_2), 69.7 (b; CH=, cod), 58.9 (s; CH_3-O), 57.7 (s; CH-S), 35.1 (s; C, ^{t}Bu), 35.0 (s; C, ^{t}Bu), 33.5 (b; CH_2, cod), 32.5 (s; CH_3, ^{t}Bu), 32.0 (b; CH_2, cod), 31.5 (s;CH_3, ^{t}Bu), 29.7 (s; CH_2, cod), 29.0 (b; CH_2, cod), 20.3 (s; CH_3), 20.2 (s; CH_3), 16.4 (s; CH_3), 16.3 ppm (s; CH_3),. MS HR-ESI [found 1005.3765, $C_{52}H_{63}IrO_4PS$ $(M)^+$ requires 1005.3785].

[Ir(cod)(L43e)]BAr$_F$. Yield: 117 mg (93%). ^{31}P NMR (162 MHz, $CDCl_3$, 25°C, H_3PO_4): δ= 108.3 ppm(s). ^{1}H NMR (400 MHz, $CDCl_3$, 25°C, TMS): δ= 7.1-8.9 (m, 32 H; CH= aromatic), 5.62 (b, 1 H; CH-O), 5.12 (s, CH-S; 1 H), 4.87 (b, 1 H; CH=, cod), 4.19 (b, 2 H; CH=, cod), 3.81 (m, 1 H; CH= cod), 3.58 (b, 2 H; CH_2), 3.12 (s, 3 H; CH_3-O), 2.81 (s, 3 H; CH_3), 2.2-2.4 (b, 4 H; CH_2, cod), 2.09 (s, 3 H; CH_3), 1.8-2.1 ppm (b, 4 H; CH_2, cod). ^{13}C NMR (126 MHz, $CDCl_3$, 25°C, TMS): δ= 161.4 (q, ^1J(C,B) = 49.8 Hz; C-B, BArF), 117.4-145.2 (aromatic carbons), 99.7 (d, J(C,P) = 14.6 Hz; CH=, cod), 98.7 (d, J(C,P) = 12.4 Hz; CH=, cod), 86.2 (d, ^2J(C,P) = 4.0 Hz; CH-O), 77.4 (s; CH=, cod), 74.2 (b; CH_2), 73.6 (s; CH=, cod), 61.7 (s; CH-S), 58.9 (s; CH_3-O), 34.6 (b; CH_2, cod), 30.3 (s; CH_2, cod), 29.7 (s; CH_2, cod), 27.1 (b; CH_2, cod), 22.1 (s; CH_3), 21.4 ppm (s; CH_3). MS HR-ESI [found 835.2472, $C_{42}H_{55}IrO_2PS$ $(M)^+$ requires 835.2478].

[Ir(cod)(L44a)]BAr$_F$. Yield: 130 mg (95%). ^{31}P NMR (162 MHz, $CDCl_3$, 25°C, H_3PO_4): δ= 94.3 ppm (s). ^{1}H NMR (400 MHz, $CDCl_3$, 25°C, TMS): δ= 7.10-7.91 (m, 19 H; CH= aromatic), 5.75 (b, 1 H; CH=, cod), 5.59 (m, 1 H; CH=, cod), 5.02 (m, 1 H; CH-O), 4.97 (s, 1 H; CH-S), 4.54 (b, 1 H; CH=, cod), 3.71 (b, 1 H; CH=, cod), 3.22 (s, 3 H; CH_3-O), 3.07 (dd, ^2J(H,H) = 9.6 Hz, ^3J(H,H) = 5.2 Hz, 1 H; CH_2), 2.84 (m, 1 H; CH_2), 2.47 (b, 2 H; CH_2, cod), 1.98-2.24 (b, 4 H; CH_2, cod), 1.74-1.88 (b, 2 H; CH_2, cod), 1.69 (s, 9 H; CH_3, ^{t}Bu), 1.42 (s, 9 H; CH_3, ^{t}Bu), 1.38 (s, 9 H; CH_3, ^{t}Bu), 1.31 (s, 9 H; CH_3, ^{t}Bu), 1.28 ppm (s, 9 H; CH_3, ^{t}Bu). ^{13}C NMR (126 MHz, $CDCl_3$, 25°C, TMS): δ= 161.7 (q, ^1J(C,B) = 50.0 Hz; C-B, BArF), 117.6-149.4 (aromatic carbons), 103.3 (d, J(C,P) = 14.0 Hz; CH=, cod), 100.3 (d, J(C,P) = 16.4 Hz; CH=, cod), 79.3 (d, ^2J(C,P) = 2.3 Hz; CH-O), 72.9 (s; CH=, cod), 71.2 (d, ^3J(C,P) = 8.7 Hz; CH_2), 67.3 (s; CH=, cod), 59.2 (s; CH_3-O), 48.5 (s; CH-S), 36.2 (s; C, ^{t}Bu), 35.6 (s; C, ^{t}Bu), 35.0 (s; C, ^{t}Bu), 34.9 (s; C, ^{t}Bu), 34.8 (d, J(C,P) = 5.2 Hz; CH_2, cod), 32.6 (s; CH_3, ^{t}Bu), 31.6 (s; CH_3, ^{t}Bu), 31.5 (s; CH_3, ^{t}Bu), 31.4 (b; CH_2, cod), 31.1 (s; CH_3, ^{t}Bu), 30.1 (b; CH_2, cod), 27.5 ppm (b; CH_2, cod). MS HR-ESI [found 991.4589, $C_{50}H_{73}IrO_4PS$ $(M)^+$ requires 991.4561]. Suitable crystals for X-ray diffraction were achieved by slow diffusion of petrolium ether to an isopropanol solution

[Ir(cod)(L44b)]BAr$_F$. Yield: 129 mg (97%). ^{31}P NMR (162 MHz, $CDCl_3$, 25°C, H_3PO_4): δ= 90.9 ppm (s). ^{1}H NMR (400 MHz, $CDCl_3$, 25°C, TMS): δ= 7.10-7.93 (m, 19 H; CH= aromatic), 5.69 (b, 1 H; CH=, cod), 5.52 (m, 1 H; CH=, cod), 4.95 (s, 1 H; CH-S), 4.92 (m, 1 H; CH-O), 4.51 (m, 1 H; CH=, cod), 3.30 (b, 1 H; CH=, cod), 3.23 (s, 3 H; CH_3-O), 3.02 (dd, ^2J(H,H) = 8.4 Hz, ^3J(H,H) = 4.4 Hz, 1 H; CH_2), 2.76 (m, 1 H; CH_2), 2.45 (b, 2 H; CH_2, cod), 2.30 (s, 3 H; CH_3), 2.20 (s, 3 H; CH_3), 1.95-2.18 (b, 4 H; CH_2, cod), 1.81 (s, 3 H; CH_3), 1,73 (s, 3 H; CH_3), 1.70 (b, 2 H; CH_2, cod), 1.65 (s, 9 H; CH_3, ^{t}Bu), 1.39 (s, 9 H; CH_3, ^{t}Bu), 1.18 ppm (s, 9 H; CH_3, ^{t}Bu). ^{13}C NMR (126 MHz, $CDCl_3$, 25°C, TMS): δ= 161.7 (q, ^1J(C,B) = 49.9 Hz; C-B, BArF,), 117.4-143.2 (aromatic carbons), 102.4 (d, J(C,P) = 13.8 Hz; CH=, cod), 99.9 (d, J(C,P) = 16.9 Hz; CH=, cod), 78.5 (s; CH-O), 72.9 (s; CH=, cod), 70.8 (s; CH_2), 66.5 (s; CH=, cod), 60.7 (s; CH=, cod), 58.8 (s;

CH_3-O), 47.9 (s; CH-S), 35.3 (s; C, ^{t}Bu), 34.8 (s; CH_2, cod), 32.8 (s; CH_3, ^{t}Bu), 31.7 (s; CH_3, ^{t}Bu), 31.4 (b; CH_2, cod), 30.8 (s; CH_3, ^{t}Bu), 29.7 (b; CH_2, cod), 27.1 (b; CH_2, cod), 20.3 (s; CH_3), 20.2 (s; CH_3), 16.6 (s; CH_3), 16.3 ppm (s; CH_3). MS HR-ESI [found 935.3963, $C_{46}H_{65}IrO_4PS$ $(M)^+$ requires 935.3942].

[Ir(cod)(L44c)]BAr$_F$. Yield: 126 mg (96%). ^{31}P NMR (162 MHz, $CDCl_3$, 25°C, H_3PO_4): δ= 100.7 ppm (s). ^{1}H NMR (400 MHz, $CDCl_3$, 25°C, TMS): δ= 7.11-7.70 (m, 19 H; CH= aromatic), 6.04 (b, 1 H; CH=, cod), 5.91 (b, 1 H; CH=, cod), 5.26 (b, 1 H; CH-O), 4.67 (s, 1 H; CH-S), 4.38 (b, 1 H; CH=, cod), 3.43 (b, 1 H; CH=, cod), 3.37 (dd, ^2J(H,H) = 9.6 Hz, ^3J(H,H) = 4.0 Hz, 1 H; CH_2), 3.27 (s, 3 H; CH_3-O), 2.75 (m, 1 H; CH_2), 2.28 (s, 3 H; CH_3), 2.22 (s, 3 H; CH_3), 2.08-2.37 (b, 4 H; CH_2, cod), 1.65-1.97 (b, 4 H; CH_2, cod), 1.74 (s, 3 H; CH_3), 1.72 (s, 9 H; CH_3, ^{t}Bu), 1.70 (s, 6 H; CH_3), 1.37 ppm (s, 18 H; CH_3, ^{t}Bu). ^{13}C NMR (126 MHz, $CDCl_3$, 25°C, TMS): δ= 161.7 (q, ^1J(C,B) = 49.9 Hz; C-B, BArF), 117.4-144.6 (aromatic carbons), 100.7 (d, J(C,P) = 15.6 Hz; CH=, cod), 98.6 (d, J(C,P) = 14.1 Hz; CH=, cod), 80.9 (d, ^2J(C,P) = 10.2 Hz; CH-O), 73.0 (s; CH=, cod), 70.0 (d, ^3J(C,P) = 12.5 Hz; CH_2), 66.1 (s; CH=, cod), 61.9 (d, J(C,P) = 3.1 Hz; CH=, cod), 58.9 (s; CH_3-O), 54.1 (s; CH-S), 34.9 (s; C, ^{t}Bu), 33.9 (d, J(C,P) = 4.7 Hz; CH_2, cod), 31.4 (s; CH_3, ^{t}Bu), 31.2 (s; CH_3, ^{t}Bu), 31.1 (s; CH_3, ^{t}Bu), 30.8 (b; CH_2, cod), 30.0 (d, J(C,P) = 3.1 Hz; CH_2, cod), 27.9 (b; CH_2, cod), 20.3 (s; CH_3), 20.1 (s; CH_3), 16.3 ppm (s; CH_3). MS HR-ESI [found 935.3898, $C_{46}H_{65}IrO_4PS$ $(M)^+$ requires 935.3942].

[Ir(cod)(L44d)]BAr$_F$. Yield: 113 mg (96%). ^{31}P NMR (162 MHz, $CDCl_3$, 25°C, H_3PO_4): δ= 100.0 ppm (s). ^{1}H NMR (400 MHz, $CDCl_3$, 25°C, TMS): δ= 7.14-7.91 (m, 27 H; CH= aromatic), 5.51 (b, 1 H; CH=, cod), 5.40 (m, 1 H; CH=, cod), 4.78 (s, 1 H; CH-S), 4.55 (m, 1 H; CH-O), 3.60 (b, 1 H; CH=, cod), 3.28 (s, 3 H; CH_3-O), 3.23 (b, 1 H; CH_2), 3.17 (b, 1 H; CH=, cod), 3.06 (m, 1 H; CH=, cod), 2.39 (b, 2 H; CH_2, cod), 2.24 (b, 2 H; CH_2, cod), 2.06 (m, 2 H; CH_2, cod), 1.72 (m, 2 H; CH_2, cod), 1.39 ppm (s, 9 H; CH_3, ^{t}Bu). ^{13}C NMR (126 MHz, $CDCl_3$, 25°C, TMS): δ= 161.7 (q, ^1J(C,B) = 49.1 Hz; C-B, BArF), 117.5-134.8 (aromatic carbons), 101.9 (d, J(C,P) = 12.3 Hz; CH=, cod), 97.0 (d, J(C,P) = 11.6 Hz; CH=, cod), 78.1 (b; CH-O), 73.7 (s; CH=, cod), 72.1 (d, ^3J(C,P) = 9.2 Hz; CH_2), 68.0 (s; CH=, cod), 59.0 (s; CH_3-O), 46.1 (s; CH-S), 33.6 (s; C, ^{t}Bu), 33.5 (s; C, ^{t}Bu), 32.1 (s; CH_3, ^{t}Bu), 31.1 (s; CH_2, cod), 30.9 (d, J(C,P) = 2.3 Hz; CH_2, cod), 30.5 (d, J(C,P) = 3.9 Hz; CH_2, cod), 28.5 ppm (b; CH_2, cod). MS HR-ESI [found 737.2318, $C_{34}H_{43}IrO_2PS$ $(M)^+$ requires 737.2322].

[Ir(cod)(L44e)]BAr$_F$. Yield: 112 mg (93%). ^{31}P NMR (162 MHz, $CDCl_3$, 25°C, H_3PO_4): δ= 107.3 ppm (s). ^{1}H NMR (400 MHz, $CDCl_3$, 25°C, TMS): δ= 6.57-8.73 (m, 21 H; CH= aromatic), 5.67 (b, 1 H; CH=, cod), 5.24 (b, 1 H; CH=, cod), 4.79 (s, 1 H; CH-S), 4.77 (b, 1 H; CH-O), 3.75 (b, 1 H; CH=, cod), 3.38 (b, 1 H; CH=, cod), 3.24 (s, 3 H; CH_3-O), 3.21 (b, 1 H; CH_2), 2.98 (m, 1 H; CH_2), 2.62 (s, 3 H; CH_3), 2.21-2.46 (b, 4 H; CH_2, cod), 2.03 (s, 3 H; CH_3), 1.52-2.12 (b, 4 H; CH_2, cod), 1.33 ppm (s, 9 H; CH_3, ^{t}Bu). ^{13}C NMR (126 MHz, $CDCl_3$, 25°C, TMS): δ= 161.7 (q, ^1J(C,B) = 49.9 Hz; C-B, BArF), 117.4-142.7 (aromatic carbons), 101.1 (d, J(C,P) = 11.0 Hz; CH=, cod), 93.3 (d, J(C,P) = 13.3 Hz; CH=, cod), 78.6 (d, ^2J(C,P) = 5.8 Hz; CH-O,), 72.3 (d, ^3J(C,P) = 9.4 Hz; CH_2), 71.7 (s; CH=, cod), 70.3 (s; CH=, cod), 58.8 (s; CH_3-O), 48.5 (s; CH-S), 35.7 (s; CH_2 cod, C ^{t}Bu), 31.2 (s; CH_3, ^{t}Bu), 31.1 (s; CH_2, cod), 28.5 (s; CH_2, cod), 26.4 (s; CH_2, cod), 23.2 (s; CH_3), 20.9 ppm (s; CH_3). MS HR-ESI [found 765.2634, $C_{36}H_{47}IrO_2PS$ $(M)^+$ requires 765.2635].

[Ir(cod)(L45a)]BAr$_F$. Yield: 135 mg (94%). ^{31}P NMR (162 MHz, $CDCl_3$, 25°C, H_3PO_4): δ= 95.6 ppm (s). ^{1}H NMR (400 MHz, $CDCl_3$, 25°C, TMS): δ= 7.08-7.85 (m, 21 H; CH= aromatic), 5.80 (b, 1 H; CH=, cod), 5.55 (b, 1 H; CH=, cod), 4.99 (m, 1 H; CH-O), 4.90 (s, 1 H; CH-S), 4.56 (b, 1 H; CH=, cod), 3.70 (b, 1 H; CH=, cod), 3.21 (s, 3 H; CH_3-O), 3.05 (dd, ^2J(H,H) = 9.6 Hz, ^3J(H,H) = 5.6 Hz, 1 H; CH_2), 2.87 (m, 1 H; CH_2), 2.46 (b, 2 H; CH_2, cod), 2.21 (b, 6 H; CH_2 cod, CH Ad), 1.99-2.07 (b, 9 H; CH_2, cod, Ad), 1.69 (s, 9 H; CH_3, ^{t}Bu), 1.66-1.85 (b, 5 H; CH_2, cod, Ad), 1.37 (s, 9 H; CH_3, ^{t}Bu), 1.29 (s, 9 H; CH_3, ^{t}Bu), 1.25 ppm (s, 9 H; CH_3, ^{t}Bu). ^{13}C NMR (126 MHz, $CDCl_3$, 25°C, TMS): δ= 161.7 (q, ^1J(C,B) = 49.9 Hz; C-B, BArF), 117.4-149.1 (aromatic carbons), 105.7 (d, J(C,P) = 14.8 Hz; CH=, cod), 100.3 (d, J(C,P) = 17.2 Hz; CH=, cod), 79.8 (s; CH-O), 73.3 (b; CH=, cod), 71.2 (d, ^3J(C,P) = 7.8 Hz; CH_2), 67.0 (b; CH=, cod), 59.0 (s; CH_3-O), 43.7 (s; CH-S), 43.3 (s; CH_2, Ad), 36.0 (s; C, ^{t}Bu), 35.4 (s; C, ^{t}Bu), 35.3 (s; CH_2), 34.8 (s; C, ^{t}Bu), 34.9 (s; CH_2), 34.7 (s; C, ^{t}Bu), 32.3 (s; CH_2, CH_3 ^{t}Bu), 31.5 (s; CH_2, CH_3 ^{t}Bu), 31.3 (CH Ad, CH_2, CH_3 ^{t}Bu), 31.2 (CH Ad, CH_2, CH_3 ^{t}Bu), 30.7 (CH Ad, CH_2), 29.7 (s; CH, Ad), 27.0 ppm (b; CH_2). MS HR-ESI found 1069.5011, $C_{56}H_{79}IrO_4PS$ $(M)^+$ requires 1069.5037].

[Ir(cod)(L45e)]BAr$_F$. Yield: 144 mg (95%). ^{31}P NMR (162 MHz, $CDCl_3$, 25°C, H_3PO_4): δ= 109.2 ppm (s). ^{1}H NMR (400 MHz, $CDCl_3$, 25°C, TMS): δ= 6.44-8.71 (m, 25 H; CH= aromatic), 5.47 (b, 1 H; CH=, cod), 4.99 (m, 1 H; CH=, cod), 4.57 (d, ^3J(H,H) = 2.0 Hz, 1 H; CH-S), 4.44 (b, 1 H; CH-O), 3.68 (b, 1 H; CH=, cod), 3.21 (m, 1 H; CH_2), 3.16 (s, 3 H; CH_3-O), 2.90 (m, 1 H; CH_2), 2.74 (b, 1 H; CH=, cod), 2.54 (s, 3 H; CH_3), 2.11-2.51 (b, 6 H; CH_2, cod, Ad), 2.02 (b, 2 H; CH_2 cod, CH Ad), 1.91 (s, 3 H; CH_3), 1.74-1.88 (m, 6 H; CH_2, cod, Ad), 1.45-1.60 ppm (m, 9 H; CH_2, cod, Ad). ^{13}C NMR (126 MHz, $CDCl_3$, 25°C, TMS): δ= 161.8 (q, ^1J(C,B) = 49.9 Hz; C-B, BArF), 117.6-143.0 (aromatic carbons), 104.7 (d, J(C,P) = 11.8 Hz; CH=, cod), 94.7 (d, J(C,P) = 12.5 Hz; CH=, cod), 79.5 (d, ^2J(C,P) = 4.6 Hz; CH-O), 73.3 (s; CH=, cod), 72.8 (d, ^3J(C,P) = 8.7 Hz; CH_2), 71.5 (s; CH=, cod), 64.8 (s; CH=, cod), 59.1 (s; CH_3-O), 43.2 (s; CH-S), 44.1 (s; CH_2, Ad), 35.8 (d, J(C,P) = 4.5 Hz; CH_2, cod), 35.5 (s; CH_2, cod, Ad), 35.4 (CH_2, cod, Ad), 30.5-33.3 (CH_2 cod Ad, CH Ad), 26.7-29.9 (CH_2, cod, Ad), 23.5 (d, ^3J(C,P) = 5.8 Hz; CH_3), 21.1 ppm (d, ^3J(C,P) = 5.1 Hz; CH_3). MS HR-ESI [found 843.3067, $C_{42}H_{53}IrO_2PS$ $(M)^+$ requires 843.3104].

[Ir(cod)(L46a)]BAr$_F$. Yield: 130 mg (92%). ^{31}P NMR (162 MHz, $CDCl_3$, 25°C, H_3PO_4): δ= 97.3 ppm (s). ^{1}H NMR (400 MHz, $CDCl_3$, 25°C, TMS): δ= 7.05-7.70 (m, 24 H; CH= aromatic), 5.45 (b, 1 H; CH-O), 4.84 (b, 1 H; CH=, cod), 4.40 (b, 1 H; CH=, cod), 4.33 (s, 1 H; CH-S), 4.15 (b, 1 H; CH=, cod), 3.50 (m, 2 H; CH_2, CH_2 cod), 3.11 (s, 3 H; CH_3-O), 3.02 (m, 1 H; CH_2), 2.86 (s, 3 H; CH_3), 2.08-2.31 (b, 4 H; CH_2, cod), 2.04 (s, 3 H; CH_3), 1.85-1.94 (b, 4 H; CH_2, cod), 1.69 (s, 9 H; CH_3, ^{t}Bu), 1.54 (s, 9 H; CH_3, ^{t}Bu), 1.36 (s, 9 H; CH_3, ^{t}Bu), 1.34 ppm (s, 9 H; CH_3, ^{t}Bu). ^{13}C NMR (126 MHz, $CDCl_3$, 25°C, TMS): δ= 161.8 (q, ^1J(C,B) = 49.9 Hz; C-B, BArF), 117.6-149.4 (aromatic carbons), 106.0 (d, J(C,P) = 16.3 Hz; CH=, cod), 104.9 (d, J(C,P) = 13,3 Hz; CH=, cod), 80.2 (d, ^2J(C,P) = 6.2 Hz; CH-O), 75.4 (s; CH=, cod), 70.8 (d, ^3J(C,P) = 10.9 Hz; CH_2), 69.3 (s; CH=, cod), 59.4 (s; CH_3-O), 58.0 (s; CH-S), 36.0 (s; C, ^{t}Bu), 35.8 (s; C, ^{t}Bu), 35.0 (s; C, ^{t}Bu), 33.7 (d, J(C,P) = 3.1 Hz; CH_2, cod), 32.3 (s; CH_3, ^{t}Bu), 32.1 (d, J(C,P) = 3.9 Hz; CH_2, cod), 31.7 (s; CH_3, ^{t}Bu), 31.5 (s; CH_3, ^{t}Bu), 29.8 (d, J(C,P) = 14.0 Hz; CH_2, cod), 27.7 (s; CH_2, cod), 22.9 (s; CH_3), 22.4 ppm (s; CH_3). MS HR-ESI [found 1039.4564, $C_{54}H_{73}IrO_4PS$ $(M)^+$ requires 1039.4568]. Suitable crystals for X-ray diffraction were achieved by slow diffusion of petrolium ether to an isopropanol solution

[Ir(cod)(L46b)]BAr$_F$. Yield: 126 mg (93%). ^{31}P NMR (162 MHz, $CDCl_3$, 25°C, H_3PO_4): δ= 91.6 ppm (s). ^{1}H NMR (400 MHz, $CDCl_3$, 25°C, TMS): δ= 6.92-7.73 (m, 22 H; CH= aromatic), 5.34 (m, 1 H; CH-O), 4.60 (b, 1 H; CH=, cod), 4.46 (b, 2 H; CH=, cod), 4.10 (d, ^3J(H,H) = 4.0 Hz, 1 H; CH-S), 3.26 (dd, ^2J(H,H) = 10.0 Hz, ^3J(H,H) = 6.6 Hz, 1 H; CH_2), 3.01 (s, 3 H; CH_3-O), 2.88 (dd, ^2J(H,H) =16.0 Hz, ^3J(H,H) = 6.4 Hz, 1 H; CH_2), 2.83 (b, 1 H; CH=, cod), 2.77 (s, 3 H; CH_3), 2.30 (s, 3 H; CH_3), 2.24 (s, 3 H; CH_3), 1.98-2.34 (b, 4 H; CH_2, cod), 1.85 (s, 3 H; CH_3), 1.96 (s, 3 H; CH_3), 1.72-1.89 (b, 4 H; CH_2, cod), 1.69 (s, 3 H; CH_3), 1.68 (s, 9 H; CH_3, ^{t}Bu), 1.56 ppm (s, 9 H; CH_3, ^{t}Bu). ^{13}C NMR (126 MHz, $CDCl_3$, 25°C, TMS): δ= 161.7 (q, ^1J(C,B) = 49.9 Hz; C-B, BArF,), 117.4-143.9 (aromatic carbons), 105.5 (d, J(C,P) = 14.6 Hz; CH=, cod), 102.8 (d, J(C,P) = 15,3 Hz; CH=, cod), 77.7 (s; CH-O), 75.9 (s; CH=, cod), 71.0 (d, ^3J(C,P) = 7.3 Hz; CH_2), 65.1 (b; CH=, cod), 58.9 (s; CH_3-O), 55.4 (s; CH-S), 35.1 (s; C, ^{t}Bu), 35.0 (s; C, ^{t}Bu), 34.3 (b; CH_2, cod), 32.3 (s; CH_3, ^{t}Bu), 31.9 (b; CH_2, cod), 31.6 (s; CH_3, ^{t}Bu), 29.2 (b; CH_2, cod), 27.2 (b; CH_2, cod), 22.8 (s; CH_3), 22.0 (s; CH_3), 20.3 (s; CH_3), 20.2 (s; CH_3), 16.5 (s; CH_3), 16.3 ppm (s; CH_3). MS HR-ESI [found 983.3946, $C_{50}H_{65}IrO_4PS$ $(M)^+$ requires 983.3942].

[Ir(cod)(L46c)]BAr$_F$. Yield: 128 mg (94%). ^{31}P NMR (162 MHz, $CDCl_3$, 25°C, H_3PO_4): δ= 97.1 ppm (s). ^{1}H NMR (400 MHz, $CDCl_3$, 25°C, TMS): δ= 7.01-7.63 (m, 22H; CH= aromatic), 5.37 (m, 1H; CH-O), 4.76 (b, 1H; CH=, cod), 4.50 (m, 1H; CH=, cod), 4.26 (d, ^3J(H,H) = 2.4 Hz; 1H, CH-S), 4.02 (m, 1H; CH=, cod), 3.45 (dd, ^2J(H,H) = 9.2 Hz, ^3J(H,H) = 4.4 Hz, 1H; CH_2), 3.07 (s, 3H; CH_3-O), 2.92 (m, 1H; CH_2), 2.96 (b, 1H; CH=, cod), 2.78 (s, 3H; CH_3), 2.22 (m, 1H; CH_2), 2.19 (s, 3H; CH_3), 2.04-2.23 (b, 4H; CH_2, cod), 1.97 (s, 3H; CH_3), 1.81-1.92 (b, 4H; CH_2, cod), 1.70 (s, 6H; CH_3), 1.60 (s, 9H; CH_3, ^{t}Bu), 1.40 ppm (s, 9H; CH_3, ^{t}Bu). ^{13}C NMR (126 MHz, $CDCl_3$, 25°C, TMS): δ= 161.7 (q, ^1J(C,B) = 49.9 Hz; C-B, BArF), 117.4-144.4 (aromatic carbons), 105.6 (d, J(C,P) = 15.6 Hz; CH=, cod), 104.3 (d, J(C,P) = 13.3 Hz; CH=, cod), 80.3 (s; CH-O), 77.2 (s; CH=, cod), 70.7 (d, ^3J(C,P) = 7.6 Hz; CH_2), 67.9 (s; CH=, cod), 59.2 (s; CH_3-O), 58.3 (s; CH-S), 35.0 (s; C, ^{t}Bu), 34.9 (s; C, ^{t}Bu), 33.5 (b; CH_2, cod), 32.4 (s; CH_3, ^{t}Bu), 32.0 (b; CH_2, cod), 31.5 (s; CH_3, ^{t}Bu), 30.8 (d, J(C,P) = 9.4 Hz; CH_2, cod), 29.6 (d, J(C,P) = 7.0 Hz; CH_2, cod), 27.5 (b; CH_2, cod), 22.5 (s; CH_3), 22.2 (s; CH_3), 20.3 (s; CH_3), 20.2 (s; CH_3), 16.3 ppm (s; CH_3). MS HR-ESI [found 983.3938, $C_{50}H_{65}IrO_4PS$ $(M)^+$ requires 983.3942].

[Ir(cod)(L46d)]BAr$_F$. Yield: 113 mg (93%). ^{31}P NMR (162 MHz, $CDCl_3$, 25°C, H_3PO_4): δ= 106.3 ppm (s). ^{1}H NMR (400 MHz, $CDCl_3$, 25°C, TMS): δ= 6.94-7.89 (m, 30 H; CH= aromatic), 5.17 (b, 1 H; CH-O), 4.65 (b, 1 H; CH=, cod), 4.16 (d, ^3J(H,H) = 2.4 Hz; 1 H; CH-S), 4.09 (b, 1 H; CH=, cod), 3.43 (b, 2 H; CH=, cod), 3.32 (dd, ^2J(H,H) = 9.6 Hz, ^3J(H,H) = 5.6 Hz, 1 H; CH_2), 3.13 (s, 3 H; CH_3-O), 2.99 (m, 1 H; CH_2), 2.87 (s, 3 H; CH_3), 2.13-2.39 (b, 6 H; CH_2, cod), 2.07 (s, 3 H; CH_3), 1.94 (b, 1 H; CH_2, cod), 1.86 ppm (b, 1 H; CH_2, cod). ^{13}C NMR (126 MHz, $CDCl_3$, 25°C, TMS): δ= 161.7 (q, ^1J(C,B) = 49.9 Hz; C-B, BArF), 117.5-142.6 (aromatic carbons), 99.9 (d, J(C,P) = 12.3 Hz; CH=, cod), 98.5 (d, J(C,P) = 9.9 Hz; CH=, cod), 82.7 (s; CH-O), 72.7 (s; CH=, cod), 71.7 (d, ^3J(C,P) = 8,5 Hz; CH_2), 70.3 (s; CH=, cod), 59.0 (s; CH_3-O), 58.0 (s; CH-S), 33.5 (d, J(C,P) = 3.8 Hz; CH_2, cod), 31.0 (d, J(C,P) = 2.1 Hz; CH_2, cod), 30.3 (s; CH_2, cod), 27.9 (b; CH_2, cod), 23.0 (s; CH_3), 22.2 ppm (s; CH_3). MS HR-ESI [found 785.2311, $C_{38}H_{43}IrO_2PS$ $(M)^+$ requires 785.2322].

[Ir(cod)(L46e)]BAr$_F$. Yield: 116 mg (94%). ^{31}P NMR (162 MHz, $CDCl_3$, 25°C, H_3PO_4): δ= 108.6 ppm (s). ^{1}H NMR (400 MHz, $CDCl_3$, 25°C, TMS): δ= 6.44-8.91 (m, 28 H; CH= aromatic), 5.31 (b, 1 H; CH-O), 4.59 (b, 1 H; CH=, cod), 4.38 (s, 1 H; CH-S), 3.98 (b, 1 H; CH=, cod), 3.40

(dd, ^2J(H,H) = 9.2 Hz, ^3J(H,H) = 4.8Hz 1 H; CH_2), 3.16 (s, 4 H; CH_3-O, CH= cod), 2.89 (m, 2 H; CH_2, CH= cod), 2.81 (s; 3 H, CH_3), 2.75 (s, 3 H; CH_3), 2.07-2.24 (b, 6 H; CH_2, cod), 2.07 (s, 3 H; CH_3), 1.94 (s, 3 H; CH_3), 1.81 ppm (b, 2 H; CH_2, cod). ^{13}C NMR (126 MHz, $CDCl_3$, 25°C, TMS): δ= 161.7 (q, ^1J(C,B) = 49.9 Hz; C-B, BArF), 117.4-143.9 (aromatic carbons), 98.6 (d, J(C,P) = 13.3 Hz; CH=, cod), 98.0 (d, J(C,P) = 9.4 Hz; CH=, cod), 84.0 (s; CH-O), 75.3 (s; CH=, cod), 71.2 (d, ^3J(C,P) = 11.0 Hz; CH_2), 69.5 (s; CH=, cod), 60.2 (s; CH-S), 59.1 (s; CH_3-O), 33.2 (d, J(C,P) = 3.1 Hz; CH_2, cod), 31.1 (d, J(C,P) = 3.1 Hz; CH_2, cod), 30.4 (s; CH_2, cod), 28.2 (s; CH_2, cod), 22.7 (s; CH_3), 22.4 (d, ^3J(C,P) = 2.3 Hz; CH_3), 22.3 (d, ^3J(C,P) = 7.0 Hz; CH_3), 22.2 ppm (s; CH_3). MS HR-ESI [found 813.2634, $C_{40}H_{47}IrO_2PS$ $(M)^+$ requires 813.2635].

[Ir(cod)(L47a)]BAr$_F$. Yield: 142 mg (92%). ^{31}P NMR (162 MHz, $CDCl_3$, 25°C, H_3PO_4): δ= 93.8 ppm (s). ^{1}H NMR (400 MHz, $CDCl_3$, 25°C, TMS): δ= 7.06-7.70 (m, 39 H; CH= aromatic), 5.22 (b, 1 H; CH-O), 5.04 (b, 1 H; CH-S), 4.79 (b, 1 H; CH=, cod), 4.54 (m, 1 H; CH=, cod), 4.32 (m, 1 H; CH=, cod), 3.61 (b, 1 H; CH=, cod), 3.19 (b, 1 H; CH_2), 2.66 (m, 1 H; CH_2), 2.00-2.20 (b, 4 H; CH_2, cod), 1.71-1.95 (b, 4 H; CH_2, cod), 1.66 (s, 9 H; CH_3, ^{t}Bu), 1.36 (s, 9 H; CH_3, ^{t}Bu), 1.34 (s, 9 H; CH_3, ^{t}Bu), 1.22 ppm (s, 9 H; CH_3, ^{t}Bu). ^{13}C NMR (126 MHz, $CDCl_3$, 25°C, TMS): δ= 161.8 (q, ^1J(C,B) = 49.9 Hz; C-B, BArF), 117.7-149.5 (aromatic carbons), 104.3 (d, J(C,P) = 14.9 Hz; CH=, cod), 102.4 (b; CH=, cod), 87.7 (s; C-O), 79.9 (s; CH-O), 75.4 (b; CH=, cod), 71.2 (b; CH=, cod), 63.6 (s; CH_2), 57.6 (b; CH-S), 36.1 (s; C, ^{t}Bu), 35.7 (s; C, ^{t}Bu), 35.1 (s; C, ^{t}Bu), 34.9 (s; C, ^{t}Bu), 33.6 (b; CH_2, cod), 32.5 (s; CH_3, ^{t}Bu), 31.6 (s; CH_3, ^{t}Bu), 31.4 (s; CH_3, ^{t}Bu), 31.2 (s; CH_2, cod), 29.3 (b; CH_2, cod),28.1 ppm (b; CH_2, cod). MS HR-ESI [found 1239.5180, $C_{70}H_{81}IrO_4PS$ $(M)^+$ requires 1239.5194].

[Ir(cod)(L47b)]BAr$_F$. Yield: 141 mg (93%). ^{31}P NMR (162 MHz, $CDCl_3$, 25°C, H_3PO_4): δ= 90.2 ppm (s). ^{1}H NMR (400 MHz, $CDCl_3$, 25°C, TMS): δ= 6.92-7.83 (m, 39 H; CH= aromatic), 5.11 (s, 1 H; CH-S), 5.04 (m, 1 H; CH-O), 4.65 (b, 1 H; CH=, cod), 4.54 (b, 1 H; CH=, cod), 4.47 (b, 1 H; CH=, cod), 3.08 (dd, ^2J(H,H) = 10.0 Hz, ^3J(H,H) = 6.0 Hz, 1 H; CH_2,), 2.98 (m, 1 H; CH=, cod), 2.49 (m, 1 H; CH_2), 2.31 (s, 3 H; CH_3), 2.16 (s, 3 H; CH_3), 2.07-2.29 (b, 4 H; CH_2, cod), 1.82 (s, 3 H; CH_3), 1.74 (s, 9 H; CH_3, ^{t}Bu), 1.75-2.04 (b, 4 H; CH_2, cod), 1.70 (s, 3 H; CH_3), 1.17 ppm (s, 9 H; CH_3, ^{t}Bu). ^{13}C NMR (126 MHz, $CDCl_3$, 25°C, TMS): δ= 161.8 (q, ^1J(C,B) = 49.9 Hz; C-B, BArF), 117.4-144.3 (aromatic carbons), 103.3 (d, J(C,P) = 18.6 Hz; CH=, cod), 109.1 (d, J(C,P) = 13.9 Hz; CH=, cod), 87.7 (s; C-O), 78.5 (s; CH-O), 76.4 (s; CH=, cod), 69.5 (s; CH=, cod), 63.7 (d, ^3J(C,P) = 3.1 Hz; CH_2), 56.2 (s; CH-S), 35.4 (s; C, ^{t}Bu), 34.7 (s; C, ^{t}Bu), 33.7 (b; CH_2, cod), 33.0 (s; CH_3, ^{t}Bu), 31.9 (b; CH_2, cod), 31.4 (s; CH_3, ^{t}Bu), 29.4 (b; CH_2, cod), 27.6 (b; CH_2, cod), 20.4 (s; CH_3), 20.2 (s; CH_3), 16.6 (s; CH_3), 16.4 ppm (s; CH_3). MS HR-ESI [found 1183.4573, $C_{66}H_{73}IrO_4PS$ $(M)^+$ requires 1183.4568].

[Ir(cod)(L47c)]BAr$_F$. Yield: 145 mg (95%). ^{31}P NMR (162 MHz, $CDCl_3$, 25°C, H_3PO_4): δ= 96.8 ppm (s). ^{1}H NMR (400 MHz, $CDCl_3$, 25°C, TMS): δ= 7.06-7.70 (m, 39 H; CH= aromatic), 5.61 (b, 1 H; CH-O), 5.14 (b, 1 H; CH-S), 4.89 (b, 1 H; CH=, cod), 4.59 (b, 2 H; CH=, cod), 3.49 (dd, ^2J(H,H) = 8.8 Hz, ^3J(H,H) = 4.4 Hz, 1 H; CH_2), 3.12 (m, 1 H; CH=, cod), 3.01 (m, 1 H; CH_2), 2.26 (s, 3 H; CH_3), 2.22 (s, 3 H; CH_3), 2.09-2.30 (b, 4 H; CH_2, cod), 1.84-2.01 (b, 4 H; CH_2, cod), 1.74 (s, 3 H; CH_3), 1.73 (s, 3 H; CH_3), 1.51 (s, 9 H; CH_3, ^{t}Bu),1.25 ppm (s, 9 H; CH_3, ^{t}Bu). ^{13}C NMR (126 MHz, $CDCl_3$, 25°C, TMS): δ= 161.8 (q, ^1J(C,B) = 49.9 Hz, C-B; BArF), 117.7-144.3 (aromatic carbons), 106.5 (d, J(C,P) = 14.8 Hz; CH=, cod), 103.5 (d, J(C,P) = 14.8 Hz; CH=, cod), 87.7 (s; C-O), 82.8 (d, ^2J(H,H) = 6.2 Hz; CH-O), 78.1 (s; CH=, cod), 70.5 (s; CH=, cod),

62.1 (d, ^{3}J(C,P) = 11.7 Hz; CH_2), 61.5 (s; CH-S), 35.3 (s; C, ^{t}Bu), 35.0 (s; C, ^{t}Bu), 33.2 (b; CH_2, cod), 32.8 (s; CH_3, ^{t}Bu), 32.5 (b; CH_2, cod), 31.5 (s; CH_3, ^{t}Bu), 28.9 (b; CH_2, cod), 28.3 (b; CH_2, cod), 20.5 (s; CH_3), 20.4 (s; CH_3), 16.6 ppm (s; CH_3). MS HR-ESI [found 1183.4554, $C_{66}H_{73}IrO_4PS$ $(M)^+$ requires 1183.4568].

[Ir(cod)(L47d)]BAr$_F$. Yield: 128 mg (94%). ^{31}P NMR (162 MHz, $CDCl_3$, 25°C, H_3PO_4): δ= 100.0 ppm (s). ^{1}H NMR (400 MHz, $CDCl_3$, 25°C, TMS): δ= 7.01-7.88 (m, 35 H; CH= aromatic), 4.69 (s, 1 H; CH-S), 4.53 (b, 2 H; CH=, cod), 4.19 (m, 1 H; CH-O), 3.63 (m, 1 H; CH=, cod), 3.11 (b, 1 H; CH=, cod), 3.07 (m, 1 H; CH_2), 2.72 (dd, ^{2}J(H,H) = 10.4 Hz, ^{3}J(H,H) = 7.6 Hz, 1 H; CH_2), 2.24 (m, 2 H; CH_2, cod), 2.08 (m, 4 H; CH_2, cod), 1.86 ppm (m, 2 H; CH_2, cod). ^{13}C NMR (126 MHz, $CDCl_3$, 25°C, TMS): δ= 161.8 (q, ^{1}J(C,B) = 49.9 Hz; C-B, BArF), 117.6-143.0 (aromatic carbons), 99.3 (d, J(C,P) = 12.6 Hz; CH=, cod), 97.7 (d, J(C,P) = 10.9 Hz; CH=, cod), 88.0 (s; C-O), 78.6 (d, ^{2}J(C,P) = 3.1 Hz; CH-O), 75.9 (s; CH=, cod), 70.2 (s; CH=, cod), 64.9 (d, ^{3}J(C,P) = 8.6 Hz; CH_2), 56.9 (s; CH-S), 33.1 (s; CH_2, cod), 32.1 (s; CH_2, cod), 29.8 (s; CH_2, cod), 29.0 ppm (b; CH_2, cod). MS HR-ESI [found 985.2934, $C_{54}H_{51}IrO_2PS$ $(M)^+$ requires 985.2948].

[Ir(cod)(L47e)]BAr$_F$. Yield: 129 mg (93%).^{31}P NMR (162 MHz, $CDCl_3$, 25°C, H_3PO_4): δ= 108.5 ppm (s). ^{1}H NMR (400 MHz, $CDCl_3$, 25°C, TMS): δ= 7.0-8.0 (m, 33 H; CH= aromatic), 4.73 (s, 1 H; CH-S), 4.56 (b, 1 H; CH=, cod), 4.37 (b, 1 H; CH=, cod),4.49 (m, 1 H; CH-O), 3.76 (m, 1 H; CH=, cod),3.15 (b, 1 H; CH=, cod), 3.07 (m, 1 H; CH_2), 2.87 (m, 1 H; CH_2), 2.1-2.4 (m, 9 H; CH_2 cod, CH_3), 1.91 (s, 3 H; CH_3), 1.86 ppm (m, 2 H; CH_2, cod). ^{13}C NMR (126 MHz, $CDCl_3$, 25°C, TMS): δ= 161.9 (q, ^{1}J(C,B) = 49.9 Hz; C-B, BArF), 117.6-143.0 (aromatic carbons), 101.4 (d, J(C,P) = 13.2 Hz; CH=, cod), 98.6 (d, J(C,P) = 11.2 Hz; CH=, cod), 80.1 (d, ^{2}J(C,P) = 3.6 Hz; CH-O), 89.1 (s; C-O), 76.3 (s; CH=, cod), 70.7 (s; CH=, cod), 65.3 (d, ^{3}J(C,P) = 6.0 Hz; CH_2), 58.4 (s; CH-S), 33.1 (s; CH_2, cod), 32.2 (s; CH_2, cod), 29.1 (b; CH_2, cod), 30.1 (s; CH_2, cod), 22.5 (s; CH_3), 21.9 ppm (s; CH_3). MS HR-ESI [found 1013.3261, $C_{56}H_{55}IrO_2PS$ $(M)^+$ requires 1013.3265].

[Ir(cod)(L47g)]BAr$_F$. Yield: 125 mg (91%). ^{31}P NMR (162 MHz, $CDCl_3$, 25°C, H_3PO_4): δ= 92.3 ppm (s). ^{1}H NMR (400 MHz, $CDCl_3$, 25°C, TMS): δ= 7.2-7.8 (m, 18 H; CH= aromatic), 4.82 (b, 1 H; CH=, cod), 4.78 (s, 1 H; CH-S), 4.62 (b, 1 H; CH=, cod), 4.40 (m, 1 H; CH-O), 3.64 (m, 1 H; CH=, cod), 3.37 (m, 1 H; CH_2), 3.16 (m, 1 H; CH_2), 2.94 (b, 1 H; CH=, cod), 2.41 (m, 2 H; CH_2 cod), 1.6-2.2 (m, 15 H; CH and CH_2), 1.42 (m, 2 H; CH), 1.0-1.4 ppm (m, 11 H; CH and CH_2). ^{13}C NMR (126 MHz, $CDCl_3$, 25°C, TMS): δ= 161.8 (q, ^{1}J(C,B) = 49.9 Hz; C-B, BArF), 117.8-132.0 (aromatic carbons), 100.1 (d, J(C,P) = 12.5 Hz; CH=, cod), 97.9 (d, J(C,P) = 10.6 Hz; CH=, cod), 88.6 (s; C-O), 79.4 (d, ^{2}J(C,P) = 3.8 Hz; CH-O), 78.1 (s; CH=, cod), 69.7 (s; CH=, cod), 64.7 (d, ^{3}J(C,P) = 4.2 Hz; CH_2), 57.1 (s; CH-S), 35.2 (d, J(C,P) = 20.8 Hz; CH_2), 32.2-33.9 (s; CH_2), 30.1 (b; CH_2), 29.0 (b; CH_2), 28.8 (b; CH_2), 28.5 (b; CH_2), 26.1 (s; CH_2), 25.9 ppm (s; CH_2). MS HR-ESI [found 997.3860, $C_{54}H_{63}IrO_2PS$ $(M)^+$ requires 997.3887].

[Ir(cod)(L48a)]BAr$_F$. Yield: 147 mg (93%). ^{31}P NMR (162 MHz, $CDCl_3$, 25°C, H_3PO_4): δ= 97.5 ppm (s). ^{1}H NMR (400 MHz, $CDCl_3$, 25°C, TMS): δ= 6.96-7.63 (m, 39 H; CH= aromatic), 5.61 (m, 1 H; CH-O), 4.71 (b, 1 H; CH=, cod), 4.48 (s, 1 H; CH-S), 4.25 (b, 1H; CH=, cod), 4.19 (b, 1 H; CH=, cod), 3.56 (b, 1 H; CH=, cod), 3.34 (dd, ^{2}J(H,H) = 8.4 Hz, ^{3}J(H,H) = 4.8 Hz, 1 H; CH_2), 2.97 (s, 3 H; CH_3), 2.89 (m, 1 H; CH_2), 2.10-2.30 (b, 4 H; CH_2, cod), 1.95 (s, 3 H; CH_3), 1.60-1.82 (b, 4 H; CH_2, cod), 1.54 (s, 9 H; CH_3, ^{t}Bu), 1.30 (s, 9 H; CH_3, ^{t}Bu), 1.26 (s, 9 H; CH_3, ^{t}Bu), 1.20 ppm (s, 9 H; CH_3, ^{t}Bu). ^{13}C NMR (126 MHz, $CDCl_3$, 25°C, TMS): δ= 161.9 (q, ^{1}J(C,B)

= 49.9 Hz; C-B, BArF), 117.7-149.4 (aromatic carbons), 106.3 (d, *J*(C,P) = 15.6 Hz; CH=, cod), 104.8 (d, *J*(C,P) = 13.2 Hz; CH=, cod), 87.7 (s; C-O), 81.4 (s; CH-O), 74.6 (b; CH=, cod), 70.5 (b; CH=, cod), 62.5 (d, ^{3}J(C,P) = 10.2 Hz; CH_2), 58.4 (s; CH-S), 36.1 (s; C, ^{t}Bu), 35.8 (s; C, ^{t}Bu), 35.1 (s; C, ^{t}Bu), 32.8 (b; CH_2, cod), 32.5 (s; CH_3, ^{t}Bu), 31.7 (s; CH_3, ^{t}Bu), 31.6 (s; CH_3, ^{t}Bu), 31.5 (s; CH_3, ^{t}Bu), 29.3 (b; CH_2, cod), 28.3 (b; CH_2, cod), 27.2 (b; CH_2, cod), 23.0 (s; CH_3), 22.5 ppm (s; CH_3). MS HR-ESI [found 1267.5498, $C_{72}H_{85}IrO_4PS$ $(M)^+$ requires 1267.5507].

[Ir(cod)(L48e)]BAr$_F$. Yield: 135 mg (96%). ^{31}P NMR (162 MHz, $CDCl_3$, 25°C, H_3PO_4): δ= 108.6 ppm (s). ^{1}H NMR (400 MHz, $CDCl_3$, 25°C, TMS): δ= 6.42-8.97 (m, 35 H; CH= aromatic), 5.50 (b, 1 H; CH-O), 4.70 (b, 1 H; CH=, cod), 4.68 (s, 1 H; CH-S), 4.1 (b, 1 H; CH=, cod), 3.48 (dd, ^{2}J(H,H) = 8.8 Hz, ^{3}J(H,H) = 4.4 Hz 1 H; CH_2), 3.24 (b, 1 H; CH=, cod), 3.07 (s, 3 H; CH_3), 2.95 (b, 1 H; CH=, cod), 2.80 (m, 1 H; CH_2), 2.18 (s, 3 H; CH_3), 1.99-2.40 (b, 6 H; CH_2, cod), 1.88 (s, 3 H; CH_3), 1.64-1.87 (b, 2 H; CH_2, cod), 1.55 ppm (s, 3 H; CH_3). ^{13}C NMR (126 MHz, $CDCl_3$, 25°C, TMS): δ= 161.9 (q, ^{1}J(C,B) = 49.9 Hz; C-B, BArF), 117.6-146.5 (aromatic carbons), 98.7 (d, *J*(C,P) = 13.3 Hz; CH=, cod), 98.5 (d, *J*(C,P) = 8.0 Hz; CH=, cod), 88.2 (s; C-O), 85.3 (s; CH-O), 75.7 (s; CH=, cod), 70.0 (s; CH=, cod), 62.6 (d, ^{3}J(C,P) = 11.7 Hz; CH_2), 61.2 (s; CH-S), 33.5 (b; CH_2, cod), 31.3 (b; CH_2, cod), 30.6 (b; CH_2, cod), 28.4 (s; CH_2, cod), 23.0 (s; CH_3), 22.9 (s; CH_3), 22.8 (s; CH_3), 22.4 ppm (s; CH_3). MS HR-ESI [found 1031.3571, $C_{58}H_{59}IrO_2PS$ $(M)^+$ requires 1041.3579].

[Ir(cod)(L49a)]BAr$_F$. Yield: 133 mg (93%). ^{31}P NMR (162 MHz, $CDCl_3$, 25°C, H_3PO_4): δ= 93.9 ppm (s). ^{1}H NMR (400 MHz, $CDCl_3$, 25°C, TMS): δ= 6.98-7.81 (m, 31 H; CH= aromatic), 5.22 (b, 1 H; CH-O), 5.13 (b, 1 H; CH-S), 4.78 (b, 1 H; CH=, cod), 4.52 (b, 1 H; CH=, cod), 4.40 (b, 1 H; CH=, cod), 4.29 (b, 2 H; CH_2-O), 3.63 (b, 1 H; CH=, cod), 3.33 (m, 1 H; CH_2), 2.95 (m, 1 H; CH_2), 2.06-2.30 (b, 4 H; CH_2, cod), 1.82-1.99 (b, 4 H; CH_2, cod), 1.70 (s, 9 H; CH_3, ^{t}Bu), 1.42 (s, 9 H; CH_3, ^{t}Bu), 1.36 (s, 9 H; CH_3, ^{t}Bu), 1.31 ppm (s, 9 H; CH_3, ^{t}Bu). ^{13}C NMR (126 MHz, $CDCl_3$, 25°C, TMS): δ= 161.8 (q, ^{1}J(C,B) = 49.9 Hz; C-B, BArF), 117.6-149.6 (aromatic carbons), 101.7 (d, *J*(C,P) = 5.5 Hz; CH=, cod), 103.9 (d, *J*(C,P) = 14.8 Hz; CH=, cod), 78.5 (s; CH-O), 75.3 (b; CH=, cod), 74.0 (s; CH_2-O), 71.3 (b; CH=, cod), 69.0 (d, ^{3}J(C,P) = 9.4 Hz; CH_2), 57.1 (s; CH-S), 36.2 (s; C, ^{t}Bu), 35.7 (s; C, ^{t}Bu), 35.1 (s; C, ^{t}Bu), 35.0 (s; C, ^{t}Bu), 33.7 (d, *J*(C,P) = 4.7 Hz; CH_2, cod), 32.7 (s; CH_3, ^{t}Bu), 32.1 (d, *J*(C,P) = 3.2 Hz; CH_2, cod), 31.6 (s; CH_3, ^{t}Bu), 31.5 (s; CH_3, ^{t}Bu), 31.4 (s; CH_3, ^{t}Bu), 29.6 (b; CH_2, cod), 27.9 ppm (b; CH_2, cod). MS HR-ESI [found 1087.4559, $C_{58}H_{73}IrO_4PS$ $(M)^+$ requires 1087.4568]. Suitable crystals for X-ray diffraction were achieved by slow diffusion of petrolium ether to an isopropanol solution.

[Ir(cod)(L49b)]BAr$_F$. Yield: 130 mg (95%). ^{31}P NMR (162 MHz, $CDCl_3$, 25°C, H_3PO_4): δ= 90.8 ppm (s). ^{1}H NMR (400 MHz, $CDCl_3$, 25°C, TMS): δ= 6.76-7.86 (m, 29 H; CH= aromatic), 5.09 (m, 1 H; CH-S), 5.06 (m, 1 H; CH-O),4.65 (b, 1 H; CH=, cod), 4.47 (b, 1 H; CH=, cod), 4.31 (b, 1 H; CH=, cod), 4.16 (m, 2 H; CH_2-O), 3.32 (m, 1 H; CH_2), 3.09 (m, 1 H; CH=, cod), 2.86 (m, 1 H; CH_2), 2.23 (s, 3 H; CH_3), 2.11-2.29 (b, 4 H; CH_2, cod),2.10 (s, 3 H; CH_3), 1.79-1.98 (b, 4 H; CH_2, cod), 1.75 (s, 3 H; CH_3), 1.65 (s, 9 H; CH_3, ^{t}Bu), 1.61 (s, 3 H; CH_3), 1.22 ppm (s, 9 H; CH_3, ^{t}Bu). ^{13}C NMR (126 MHz, $CDCl_3$, 25°C, TMS): δ= 161.7 (q, ^{1}J(C,B) = 49.9 Hz; C-B, BArF), 117.4-143.7 (aromatic carbons), 103.4 (d, *J*(C,P) = 14.8 Hz; CH=, cod), 100.0 (d, *J*(C,P) = 15.6 Hz; CH=, cod), 77.7 (s; CH-O), 77.2 (s; CH=, cod), 75.8 (s; CH_2-O), 70.1 (s; CH=, cod), 69.2 (d, ^{3}J(C,P) = 7.8 Hz; CH_2), 56.1 (s; CH-S), 35.5 (s; C, ^{t}Bu), 34.9 (s; C, ^{t}Bu), 34.0 (b; CH_2, cod), 33.1 (s; CH_3, ^{t}Bu), 31.7 (s; CH_3, ^{t}Bu), 31.5 (b; CH_2, cod), 29.8 (b; CH_2, cod), 27.3 (b; CH_2, cod), 20.3

(s; CH_3), 20.2 (s; CH_3), 16.6 (s; CH_3), 16.4 ppm (s; CH_3). MS HR-ESI [found 1031.3915, $C_{54}H_{65}IrO_4PS$ $(M)^+$ requires 1031.3942].

[Ir(cod)(L49c)]BAr_F. Yield: 132 mg (96%). ^{31}P NMR (162 MHz, $CDCl_3$, 25°C, H_3PO_4): δ= 97.6 ppm (s). ^1H NMR (400 MHz, $CDCl_3$, 25°C, TMS): δ= 7.04-7.63 (m, 29 H; CH= aromatic), 5.43 (m, 1 H; CH-O), 4.75 (d, ^3J(H,H) = 1.2 Hz, 1 H; CH-S), 4.67 (b, 1 H; CH=, cod), 4.58 (b, 1 H; CH=, cod), 4.50 (b, 1 H; CH=, cod), 4.25 (d, ^2J(H,H) = 12.0 Hz, 1 H; CH_2-O), 4.13 (d, ^2J(H,H) = 12.0 Hz, 1 H; CH_2-O), 3.46 (dd, ^2J(H,H) = 9.2 Hz, ^3J(H,H) = 4.0 Hz, 1 H; CH_2), 3.23 (m, 1 H; CH=, cod), 2.94 (m, 1 H; CH_2), 2.19 (s, 3 H; CH_3), 2.16 (s, 3 H; CH_3), 2.02-2.30 (b, 4 H; CH_2, cod), 1.81-1.94 (b, 4 H; CH_2, cod), 1.69 (s, 3 H; CH_3), 1.66 (s, 3 H; CH_3), 1.57 (s, 9 H; CH_3, ^{t}Bu), 1.28 ppm (s, 9 H; CH_3, ^{t}Bu). ^{13}C NMR (126 MHz, $CDCl_3$, 25°C, TMS): δ= 161.7 (q, ^1J(C,B) = 49.9 Hz; C-B, BArF), 117.4-144.2 (aromatic carbons), 106.0 (d, J(C,P) = 14.9 Hz; CH=, cod), 102.8 (d, J(C,P) = 15.6 Hz; CH=, cod), 81.0 (d, ^2J(H,H) = 7.0 Hz; CH-O), 77.6 (s; CH=, cod), 73.7 (s; CH_2-O), 70.2 (s; CH=, cod), 68.2 (d, ^3J(C,P) = 11.7 Hz; CH_2), 61.2 (s; CH-S), 35.1 (s; C, ^{t}Bu), 34.9 (s; C, ^{t}Bu), 33.2 (s; CH_2, cod), 32.8 (b; CH_2, cod), 32.5 (s; CH_3, ^{t}Bu), 32.4 (s; CH_2, cod), 31.3 (s; CH_3, ^{t}Bu), 28.5 (b; CH_2, cod), 20.3 (s; CH_3), 16.4 (s; CH_3), 16.3 ppm (s; CH_3). MS HR-ESI [found 1031.3921, $C_{54}H_{65}IrO_4PS$ $(M)^+$ requires 1031.3942].

[Ir(cod)(L49d)]BAr_F. Yield: 117 mg (93%). ^{31}P NMR (162 MHz, $CDCl_3$, 25°C, H_3PO_4): δ= 99.9 ppm (s). ^1H NMR (400 MHz, $CDCl_3$, 25°C, TMS): δ= 7.05-7.93 (m, 37 H; CH= aromatic), 4.88 (s, 1 H; CH-S), 4.58 (b, 3 H; CH= cod, CH-O), 4.32 (s, 2 H; CH_2-O), 3.68 (b, 1 H; CH=, cod), 3.26 (m, 1 H; CH_2), 3.22 (b, 1 H; CH=, cod), 3.12 (m, 1 H; CH_2), 2.24 (b, 2 H; CH_2, cod), 2.20 (b, 4 H; CH_2, cod), 1.95 ppm (b, 2 H; CH_2, cod). ^{13}C NMR (126 MHz, $CDCl_3$, 25°C, TMS): δ= 161.7 (q, ^1J(C,B) = 49.2 Hz; C-B, BArF), 117.4-136.5 (aromatic carbons), 98.6 (d, J(C,P) = 12.5 Hz; CH=, cod), 97.4 (d, J(C,P) = 11.0 Hz; CH=, cod), 78.1 (s; CH-O), 77.2 (s; CH=, cod), 75.0 (s; CH=, cod), 73.7 (s; CH_2-O), 70.2 (s; CH=, cod), 69.8 (d, ^3J(C,P) = 8.6 Hz; CH_2), 56.8 (s; CH-S),31.8 (d, J(C,P) = 3.1 Hz; CH_2, cod), 33.0 (b; CH_2, cod), 29.6 (s; CH_2, cod), 28.7 ppm (b; CH_2, cod). MS HR-ESI [found 833.2329, $C_{42}H_{43}IrO_2PS$ $(M)^+$ requires 833.2322].

[Ir(cod)(L50d)]BAr_F. Yield: 116 mg (95%). ^{31}P NMR (162 MHz, $CDCl_3$, 25°C, H_3PO_4): δ= 108.6 ppm (s). ^1H NMR (400 MHz, $CDCl_3$, 25°C, TMS): δ= 6.62-7.93 (m, 27 H; CH= aromatic), 4.77 (m, 1 H; CH-O), 4.54 (m, 2 H; CH-S, CH= cod), 4.14 (b, 1 H; CH=, cod), 3.56 (b, 2 H; CH=, cod), 3.18 (m, 2 H; CH_2, CH_2 cod), 2.95 (s, 3 H; CH_3), 2.84 (s, 3 H; CH_3-O), 2.81 (b, 1 H; CH_2), 2.64 (s, 3 H; CH_3), 2.25-2.54 (b, 3 H; CH_2, cod), 2.22 (s, 3 H; CH_3), 2.15 (b, 3 H; CH_2, cod),2.02 (b, 1 H; CH_2, cod), 1.89 (s, 3 H; CH_3), 1.83 (b, 1 H; CH_2, cod), 1.69 (b, 2 H; CH_2, cod), 1.40 ppm (s, 3 H; CH_3). ^{13}C NMR (126 MHz, $CDCl_3$, 25°C, TMS): δ= 161.7 (q, ^1J(C,B) = 50.5 Hz; C-B, BArF), 117.4-143.4 (aromatic carbons), 100.7 (d, J(C,P) = 12.3 Hz; CH=, cod), 98.5 (d, J(C,P) = 11.5 Hz; CH=, cod), 78.2 (s; CH-O), 73.1 (s; CH=, cod), 72.8 (d, ^3J(C,P) = 6.9 Hz; CH_2),69.5 (s; CH=, cod), 58.6 (s; CH_3-O), 49.3 (s; CH-S), 34.2 (d, J(C,P) = 3.8 Hz; CH_2, cod), 30.3 (d, J(C,P) = 3.5 Hz; CH_2, cod), 30.2 (s; CH_2, cod), 27.2 (s; CH_2, cod), 23.3 (s; CH_3), 22.9 (s; CH_3), 21.6 (s; CH_3), 19.5 ppm (s; CH_3), 20.7 (s; CH_3). MS HR-ESI [found 827.2790, $C_{41}H_{49}IrO_2PS$ $(M)^+$ requires 827.2791].

[Ir(cod)(L50e)]BAr_F. Yield: 115 mg (92%). ^{31}P NMR (162 MHz, $CDCl_3$, 25°C, H_3PO_4): δ= 105.2 ppm (s). ^1H NMR (400 MHz, $CDCl_3$, 25°C, TMS): δ= 6.62-7.93 (m, 25 H; CH= aromatic), 4.79 (m, 1 H; CH-O), 4.61 (m, 1 H; = cod), 4.17 (b, 2 H; CH-S, CH=, cod), 3.91 (b, 1 H; CH=, cod), 3.12 (m, 2 H; CH_2, CH= cod), 2.99 (s, 3 H; CH_3-O), 2.96 (b, 1 H; CH_2), 2.93 (s, 3 H; CH_3),

2.67 (s, 3 H; CH_3), 2.54 (b, 1 H; CH_2, cod), 2.52 (s, 3 H; CH_3), 2.13 (s, 6 H; CH_3), 1.9-2.4 (b, 7 H; CH_2, cod), 1.72 (s, 3 H; CH_3), 1.12 ppm (s, 3 H; CH_3). ^{13}C NMR (126 MHz, $CDCl_3$, 25°C, TMS): δ= 161.8 (q, ^1J(C,B) = 49.8 Hz; C-B, BArF), 117.6-144.5 (aromatic carbons), 101.2 (d, J(C,P) = 12.5 Hz; CH=, cod), 99.1 (d, J(C,P) = 12.1 Hz; CH=, cod), 73.4 (s; CH=, cod), 79.5 (s; CH-O), 72.4 (d, ^3J(C,P) = 6.9 Hz; CH_2), 70.2 (s; CH=, cod), 58.9 (s; CH_3-O), 50.1 (s; CH-S), 34.0 (b; CH_2, cod), 30.3 (d, J(C,P) = 3.2 Hz; CH_2, cod), 30.1 (s; CH_2, cod), 27.0 (s; CH_2, cod), 23.6 (s; CH_3), 22.9 (s; CH_3), 22.4 (s; CH_2), 21.6 (s; CH_3), 21.3 (s; CH_2), 20.7 (s; CH_3), 19.3 ppm (s; CH_3). MS HR-ESI [found 855.3103, $C_{43}H_{53}IrO_2PS$ $(M)^+$ requires 855.3104].

3.4.4.7. Typical procedure for the hydrogenation of olefins

The alkene (0.5 mmol) and Ir complex (2 mol%) were dissolved in CH_2Cl_2 (2 mL) in a high-pressure autoclave, which was purged four times with hydrogen. Then, it was pressurized at the desired pressure. After the desired reaction time, the autoclave was depressurized and the solvent evaporated off. The residue was dissolved in Et_2O (1.5 ml) and filtered through a short celite plug. The enantiomeric excess was determined by chiral GC or chiral HPLC and conversions were determined by ^{1}H NMR. The enantiomeric excesses of hydrogenated products from **S1**,[14a] **S2**,[41] **S3-S4**,[14a] **S5**,[42] **S6**,[14a] **S7**-**S9**,[10m] **S10**,[43] **S11**-**S12**,[14a] **S13**-**S15**,[10j] **S16**,[28] **S17**,[29a] **S18**,[29b] **S19**,[14a] **S20**,[10g] **S21**,[14a] **S22**,[43] **S23**,[44] **S24**,[10k] **S25-S29**[29b] and **S30**[14a] were determined using the conditions previously described.

3.4.4.8. Typical procedure for reutilization of catalysts using PC as solvent

After each catalytic experiment, the autoclave was depressurised. We then extracted the colourless propylene carbonate solution with dry/deoxygenated hexane under argon atmosphere with the aim to remove the remaining substrate and the hydrogenated olefin. After the extractions, the corresponding amount of substrate (0.5 mmol) was then added and a new catalytic experiment was started.

3.4.5. Acknowledgements

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3.4.6. References

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3.4.7. Supporting information

3.4.7.1. Table SI.1. Results for the Ir-catalyzed hydrogenation of **S2-S18** using the P,S-ligand library **L41-L50a-g**[a]

Entry	Substrate	L	% Conv	%ee[b]	Entry	Substrate	L	% Conv	%ee[b]
1	**S2**	**L41a**	100	29 (*R*)	45	**S4**	**L46c**	100	62 (*S*)
2	**S2**	**L41b**	100	41 (*R*)	46	**S4**	**L46d**	100	50 (*S*)
3	**S2**	**L41c**	100	19 (*R*)	47	**S4**	**L46e**	100	41 (*S*)
4	**S2**	**L41d**	100	49 (*R*)	48	**S4**	**L47a**	100	31 (*S*)
5	**S2**	**L42e**	100	83 (*R*)	49	**S4**	**L47b**	100	30 (*S*)
6	**S2**	**L43e**	100	87 (*R*)	50	**S4**	**L47c**	100	3 (*S*)
7	**S2**	**L44e**	100	33 (*R*)	51	**S4**	**L47d**	100	53 (*S*)
8	**S2**	**L45e**	100	48 (*R*)	52	**S4**	**L47e**	100	53 (*S*)
9	**S2**	**L46d**	100	68 (*R*)	53	**S4**	**L47g**	100	30 (*S*)
10	**S2**	**L46e**	100	95 (*R*)	54	**S4**	**L48a**	100	56 (*S*)
11	**S2**	**L47a**	100	32 (*R*)	55	**S4**	**L48e**	100	42 (*S*)
12	**S2**	**L48e**	100	99 (*R*)	56	**S4**	**L49a**	100	21 (*S*)
13	**S2**	**L49a**	100	33 (*R*)	57	**S4**	**L49b**	100	41 (*S*)
14	**S2**	**L50d**	100	99 (*R*)	58	**S4**	**L49c**	100	9 (*S*)
15	**S2**	**L50e**	100	>99 (*R*)	59	**S4**	**L49d**	100	54 (*S*)
16	**S3**	**L41a**	100	24 (*R*)	60	**S4**	**L50d**	100	53 (*S*)
17	**S3**	**L41b**	100	42 (*R*)	61	**S4**	**L50e**	100	58 (*S*)
18	**S3**	**L41c**	100	17 (*R*)	62	**S5**	**L41a**	100	6 (*R*)
19	**S3**	**L41d**	100	51 (*R*)	63	**S5**	**L41b**	100	2 (*R*)
20	**S3**	**L46d**	100	72 (*R*)	64	**S5**	**L41c**	100	12 (*R*)
21	**S3**	**L46e**	100	93 (*R*)	65	**S5**	**L41d**	100	36 (*R*)
22	**S3**	**L48e**	100	97 (*R*)	66	**S5**	**L42e**	100	22 (*R*)
23	**S3**	**L50d**	100	98 (*R*)	67	**S5**	**L44e**	100	1 (*S*)
24	**S3**	**L50e**	100	99 (*R*)	68	**S5**	**L45e**	100	8 (*S*)
25	**S4**	**L41a**	100	18 (*S*)	69	**S5**	**L46b**	100	4 (*R*)
26	**S4**	**L41b**	100	27 (*S*)	70	**S5**	**L46c**	100	15 (*R*)
27	**S4**	**L41c**	100	13 (*S*)	71	**S5**	**L46e**	100	76 (*R*)
28	**S4**	**L41d**	100	40 (*S*)	72	**S5**	**L47d**	100	35 (*R*)
29	**S4**	**L42b**	100	41 (*S*)	73	**S5**	**L48c**	100	36 (*R*)
30	**S4**	**L42c**	100	25 (*S*)	74	**S5**	**L48e**	100	78 (*R*)
31	**S4**	**L42e**	100	58 (*S*)	75	**S5**	**L49d**	100	36 (*R*)
32	**S4**	**L43a**	100	28 (*S*)	76	**S5**	**L50e**	100	82 (*R*)
33	**S4**	**L43b**	100	26 (*S*)	77	**S6**	**L41a**	100	34 (*R*)
34	**S4**	**L43c**	100	6 (*R*)	78	**S6**	**L41b**	100	44 (*R*)
35	**S4**	**L43e**	100	40 (*S*)	79	**S6**	**L41c**	100	18 (*R*)
36	**S4**	**L44a**	100	11 (*R*)	80	**S6**	**L41d**	100	54 (*R*)
37	**S4**	**L44b**	100	20 (*R*)	81	**S6**	**L42e**	100	87 (*R*)
38	**S4**	**L44c**	100	2 (*S*)	82	**S6**	**L43e**	100	88 (*R*)
39	**S4**	**L44d**	100	7 (*S*)	83	**S6**	**L44e**	100	44 (*R*)
40	**S4**	**L44e**	100	11 (*S*)	84	**S6**	**L45e**	100	53 (*R*)
41	**S4**	**L45a**	100	10 (*R*)	85	**S6**	**L46e**	100	98 (*R*)
42	**S4**	**L45e**	100	7 (*S*)	86	**S6**	**L47a**	100	36 (*R*)
43	**S4**	**L46a**	100	62 (*S*)	87	**S6**	**L48a**	100	32 (*R*)
44	**S4**	**L46b**	100	62 (*S*)	88	**S6**	**L48e**	100	>99(*R*)

(Continuation I) **Table SI.1.** Results for the Ir-catalyzed hydrogenation of **S2**-**S18** using the P,S-ligand library **L41**-**L50a-g**[a]

Entry	Substrate	L	% Conv	%ee[b]	Entry	Substrate	L	% Conv	%ee[b]
89	**S6**	**L49a**	100	35 (*R*)	133	**S13**	**L41d**	100	53 (*S*)
90	**S6**	**L50d**	100	99 (*R*)	134	**S13**	**L43e**	100	31 (*S*)
91	**S6**	**L50e**	100	>99 (*R*)	135	**S13**	**L44e**	100	81 (*S*)
92	**S7**	**L48e**	100	99 (*R*)	136	**S13**	**L45e**	100	93 (*S*)
93	**S7**	**L50d**	100	99 (*R*)	137	**S13**	**L46a**	100	24 (*S*)
94	**S7**	**L50e**	100	99 (*R*)	138	**S13**	**L46b**	100	57 (*S*)
95	**S8**	**L48e**	100	98 (*R*)	139	**S13**	**L46c**	100	43 (*S*)
96	**S8**	**L50d**	100	98 (*R*)	140	**S13**	**L46d**	100	94 (*S*)
97	**S8**	**L50e**	100	99 (*R*)	141	**S13**	**L46e**	100	93 (*S*)
98	**S9**	**L48e**	100	99 (*R*)	142	**S13**	**L47d**	100	48 (*S*)
99	**S9**	**L50d**	100	99 (*R*)	143	**S13**	**L47e**	100	83 (*S*)
100	**S9**	**L50e**	100	99 (*R*)	144	**S13**	**L47g**	100	33 (*S*)
101	**S10**	**L41a**	100	3 (*R*)	145	**S13**	**L48e**	100	94 (*S*)
102	**S10**	**L41b**	100	18 (*R*)	146	**S13**	**L49d**	100	51 (*S*)
103	**S10**	**L41c**	100	9 (*R*)	147	**S13**	**L50d**	100	98 (*S*)
104	**S10**	**L41d**	100	5 (*R*)	148	**S13**	**L50e**	100	99 (*S*)
105	**S10**	**L43e**	100	23 (*R*)	149	**S14**	**L41d**	100	53 (*S*)
106	**S10**	**L44e**	100	16 (S)	150	**S14**	**L44e**	100	79 (*S*)
107	**S10**	**L45e**	100	18 (R)	151	**S14**	**L46d**	100	96 (*S*)
108	**S10**	**L46e**	100	59 (R)	152	**S14**	**L50d**	100	97 (*S*)
109	**S10**	**L47d**	100	27 (R)	153	**S14**	**L50e**	100	99 (*S*)
110	**S10**	**L47e**	100	60 (R)	154	**S15**	**L41d**	100	48 (*S*)
111	**S10**	**L47g**	100	6 (R)	155	**S15**	**L44e**	100	80 (*S*)
112	**S10**	**L48a**	100	40 (R)	156	**S15**	**L46d**	100	95 (*S*)
113	**S10**	**L48e**	100	61 (R)	157	**S15**	**L50d**	100	98 (*S*)
114	**S10**	**L49d**	100	12 (R)	158	**S15**	**L50e**	100	98 (*S*)
115	**S10**	**L50e**	100	68 (R)	159	**S16**	**L41d**	100	28 (*S*)
116	**S11**	**L41d**	100	47 (R)	160	**S16**	**L43e**	100	61 (*S*)
117	**S11**	**L43e**	100	55 (R)	161	**S16**	**L44e**	100	42 (*S*)
118	**S11**	**L44e**	100	35 (R)	162	**S16**	**L45e**	100	38 (*S*)
119	**S11**	**L45e**	100	18 (R)	163	**S16**	**L46a**	100	51 (*R*)
120	**S11**	**L46a**	100	48 (R)	164	**S16**	**L46d**	100	55 (*S*)
121	**S11**	**L46b**	100	52 (R)	165	**S16**	**L46b**	100	48 (*R*)
122	**S11**	**L46c**	100	4 (S)	166	**S16**	**L46c**	100	11 (*S*)
123	**S11**	**L46e**	100	75 (R)	167	**S16**	**L46e**	100	70 (*S*)
124	**S11**	**L47d**	100	60 (R)	168	**S16**	**L47d**	100	38 (*S*)
125	**S11**	**L47e**	100	78 (R)	169	**S16**	**L47e**	100	48 (*S*)
126	**S11**	**L47g**	100	40 (R)	170	**S16**	**L47g**	100	37 (*S*)
127	**S11**	**L48e**	100	79 (R)	171	**S16**	**L48b**	100	54 (*R*)
128	**S11**	**L49d**	100	53 (R)	172	**S16**	**L48c**	100	2 (*S*)
129	**S11**	**L50e**	100	81 (R)	173	**S16**	**L48e**	100	70 (*S*)
130	**S12**	**L47e**	100	81 (R)	174	**S16**	**L49d**	100	26 (*S*)
131	**S12**	**L48e**	100	80 (R)	175	**S16**	**L50d**	100	69 (*S*)
132	**S12**	**L50e**	100	85 (*R*)	176	**S16**	**L50e**	100	72 (*S*)

Continuation II) **Table SI.1.** Results for the Ir-catalyzed hydrogenation of **S2-S18** using the P,S-ligand library **L41-L50a-g**[a]

Entry	Substrate	L	% Conv	%ee[b]	Entry	Substrate	L	% Conv	%ee[b]
177	**S17**	**L41d**	100	2 (*R*)	203	**S18**	**L44c**	24	76 (+)
178	**S17**	**L43e**	100	14 (*R*)	204	**S18**	**L44d**	15	52 (+)
179	**S17**	**L44d**	100	12 (*R*)	205	**S18**	**L44e**	19	47 (+)
180	**S17**	**L44e**	100	42 (*R*)	206	**S18**	**L45e**	47	81 (+)
181	**S17**	**L45e**	100	18 (*R*)	207	**S18**	**L46a**	94	89 (+)
182	**S17**	**L46a**	100	12 (*R*)	208	**S18**	**L46b**	100	72 (+)
183	**S17**	**L46d**	100	26 (*R*)	209	**S18**	**L46c**	100	90 (+)
184	**S17**	**L46e**	100	30 (*R*)	210	**S18**	**L46d**	100	56 (+)
185	**S17**	**L47d**	100	3 (*S*)	211	**S18**	**L46e**	72	48 (+)
186	**S17**	**L47e**	100	7 (*S*)	212	**S18**	**L47a**	100	94 (+)
187	**S17**	**L47g**	100	4 (*S*)	213	**S18**	**L47b**	100	88 (+)
188	**S17**	**L48b**	100	11 (*R*)	214	**S18**	**L47c**	100	93 (+)
189	**S17**	**L48c**	100	8 (*R*)	215	**S18**	**L47d**	100	79 (+)
190	**S17**	**L49d**	100	43 (*R*)	216	**S18**	**L47e**	100	82 (+)
191	**S17**	**L50d**	100	44 (*R*)	211	**S18**	**L46e**	72	48 (+)
192	**S17**	**L50e**	100	45 (*R*)	212	**S18**	**L47a**	100	94 (+)
193	**S18**	**L41a**	100	81 (+)	213	**S18**	**L47b**	100	88 (+)
194	**S18**	**L41b**	100	74 (+)	214	**S18**	**L47c**	100	93 (+)
195	**S18**	**L41c**	100	84 (+)	215	**S18**	**L47d**	100	79 (+)
196	**S18**	**L41d**	98	72 (+)	216	**S18**	**L47e**	100	82 (+)
197	**S18**	**L42b**	99	68 (+)	217	**S18**	**L47g**	100	34 (+)
198	**S18**	**L42c**	97	58 (+)	218	**S18**	**L48b**	100	76 (+)
199	**S18**	**L43b**	100	88 (+)	219	**S18**	**L48c**	100	71 (+)
200	**S18**	**L43c**	99	69 (+)	220	**S18**	**L49d**	100	72 (+)
201	**S18**	**L43e**	86	79 (+)	221	**S18**	**L50d**	100	82 (+)
202	**S18**	**L44b**	32	90 (+)	222	**S18**	**L50e**	84	83 (+)

[a] Reactions carried out using 0.5 mmol of substrate, 2 mol% of Ir-catalyst precursor, CH2Cl2 as solvent, 100 bar H2, 4 h. [b] Enantiomeric excesses determined by chiral GC or HPLC.

3.4.7.2. Table SI.2. Results for the Ir-catalyzed hydrogenation of **S20**-**S30** using the P,S-ligand library **L41-L50a-g**[a]

Entry	Substrate	L	% Conv	%ee[b]	Entry	Substrate	L	% Conv	%ee[b]
1	**S22**	**L41a**	100	10 (*R*)	46	**S23**	**L44e**	100	39 (*R*)
2	**S22**	**L41b**	100	27 (*R*)	47	**S23**	**L45e**	100	48 (*R*)
3	**S22**	**L41c**	100	47 (*R*)	48	**S23**	**L47a**	100	43 (*R*)
4	**S22**	**L41d**	100	35 (*R*)	49	**S23**	**L47c**	100	52 (*R*)
5	**S22**	**L42b**	100	11 (*R*)	50	**S23**	**L48e**	100	60 (*R*)
6	**S22**	**L42c**	100	24 (*R*)	51	**S23**	**L49d**	100	51 (*R*)
7	**S22**	**L42e**	100	29 (*R*)	52	**S23**	**L50e**	100	68 (*R*)
8	**S22**	**L43a**	100	21 (*R*)	53	**S24**	**L41a**	100	99 (-)
9	**S22**	**L43b**	100	15 (*R*)	54	**S24**	**L41b**	100	99 (-)
10	**S22**	**L43c**	100	29 (*R*)	55	**S24**	**L41c**	100	99 (-)
11	**S22**	**L43e**	100	29 (*R*)	56	**S24**	**L41d**	100	24 (-)
12	**S22**	**L44a**	100	17 (*R*)	57	**S24**	**L48e**	100	99 (-)
13	**S22**	**L44b**	100	4 (*R*)	58	**S25**	**L41b**	100	70 (*S*)
14	**S22**	**L44c**	100	24 (*R*)	59	**S25**	**L41c**	100	71 (*S*)
15	**S22**	**L44d**	100	31 (*R*)	60	**S25**	**L42b**	100	66 (*S*)
16	**S22**	**L44e**	100	42 (*R*)	61	**S25**	**L42c**	100	68 (*S*)
17	**S22**	**L45a**	100	4 (*R*)	62	**S25**	**L42e**	100	40 (*S*)
18	**S22**	**L45e**	100	19 (*R*)	63	**S25**	**L43b**	100	52 (*S*)
19	**S22**	**L46a**	100	24 (*R*)	64	**S25**	**L43c**	100	74 (*S*)
20	**S22**	**L46b**	100	19 (*R*)	65	**S25**	**L43e**	100	52 (*S*)
21	**S22**	**L46c**	100	41 (*R*)	66	**S25**	**L44c**	100	26 (*S*)
22	**S22**	**L46d**	100	48 (*R*)	67	**S25**	**L44d**	100	49 (*S*)
23	**S22**	**L46e**	100	50 (*R*)	68	**S25**	**L45e**	100	41 (*S*)
24	**S22**	**L47a**	100	29 (*R*)	69	**S25**	**L46a**	100	68 (*S*)
25	**S22**	**L47b**	100	24 (*R*)	70	**S25**	**L46b**	100	62 (*S*)
26	**S22**	**L47c**	100	58 (*R*)	71	**S25**	**L46c**	100	70 (*S*)
27	**S22**	**L47d**	100	49 (*R*)	72	**S25**	**L46d**	100	61 (*S*)
28	**S22**	**L47e**	100	67 (*R*)	73	**S25**	**L46e**	100	42 (*S*)
29	**S22**	**L47g**	100	18 (*R*)	74	**S25**	**L47b**	100	13 (*S*)
30	**S22**	**L48a**	100	41 (*R*)	75	**S25**	**L47c**	100	62 (*S*)
31	**S22**	**L48e**	100	69 (*R*)	76	**S25**	**L47d**	100	55 (*S*)
32	**S22**	**L49a**	100	14 (*R*)	77	**S25**	**L48e**	100	32 (*S*)
33	**S22**	**L49b**	100	2 (*S*)	78	**S25**	**L49b**	100	40 (*S*)
34	**S22**	**L49c**	100	29 (*R*)	79	**S25**	**L49e**	100	66 (*S*)
35	**S22**	**L49d**	100	51 (*R*)	80	**S25**	**L50d**	100	55 (*S*)
36	**S22**	**L50d**	100	67 (*R*)	81	**S25**	**L50e**	100	53 (*S*)
37	**S22**	**L50e**	100	71 (*R*)	82	**S26**	**L41a**	100	46 (*R*)
38	**S23**	**L41a**	100	40 (*R*)	83	**S26**	**L41b**	100	4 (*R*)
39	**S23**	**L41b**	100	26 (*R*)	84	**S26**	**L41c**	100	72 (*R*)
40	**S23**	**L41c**	100	49 (*R*)	85	**S26**	**L41d**	100	12 (R)
41	**S23**	**L41d**	100	29 (*R*)	86	**S26**	**L42c**	100	69 (R)
42	**S23**	**L43a**	100	29 (*R*)	87	**S26**	**L43c**	100	74 (*R*)
43	**S23**	**L43b**	100	10 (*S*)	88	**S26**	**L44c**	100	34 (*R*)
44	**S23**	**L43c**	100	48 (*R*)	89	**S26**	**L45e**	100	29 (*R*)
45	**S23**	**L43d**	100	50 (*R*)	90	**S26**	**L46c**	100	69 (*R*)

(Continuation I) **Table SI.2.** Results for the Ir-catalyzed hydrogenation of **S20**-**S30** using the P,S-ligand library **L41**-**L50a**-**g**[a]

Entry	Substrate	L	% Conv	%ee[b]	Entry	Substrate	L	% Conv	%ee[b]
91	**S26**	**L47c**	100	71 (*R*)	115	**S28**	**L45e**	100	25 (*S*)
92	**S26**	**L49c**	100	68 (*R*)	116	**S28**	**L46c**	100	77 (*R*)
93	**S26**	**L50d**	100	28 (*R*)	117	**S28**	**L46d**	100	22 (*R*)
94	**S27**	**L41a**	100	40 (*R*)	118	**S28**	**L47c**	100	32 (*R*)
95	**S27**	**L41b**	100	10 (*S*)	119	**S28**	**L48e**	100	21 (*R*)
96	**S27**	**L41c**	100	76 (*R*)	120	**S28**	**L49c**	100	55 (*R*)
97	**S27**	**L41d**	100	4 (*R*)	121	**S28**	**L50d**	100	58 (*R*)
98	**S27**	**L42c**	100	69 (*R*)	122	**S28**	**L50e**	100	62 (*R*)
99	**S27**	**L43c**	100	81 (*R*)	123	**S29**	**L41a**	100	31 (*S*)
100	**S27**	**L45e**	100	33 (*S*)	124	**S29**	**L41b**	100	15 (*R*)
101	**S27**	**L46c**	100	59 (*R*)	125	**S29**	**L41c**	100	76 (*S*)
102	**S27**	**L47c**	100	51 (*R*)	126	**S29**	**L41d**	100	75 (*R*)
103	**S27**	**L47d**	100	6 (*S*)	127	**S29**	**L42c**	100	74 (*S*)
104	**S27**	**L47e**	100	11 (*R*)	128	**S29**	**L43c**	100	56 (*S*)
105	**S27**	**L49c**	100	32 (*R*)	129	**S29**	**L44b**	100	32 (*S*)
106	**S27**	**L50d**	100	19 (*R*)	130	**S29**	**L44c**	100	63 (*S*)
107	**S27**	**L50e**	100	21 (*R*)	131	**S29**	**L46c**	100	70 (*S*)
108	**S28**	**L41a**	100	39 (*R*)	132	**S29**	**L47c**	100	69 (*S*)
109	**S28**	**L41b**	100	6 (*R*)	133	**S29**	**L49c**	100	67 (*S*)
110	**S28**	**L41c**	100	76 (*R*)	134	**S29**	**L50d**	100	75 (*R*)
111	**S28**	**L41d**	100	28 (*R*)	135	**S29**	**L50e**	100	84 (*R*)
112	**S28**	**L42c**	100	59 (*R*)	136	**S30**	**L46b**	100	95 (+)
113	**S28**	**L43e**	100	24 (R)	137	**S30**	**L46c**	100	94 (-)
114	**S28**	**L44c**	100	25 (R)	138	**S30**	**L50e**	100	96 (+)

[a] Reactions carried out using 0.5 mmol of substrate, 2 mol% of Ir-catalyst precursor, CH2Cl2 as solvent, 1 bar H2, 4 h. [b] Enantiomeric excesses determined by chiral GC or HPLC.

3.4.7.3. Table SI. 3. Comparison of the barrier for interconversion of **A7** and **A8** with their corresponding barriers for migratory insertion.[a]

	L41d	**L46d**
TSA7$_{MI}$	18.2	20.5
A7	-60.2	-54.1
TSA7-A8$_{INV}$	-16.9	-24.3
A8	-50.3	-46.4
TSA8$_{MI}$	4.5	8.5

[a] Energies in kJ/mol.

UNIVERSITAT ROVIRA I VIRGILI
SCREENING OF MODULAR AND READILY AVAILABLE LIGAND LIBRARIES FOR C-X (X=H, C, N AND O) BOND FORMING REACTIONS. THE USE OF DFT STUDIES FOR CATALYSTS OPTIMIZATION
Jèssica Margalef Pallarès

3.5. Screening of an indene-based phosphite/phosphinite-thioether ligands in the asymmetric Ir-hydrogenation of minimally functionalized olefins

Jèssica Margalef, Xisco Caldentey, Erik A. Karlsson, Carlos Rodriguez, Miquel A. Pericàs, Oscar Pàmies and Montserrat Diéguez (preliminary results)

***Abstract**: An indene-based phosphite/phosphinite-thioether ligand family (**L51**-**57a**-**e**) was successfully synthesized in only three simple steps procedure. The synthetic strategy used allowed us to systematically modify the substituents of the thioether and the phosphorus groups. Although poor to moderate enantioselectivities were only achieved in the hydrogenation of (E)- and (Z)-trisubstituted olefins **S1** and **S2** (ee's up to 63% ee), we were able to identify ligand **L55c**, which enantioselectively catalyzed the hydrogenation of 1,1-disubstituted olefin **S3** in excellent enantioselectivity (97%).*

3.5.1. Introduction

The asymmetric hydrogenation of alkenes using transition metal catalysts is a uniquely mild and clean chemical transformation that allows the obtaining of chiral compounds in excellent chemo-, regio- and enantioselectivities. Therefore it has become a fundamental tool for organic synthetic chemists.[1]

For the asymmetric hydrogenation of alkenes bearing coordinating functional goups such as amides and carboxylic acids in close proximity to the double bound, Rh(I) and Ru(II) species bearing diphosphine ligands are the catalysts of choice. As a complement, chiral mimics of Crabtree's catalyst $[Ir(cod)(Py)(PCy_3)][PF_6]$, have been developed into versatile reagents that can reduce nonfunctionalized olefins carrying no neighboring coordinating group. Among the most studied P,N-ligands are the phosphine/phosphinite-oxazoline ligands.[2] The latest innovation in the design of ligands for this process was the replacement of the phosphine/phosphinite moiety by a biaryl phosphite group.[3] The presence of biaryl-phosphite moieties in these P,N-ligands provides greater substrate versatility than previous Ir-phosphine/phosphinite,N catalyst systems. More recently, our group has shown that Ir-complexes based on P-containing ligands bearing a thioether moiety instead of N-coordinating function are also highly enanatioselective hydrogenation catalysts.[4]

In order to further study the potential of this new class of P,S-ligands in this catalytic process we report in this chapter the synthesis and the preliminary results of the application of a phosphite/phosphinite-thioether ligand library (**L51**-**L57a**-**e**) in the Ir-catalyzed hydrogenation of minimally functionalized olefins. These ligands are synthesized in only three steps from commercially available indene. They also benefit from the robustness of the thioether. In addition, their synthesis allow to fine tune the chiral cavity by systematically varying: (a) the electronic and steric properties of the thioether group (**L51**-**57**), (b) the biaryl phosphite moiety (**a**-**c**), and (c) the phosphorus group (phosphite versus phosphinite groups, **d**-**e**). The new P,S-ligands **L51**-**L57a**-**g** have been applied in the hydrogenation of the model (*E*)- and (*Z*)-trisubstituted alkenes (**S1** and **S2**) and the model disubstituted one **S3**.

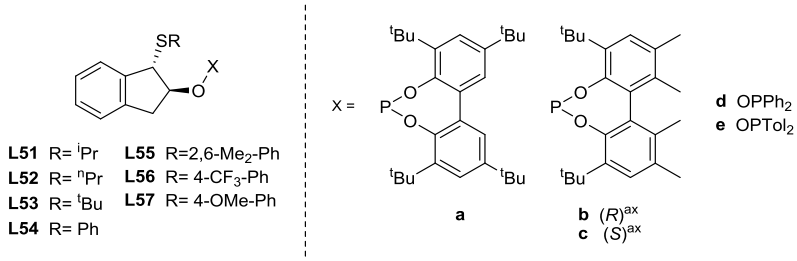


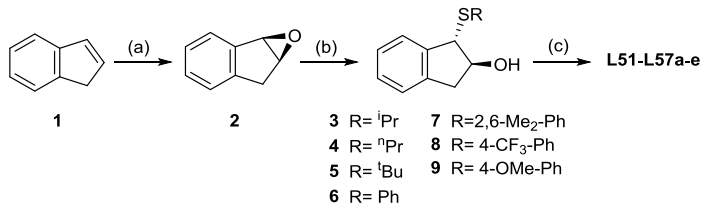
Figure 3.5.1. Phosphite/phosphinite-thioether ligand library **L51**-**57a**-**e**.

3.5.2. Results and Discussion

3.5.2.1. Synthesis of ligands

The synthesis of phosphite/phosphinite-thioether ligands **L51**-**57a**-**e** is straightforward. They were successfully synthesized from the readily available indene (**1**).[5] The first step of the synthesis is the enantioselective epoxidation of **1** (Scheme 3.5.1, step (a)).[6] The second step is the regioselective and stereospecific ring-opening of **2** by thiolates to yield the corresponding hydroxyl-thioethers (**3**-**9**) (Scheme 3.5.1, step (b)), which allows a high diversity on the thioether substituents. The last step of the ligand synthesis (Scheme 3.5.1) is the reaction of the corresponding thioether-hydroxyl in the presence of base with one equivalent of either the corresponding biaryl phosphorochloridite ($ClP(OR)_2$; $P(OR)_2$ = **a**-**c**) to provide phosphite-thioether ligands (**L51**-**L57a**-**c**) or the required chlorophosphine ($ClPR_2$; PR_2 = **d**-**e**) to achieve the new phosphinite-thioether ligands (**L51**-**L57d**-**e** (Scheme 3.5.1).

All of the ligands were isolated in good yields as white solids or colorless oils after purification on neutral alumina. HRMS-ESI spectra were in agreement with the assigned structures. The ^{1}H, ^{31}P and ^{13}C NMR spectra were as expected for these ligands.



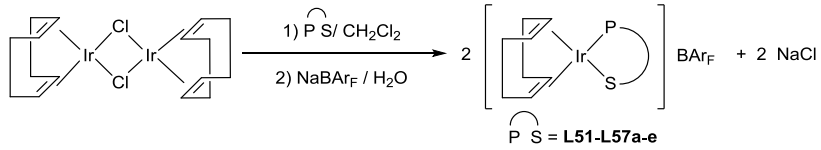
Scheme 3.5.1. Synthesis of new thioether-phosphite/phosphinite ligands **L51-L57a**-**e**. (a) aq. NaOCl/Mn-salen cat./CH_2Cl_2; (b) R^2SH/NaOH/dioxane/H_2O; (c) $ClP(OR)_2$/pyridine/toluene/80 °C or $ClPR_2$/NEt_3/toluene.

3.5.2.2. Synthesis of Ir-catalyst precursors

The catalyst precursors were prepared by treating 0.5 equivalent of $[Ir(\mu\text{-}Cl)(cod)]_2$ with an equimolar amount of the appropriate P,S-ligand (**L51**-**L57a**-**e**) in dichloromethane under reflux for 1 h. The Cl^-/BAr_F^- counterion exchange was then performed by reaction with sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate ($NaBAr_F$) (1 equiv) in water (Scheme

3.5.2). The catalyst precursors were obtained in pure form as air-stable red-orange solids. No further purification was thus needed.

The HRMS-ESI spectra show the heaviest ions at m/z which correspond to the loss of the BAr_F anion from the molecular species. The complexes were also characterized by ^{1}H, ^{13}C, and ^{31}P NMR spectroscopy. The spectral assignments, made using $^{1}H–^{1}H$ and $^{13}C–^{1}H$ correlation measurements, were as expected for these C_1-symmetric iridium complexes.



Scheme 3.5.2. Synthesis of Ir-precursors [Ir(cod)(P-S)]BAr_F (P-S **= L51**-**L57a**-**c**).

3.5.2.3. Asymmetric hydrogenation

*Asymmetric hydrogenation of the minimally functionalized model olefin (E)-2-(4-methoxyphenyl)-2-butene (**S1**)*

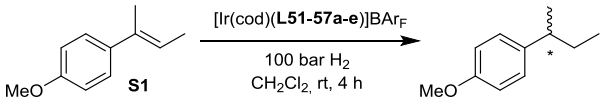
Ligands **L51**-**57a**-**e** were initially tested in the Ir-catalyzed hydrogenation of the minimally functionalized model olefin (*E*)-2-(4-methoxyphenyl)-2-butene (**S1**). Table 3.5.1 shows the catalytic results. We first studied the effect of the phosphite moiety on enantioselectivity using **L51a**-**c**. The results indicated that the presence of chiral biaryl phosphite groups is necessary to maximize enantioselectivities (Table 3.5.1, entries 1-3). Results also indicated a cooperative effect between the configuration of the biaryl phosphite group and the ligand backbone, that results in a matched combination with ligand **L51b** containing an (*R*)-biaryl phosphite moiety (entry 2 vs 3).

We next studied the effect of replacing the phoshpite moiety by a phosphinite group and we found that it is affected by the nature of the thioether group. Thus, while for alkyl substituted thioether groups (**L51**-**L53**) the replacement of the phosphite by a phosphinite group has a negative effect on enantioselectivity (entries 2-8), the use of phosphinite moieties in ligands **L54**-**L57**, containing an aryl thioether group, has a positive effect on enantioselectivity.

The results using ligands **L51**-**L57**, with different thioether moieties indicated that the thioether group also affected enantioselectivity. Thus, for instance, the presence of electron-poor thioether group (ligand **L56**) had a negative effect on enantioselectivity (entry 14 vs 15 and 9); and also while ligands **L51**-**L52b** gave the (*R*)-hydrogenated product, ligands (**L54**-**L57b**) gave access to the (*S*)-enantiomer of the reduced product.

In summary, the highest enantioselectivity was achieved using ligands **L55d** and **L55e**, which contains the optimal combination of ligand parameters (ee's up to 63%).

Table 3.5.1. Selected results for the Ir-catalyzed hydrogenation of **S1** using phosphite/phosphinite-thioether ligands **L51**-**57a**-**e**.[a]



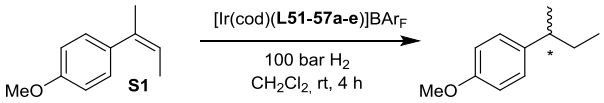
Entry	Ligand	% Conv[b]	ee%[b]
1	**L51a**	100	5 (*R*)
2	**L51b**	100	48 (*R*)
3	**L51c**	98	35 (*S*)
4	**L51d**	100	21 (*S*)
5	**L51e**	100	33 (*S*)
6	**L52b**	100	54 (*R*)
7	**L53b**	100	61 (*S*)
8	**L53e**	100	41 (*S*)
9	**L54b**	100	33 (*S*)
10	**L55b**	100	38 (*S*)
11	**L55c**	100	11 (*S*)
12	**L55d**	100	63 (*S*)
13	**L55e**	100	63 (*S*)
14	**L56b**	100	17 (*S*)
15	**L57b**	100	29 (*S*)

[a] Reactions carried out using 0.5 mmol of **S1** and 2 mol% of Ir-catalyst precursor. [b] Conversion and enantiomeric excesses determined by chiral GC.

*Asymmetric hydrogenation of the minimally functionalized model olefin (Z)-2-(4-methoxyphenyl)-2-butene (**S2**)*

We then moved to examine the new P,S-ligands **L51**-**L57a**-**e** in the hydrogenation of the more demanding trisubstituted (*Z*)-2-(4-methoxyphenyl)-2-butene (**S2**) (Table 3.5.2). As expected, the hydrogenation of substrate **S2** proceeded in lower enantiocontrol than in the hydrogenation of the (*E*)-substrate **S1**. Enantioselectivities up to 35% ee were achieved (entry 13). Catalytic results show a similar trend than for substrate **S1**. Therefore, the best enantioselectivities were achieved when using phosphinite-thioether ligands **L55d**-**e** (Table 3.5.2, entries 12 and 13).

Table 3.5.2. Selected results for the Ir-catalyzed hydrogenation of **S2** using phosphite/phosphinite-thioether ligands **L51**-**57a**-**e**.[a]



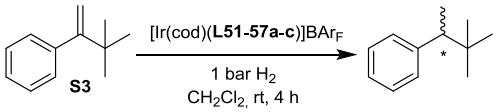
Entry	Ligand	% Conv[b]	ee%[b]
1	**L51a**	100	2 (*R*)
2	**L51b**	100	28 (*R*)
3	**L51c**	100	30 (*S*)
4	**L51d**	100	0
5	**L51e**	100	13 (*S*)
6	**L52b**	100	17 (*S*)
7	**L53b**	100	33 (*R*)
8	**L53e**	100	0
9	**L54b**	100	20 (*R*)
10	**L55b**	100	16 (*R*)
11	**L55c**	100	25 (*R*)
12	**L55d**	100	35 (*R*)
13	**L55e**	100	34 (*R*)
14	**L56b**	100	26 (*R*)
15	**L57b**	100	28 (*R*)

[a] Reactions carried out using 0.5 mmol of **S2** and 2 mol% of Ir-catalyst precursor. [b] Conversion and enantiomeric excesses determined by chiral GC.

*Asymmetric hydrogenation of minimally functionalized disubstituted olefin 3,3-dimethyl-2-phenyl-1-butene (**S3**)*

Enantioselectivity in the hydrogenation of disubstituted substrates is more difficult to control than in trisubstituted olefins. There are two main reasons for this: a) the two substituents in the substrate can easily exchange positions in the chiral environment formed by the catalysts, thus reversing the face selectivity; and b) the terminal double bond can isomerize to form the more stable internal (*E*)-alkene, which usually leads to the predominant formation of the opposite enantiomer of the hydrogenated product. Few known catalytic systems therefore can provide high enantioselectivities for these substrates, and those that do are usually limited in substrate scope.[2l,3c-d,7] In contrast to the hydrogenation of trisubstituted olefins, the enantioselectivity in the reduction of terminal alkenes is highly pressure dependent. Therefore, hydrogenation at an atmospheric pressure of H_2 gave, in general, significantly higher ee values than at higher pressures.[7,8] In this context we chose 3,3-dimethyl-2-phenyl-1-butene (**S3**) as a model substrate for testing new ligands **L51**-**57a**-**e** in the hydrogenation of this kind of challenging substrates. We were pleased to find out that enantioselectivities (up to 97% ee) were higher than those achieved using trisubstituted olefins **S1** and **S2** (Table 3.5.1 and Table 3.5.2).

Table 3.5.3. Selected results for the Ir-catalyzed hydrogenation of **S3** using phosphite/phosphinite-thioether ligands **L51**-**57a**-**e**.[a]



Entry	Ligand	% Conv[b]	ee%[b]
1	**L51a**	100	24 (*S*)
2	**L51b**	100	82 (*S*)
3	**L51c**	100	60 (*R*)
4	**L51d**	100	15 (*S*)
5	**L51e**	100	9 (*S*)
6	**L52b**	100	80 (*S*)
7	**L53b**	100	50 (*S*)
8	**L53e**	100	77 (*R*)
9	**L54b**	100	56 (*S*)
10	**L55b**	100	66 (*S*)
11	**L55c**	100	97 (*R*)
12	**L55d**	100	90 (*R*)
13	**L55e**	100	87 (*R*)
14	**L56b**	100	41 (*S*)
15	**L57b**	100	54 (*S*)

[a] Reactions carried out using 0.5 mmol of **S3** and 2 mol% of Ir-catalyst precursor. [b] Conversion and enantiomeric excesses determined by chiral GC.

The results also indicated a different trend of the ligand parameters on enantioselectivity. Thus, in contrast to hydrogenation of **S1** and **S2**, the use of phosphite moieties instead of phosphinite groups led to higher ee's. The results also indicated that the configuration of the biaryl phosphite group controls the sense of asymmetric induction. Thus, ligands containing an (*R*)-biaryl phosphite group led to the (*S*)-product, whereas those with an (*S*)-biaryl phosphite moiety led to the (*R*)-hydrogenated product. The results also indicated that there is a cooperative effect between the configuration of the biaryl group and the ligand backbone. This cooperative effect, that depends on the nature of the thioether group, allowed us to achieve enantioselectivities up to 97 % ee when using ligand **L55c**.

3.5.3. Conclusions

A new phosphite/phosphinite-thioether ligand family (**L51**-**57a**-**e**) was successfully synthesized in only three simple steps procedure from readily available indene. The synthetic procedure used allowed the systematic variation of the substituents of the thioether and the phosphorus groups. Both groups have been found to be highly important for the enantioselectivity of the process. Alkyl and aryl thioether groups showed a different trend in the catalytic performance. When alkyl thioether containing ligands were used, the presence of a chiral phosphite moiety was necessary to achieve high levels of enantioselectivity. In contrast with aryl thioether containing ligand the enantioselectivity improved by the use of phosphinite ligands. Unfortunatelly, poor to moderate

enantioselectivities were only achieved in the hydrogenation of (*E*)- and (*Z*)-trisubstituted olefins **S1** and **S2** (ee's up to 63% ee). Interestingly, enantioselectivities were higher in the hydrogenation of 1,1-disubstituted olefin **S3**. The use of Ir/**L55c** catalytic system, afforded the hydrogenated product in excellent enantioselectivity (97%). Therefore, ligands **L51**-**57a**-**e** could be effective ligands for the hydrogenation of this class of challenging substrates.

3.5.4. Experimental part

3.5.4.1. General considerations

All reactions were carried out using standard Schlenk techniques under an argon atmosphere. Solvents were purified and dried by standard procedures. Phosphorochloridites are easily prepared in one step from the corresponding biaryls.[9] Thioether-phosphinite ligand **L51d** and **L55d** were prepared as previously reported.[5] ^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded using a 400 MHz spectrometer. Chemical shifts are relative to that of $SiMe_4$ (^{1}H and ^{13}C) as internal standard or H_3PO_4 (^{31}P) as external standard. ^{1}H, ^{13}C and ^{31}P assignments were made on the basis of ^{1}H-^{1}H gCOSY, ^{1}H-^{13}C gHSQC and ^{1}H-^{31}P gHMBC experiments.

3.5.4.2. General procedure for the preparation of tioether-alcohols 3-9

A solution of indene oxide (2 mmol, 264 mg) in dioxane (4.5 mL/mmol of indene oxide) is treated with the corresponding thiol (3 mmol). Then, a solution of NaOH (3 mmol, 120 mg) in water (0.45 mL/mmol of indene oxide) is added dropwise. The reaction mixture is capped and stirred at 55 °C until the epoxide is consumed according to TLC analysis (*ca*. 45-60 min). After this, the mixture is cooled to RT, diluted with water and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers are dried over Na_2SO_4 and concentrated to give a residue that is purified by flash chromatography on silica gel (eluent specified in each case) to give the desired hydroxysulfide.

(*1S*,*2S*)-1-(isopropylthio)-2,3-dihydro-1H-inden-2-ol (3). Yield: 308 mg (74%), white solid. SiO_2-chromatography (gradient from cyclohexane/EtOAc = 100:0 to cyclohexane/EtOAc = 80:20). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.34 (d, 3H, CH_3, ^{i}Pr, $^{3}J_{H\text{-}H}$ =6.7 Hz), 1.38 (d, 3H, CH_3, ^{i}Pr, $^{3}J_{H\text{-}H}$ =6.7 Hz), 2.07 (bs, 1H, OH), 2.86 (dd, 1H, CH_2, $^{2}J_{H\text{-}H}$ =16.1, $^{3}J_{H\text{-}H}$ =4.4 Hz), 3.14 (hept, 1H, CH, ^{i}Pr, $^{3}J_{H\text{-}H}$ =6.7 Hz), 3.38 (dd, 1H, CH_2, $^{2}J_{H\text{-}H}$ =16.1, $^{3}J_{H\text{-}H}$ =6.2 Hz), 4.13 (d, 1H, CH-S, $^{3}J_{H\text{-}H}$ =4.1 Hz), 4.46-4.49 (m, 1H, CH-O), 7.22 (bs, 3H, CH=), 7.36 (m , 1H, CH=).^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 23.8 (CH_3), 24.2 (CH_3), 35.5 (CH), 39.9 (CH_2), 55.9 (CH-S), 79.9 (CH-O), 125.1 (CH=), 125.4 (CH=), 127.1 (CH=), 127.9 (CH=), 140.0 (C=), 141.3 (CH).

(1*S*,2*S*)-1-(Propylthio)-2,3-dihydro-1*H*-inden-2-ol (4). Yield: 325 mg (78%), white solid. SiO_2-chromatography (gradient from cyclohexane/EtOAc = 100:0 to cyclohexane/EtOAc = 80:20). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.01 (t, 3H, CH_3, ^{n}Pr, $^{3}J_{H\text{-}H}$ =7.3 Hz), 1.66 (sext, 2H, CH_2, ^{n}Pr, $^{3}J_{H\text{-}H}$ =7.3 Hz), 2.10 (bs, 1H, OH), 2.53 (dt, 1H, CH_2, $^{2}J_{H\text{-}H}$ =12.3, $^{3}J_{H\text{-}H}$ =7.3 Hz), 2.60 (dt, 1H, CH_2, $^{2}J_{H\text{-}H}$ =12.3, $^{3}J_{H\text{-}H}$ =7.3 Hz), 2.87 (dd, 1H, CH_2, $^{2}J_{H\text{-}H}$ =16.1, $^{3}J_{H\text{-}H}$ =4.7 Hz), 3.37 (dd, 1H, CH_2, $^{2}J_{H\text{-}H}$ =16.1, $^{3}J_{H\text{-}H}$ =6.3 Hz), 4.09 (d, 1H, CH-S, $^{3}J_{H\text{-}H}$ =4.3 Hz), 4.49 (quint, 1H, CH-O, $^{3}J_{H\text{-}H}$ =5.0 Hz), 7.32-7.40 (m, 1H, CH=), 7.20-7.25 (m, 3H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 13.6 (CH_3), 23.2 (CH_2), 33.0 (CH_2), 39.8 (CH_2), 57.0 (CH-S), 79.3 (CH-O), 125.1 (CH=), 125.3 (CH=), 127.1 (CH=), 127.9 (CH=), 140.1 (C=), 140.6 (C=).

(1*S*,2*S*)-1-(*tert*-Butylthio)-2,3-dihydro-1*H*-inden-2-ol (5). Yield: 320 mg (72%), pale orange solid. SiO_2-chromatography (gradient from cyclohexane/EtOAc = 100:0 to cyclohexane/EtOAc = 80:20). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.45 (s, 3H, CH_3, ^{t}Bu), 2.29 (bs, 1H, OH), 2.86 (dd, 1H, CH_2, $^2J_{H-H}$ =15.8, $^3J_{H-H}$ =5.6 Hz), 3.32 (dd, 1H, CH_2, $^2J_{H-H}$ =15.8, $^3J_{H-H}$ =6.4 Hz), 4.03 (d, 1H, CH-S, $^3J_{H-H}$ =5.3 Hz), 4.39-4.44 (m, 1H, CH-O), 7.19-7.25 (m, 3H, CH=), 7.38 (m, 1H, CH=), 7.36 (m , 1H, CH=).^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 31.7 (CH_3, ^{t}Bu), 39.9 (CH_2), 43.7 (C, ^{t}Bu), 54.6 (CH-S), 80.8 (CH-O), 124.8 (CH=), 125.6 (CH=), 127.2 (CH=), 127.7 (CH=), 139.7 (C=), 142.0 (C=).

(1*S*,2*S*)-1-(Phenylthio)-2,3-dihydro-1*H*-inden-2-ol (6). Yield: 373 mg (77%), white solid. SiO_2-chromatography (gradient from cyclohexane/EtOAc = 100:0 to cyclohexane/EtOAc = 80:20). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 2.09 (bs, 1H, OH), 2.82 (dd, 1H, CH_2, $^2J_{H-H}$ =16.3, $^3J_{H-H}$ =3.5 Hz), 3.32 (dd, 1H, CH_2, $^2J_{H-H}$ =16.3, $^3J_{H-H}$ =6.2 Hz), 4.50 (dt, 1H, CH-O, $^3J_{H-H}$ =6.2 Hz, $^3J_{H-H}$ =3.4 Hz), 4.55 (d, 1H, CH-S, $^3J_{H-H}$ =3.3 Hz), 7.19-7.24 (m, 4H, CH=), 7.26-7.31 (m, 2H, CH=), 7.34-7.37 (m, 1H, CH=), 7.40-7.43 (m, 2H, CH=).^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 39.9 (CH_2), 59.1 (CH-S), 79.6 (CH-O), 125.2 (CH=), 125.7 (CH=), 126.9 (CH=), 127.2 (CH=), 128.3 (CH=), 129.0 (CH=), 130.9 (CH=), 135.2 (CH=), 139.9 (CH=), 135.2 (C=), 139.9 (C=), 140.6 (C=).

(1*S*,2*S*)-1-((2,6-Dimethylphenyl)thio)-2,3-dihydro-1*H*-inden-2-ol (7). Yield: 427 mg (79%), white solid. SiO_2-chromatography (gradient from cyclohexane/EtOAc = 100:0 to cyclohexane/EtOAc = 80:20). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.75 (bs, 1H, OH), 2.47 (s, 6H, CH_3), 2.82 (dd, 1H, CH_2, $^2J_{H-H}$ =16.6, $^3J_{H-H}$ =2.1 Hz), 3.52 (dd, 1H, CH_2, $^2J_{H-H}$ =16.6, $^3J_{H-H}$ =5.5 Hz), 4.32 (d, 1H, CH-S, $^3J_{H-H}$ =2.0 Hz), 4.36 (tt, 1H, CH-O, $^3J_{H-H}$ =5.5 Hz, $^3J_{H-H}$ =2.1 Hz), 6.94 (d, 1H, CH=, $^3J_{H-H}$ =7.5 Hz), 7.06-7.16 (m, 4H, CH=), 7.18-7.26 (m, 2H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 21.9 (CH_3), 40.3 (CH_2), 58.8 (CH-S), 78.5 (CH-O), 125.3 (CH=), 125.4 (CH=), 126.7 (CH=), 128.1 (CH=), 128.2 (CH=), 128.7 (CH=), 132.0 (CH=), 140.4 (C=), 140.7 (C=), 143.6 (C=).

(1*S*,2*S*)-1-((4-(Trifluoromethyl)phenyl)thio)-2,3-dihydro-1*H*-inden-2-ol (8). Yield: 478 mg (77%), yellow oil. SiO_2-chromatography (gradient from cyclohexane/EtOAc = 100:0 to cyclohexane/EtOAc = 80:20). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 2.06 (d, 1H, OH, $^3J_{H-H}$ =4.9 Hz), 2.91 (dd, 1H, CH_2, $^2J_{H-H}$ =16.5, $^3J_{H-H}$ =3.5 Hz), 3.42 (dd, 1H, CH_2, $^2J_{H-H}$ =16.5, $^3J_{H-H}$ =6.0 Hz), 4.55 (m, 1H, CH-O), 4.69 (d, 1H, CH-S, $^3J_{H-H}$ =3.2 Hz), 7.21-7.30 (m, 3H, CH=), 7.36-7.41 (m, 1H, CH=), 7.46-7.57 (m, 4H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 40.2 (CH_2), 58.0 (CH-S), 78.6 (CH-O), 124.1 (CH=), 125.4 (CH=), 125.7 (CH=), 125.8 (q, CH=, $^3J_{H-F}$ =3.8 Hz), 127.4 (CH=), 128.2 (q, C=, $^2J_{H-F}$ =32.8 Hz), 128.7 (CH=), 128.8 (CH=), 139.0 (C=), 140.6 (C=), 141.3 (C=).

(1*S*,2*S*)-1-((4-Methoxyphenyl)thio)-2,3-dihydro-1*H*-inden-2-ol (9). Yield: 541 mg (79%), yellow oil. SiO_2-chromatography (gradient from cyclohexane/EtOAc = 100:0 to cyclohexane/EtOAc = 75:25). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.97 (d, 1H, OH, $^3J_{H-H}$ =5.2 Hz), 2.81 (dd, 1H, CH_2, $^2J_{H-H}$ =16.3, $^3J_{H-H}$ =3.5 Hz), 3.25 (dd, 1H, CH_2, $^2J_{H-H}$ =16.3, $^3J_{H-H}$ =6.1 Hz), 3.79 (s, 3H, CH_3O), 4.38 (d, 1H, CH-S, $^3J_{H-H}$ =3.3 Hz), 4.50 (tt, 1H, CH-O, $^3J_{H-H}$ =6.1 Hz, $^3J_{H-H}$ =3.5 Hz), 6.82 (d, 2H, CH=, $^3J_{H-H}$ =8.7 Hz), 7.19-7.27 (m, 3H, CH=), 7.35-7.42 (m, 3H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 39.9 (CH_2), 55.3 (CH-S), 60.6 (CH_3O), 78.6 (CH-O), 114.6 (CH=), 124.4 (CH=), 125.2 (CH=), 125.6 (CH=), 127.0 (CH=), 128.1 (CH=), 135.1 (C=), 140.2 (C=), 140.6 (C=), 159.6 (C=).

3.5.4.3. General procedure for the preparation of phosphite-tioether ligands L51-L57a-c

The corresponding phosphorochloridite (1.1 mmol) produced in situ was dissolved in toluene (5 mL), and pyridine (0.3 mL, 3.9 mmol) was added. The corresponding thioether-hydroxyl compound (1 mmol) was azeotropically dried with toluene (3 x 2 mL) and then dissolved in toluene (5 mL) to which pyridine (0.3 mL, 3.9 mmol) was added. The alcohol solution was transferred slowly to a solution of phosphorochloridite. The reaction mixture was stirred at 80°C for 90 min, after which the pyridine salts were removed by filtration. Evaporation of the solvent gave a white foam, which was purified by flash chromatography in silica (Hexane/Toluene/NEt_3 = 7/3/1) to produce the corresponding ligand as a white solid.

L51a. Yield: 320.8 mg (50%). ^{31}P NMR (161.9 MHz, C_6D_6): δ=141.5 (s). ^{1}H NMR (400 MHz, C_6D_6): δ=1.09 (d, 3H, CH_3, ^{i}Pr, $^3J_{H-H}$ =6.4 Hz), 1.07 (d, 3H, CH_3, ^{i}Pr, $^3J_{H-H}$ =6.8 Hz), 1.26 (s, 9H, CH_3, ^{t}Bu), 1.28 (s, 9H, CH_3, ^{t}Bu), 1.54 (s, 9H, CH_3, ^{t}Bu), 1.56 (s, 9H, CH_3, ^{t}Bu), 2.90-2.96 (m, 2H, CH_2, CH ^{i}Pr), 3.23 (dd, 1H, CH_2, $^2J_{H-H}$ =16.4 Hz, $^3J_{H-H}$ =5.6 Hz), 4.57 (b, 1H, CH-S), 5.18 (m, 1H, CH-OP), 6.94-7.12 (m, 3H, CH=), 7.31 (s, 1H, CH=), 7.33 (d, 1H, CH=, $^4J_{H-H}$ =2.8 Hz), 7.34 (d, 1H, CH=, $^4J_{H-H}$ =2.4 Hz), 7.57 (d, 1H, CH=, $^4J_{H-H}$ =2.4 Hz), 7.59 (d, 1H, CH=, $^4J_{H-H}$ =2.4 Hz), ^{13}C NMR (100.6 MHz, C_6D_6): δ=23.4 (CH_3, ^{i}Pr), 23.8 (CH_3, ^{i}Pr), 31.0 (d, CH_3, ^{t}Bu, J_{C-P} =7.6 Hz), 31.1 (CH_3, ^{t}Bu), 34.2 (C, ^{t}Bu), 34.9 (C, ^{t}Bu), 35.3 (CH, ^{i}Pr), 39.1 (CH_2), 54.7 (CH-S), 82.8 (CH-OP), 124.1-146.6 (aromatic carbons). MS HR-ESI [found 669.3498, $C_{40}H_{55}O_3PS$ (M-Na)$^+$ requires 669.3502].

L51b. Yield: 220.8 mg (37%). ^{31}P NMR (161.9 MHz, C_6D_6): δ=130.2 (s). ^{1}H NMR (400 MHz, C_6D_6): δ=1.03 (d, 3H, CH_3, ^{i}Pr, $^3J_{H-H}$ =6.8 Hz), 1.23 (d, 3H, CH_3, ^{i}Pr, $^3J_{H-H}$ =6.4 Hz), 1.49 (s, 9H, CH_3, ^{t}Bu), 1.53 (s, 9H, CH_3, ^{t}Bu), 1.64 (s, 3H, CH_3), 1.76 (s, 3H, CH_3), 2.01 (s, 3H, CH_3), 2.07 (s, 3H, CH_3), 2.71-2.77 (m, 1H, CH, ^{i}Pr), 2.88 (d, 1H, CH_2, $^2J_{H-H}$ =16.4 Hz), 3.27 (dd, 1H, CH_2, $^2J_{H-H}$ =16.4 Hz, $^3J_{H-H}$ =4.8 Hz), 4.81 (b, 1H, CH-S), 4.92 (m, 1H, CH-OP), 6.89-7.12 (m, 3H, CH=), 7.19 (m, 2H, CH=), 7.35 (d, 1H, CH=, $^3J_{H-H}$ =8.8 Hz). ^{13}C NMR (100.6 MHz, C_6D_6): δ=16.3 (CH_3), 16.6 (CH_3), 20.0 (CH_3), 20.1 (CH_3), 23.3 (CH_3, ^{i}Pr), 24.2 (CH_3, ^{i}Pr), 31.3 (CH_3, ^{t}Bu), 31.4 (d, CH_3, ^{t}Bu, J_{C-P} =5.3 Hz), 34.6 (C, ^{t}Bu), 34.7 (C, ^{t}Bu), 34.8 (CH, ^{i}Pr), 39.3 (CH_2), 55.0 (CH-S), 82.9 (CH-OP), 124.9-146.4 (aromatic carbons). MS HR-ESI [found 613.2903, $C_{36}H_{47}O_3PS$ (M-Na)$^+$ requires 613.2876].

L51c. Yield: 202.0 mg (34%). ^{31}P NMR (161.9 MHz, C_6D_6): δ=139.4 (s). ^{1}H NMR (400 MHz, C_6D_6): δ=1.09 (d, 3H, CH_3, ^{i}Pr, $^3J_{H-H}$ =6.8 Hz), 1.12 (d, 3H, CH_3, ^{i}Pr, $^3J_{H-H}$ =6.8 Hz), 1.47 (s, 9H, CH_3, ^{t}Bu), 1.61 (s, 9H, CH_3, ^{t}Bu), 1.69 (s, 3H, CH_3), 1.75 (s, 3H, CH_3), 2.05 (s, 6H, CH_3), 2.85-2.91 (m, 1H, CH, ^{i}Pr), 3.37 (d, 1H, CH_2, $^2J_{H-H}$ =16.4 Hz), 3.38 (dd, 1H, CH_2, $^2J_{H-H}$ =16.8 Hz, $^3J_{H-H}$ =6.0 Hz), 4.24 (d, 1H, CH-S, $^3J_{H-H}$ =4.8 Hz), 5.07-5.11 (m, 1H, CH-OP), 6.95-7.03 (m, 3H, CH=), 7.18 (s, 1H, CH=), 7.23 (2H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ=16.3 (CH_3, ^{i}Pr), 16.5 (CH_3, ^{i}Pr), 20.1 (CH_3), 23.5 (CH_3), 23.9 (CH_3), 31.3 (CH_3, ^{t}Bu), 31.4 (d, CH_3, ^{t}Bu, J_{C-P} =5.3 Hz), 34.6 (C, ^{t}Bu), 34.8 (CH, ^{i}Pr), 39.7 (CH_2), 54.7 (CH-S), 82.7 (d, CH-OP, $^2J_{C-P}$ =6.1 Hz), 124.9-145.5 (aromatic carbons). MS HR-ESI [found 613.2869, $C_{36}H_{47}O_3PS$ (M-Na)$^+$ requires 613.2876].

L52c. Yield: 352.2 mg (59%). ^{31}P NMR (161.9 MHz, C_6D_6): δ=132.4 (s). ^{1}H NMR (400 MHz, C_6D_6): δ=0.82 (pt, 3H, CH_3, Pr, $^3J_{H-H}$ =7.2 Hz), 1.41-1.53 (m, 2H, CH_2, Pr), 1.53 (s, 9H, CH_3, ^{t}Bu), 1.58 (s, 9H, CH_3, ^{t}Bu), 1.69 (s, 3H, CH_3), 1.80 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 2.09 (s, 3H, CH_3),

2.23-2.30 (m, 1H, CH_2, Pr), 2.44-2.50 (m, 2H, CH_2, Pr), 2.93 (d, 1H, CH_2, $^2J_{H-H}$ =16.8 Hz), 3.25 (dd, 1H, CH_2, $^2J_{H-H}$ =16.4 Hz, $^3J_{H-H}$ =5.2 Hz), 4.72 (b, 1H, CH-S), 4.90-4.94 (m, 1H, CH-OP), 6.92 (d, 1H, CH=, $^3J_{H-H}$ =6.4 Hz), 7.00-7.03 (m, 2H, CH=), 7.22 (d, 2H, CH=, $^3J_{H-H}$ =8.0 Hz), 7.37 (d, 2H, CH=, $^3J_{H-H}$ =6.8 Hz). ^{13}C NMR (100.6 MHz, C_6D_6): δ=13.2 (CH_3, Pr), 16.2 (CH_3), 16.5 (CH_3), 20.0 (CH_3), 20.1 (CH_3), 23.0 (CH_2, Pr), 31.3 (CH_3, ^{t}Bu, J_{C-P} =5.3 Hz), 31.4 (CH_3, ^{t}Bu), 33.1 (CH_2, Pr), 34.6 (C, ^{t}Bu), 34.7 (C, ^{t}Bu), 39.2 (d, CH_2, $^3J_{C-P}$ =3.8 Hz), 56.1 (d, CH-S, $^3J_{C-P}$ =3.0 Hz), 82.4 (CH-OP), 124.8-146.1 (aromatic carbons). MS HR-ESI [found 613.2903, $C_{36}H_{47}O_3PS$ $(M-Na)^+$ requires 613.2876].

L53b. Yield: 283.6 mg (47%). ^{31}P NMR (161.9 MHz, C_6D_6): δ=134.2 (s). ^{1}H NMR (400 MHz, C_6D_6): δ=1.34 (s, 9H, CH_3, ^{t}Bu), 1.48 (s, 9H, CH_3, ^{t}Bu), 1.58 (s, 9H, CH_3, ^{t}Bu), 1.69 (s, 3H, CH_3), 1.74 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 2.06 (s, 3H, CH_3), 2.71 (d, 1H, CH_2, $^2J_{H-H}$ =16.0 Hz), 3.12 (dd, 1H, CH_2, $^2J_{H-H}$ =16.4 Hz, $^3J_{H-H}$ =5.2 Hz), 4.56 (b, 1H, CH-S), 5.22-5.25 (m, 1H, CH-OP), 6.83 (d, 1H, CH=, $^3J_{H-H}$ =7.2 Hz), 6.96-7.21 (m, 1H, CH=), 7.41 (d, 1H, CH=, $^3J_{H-H}$ =7.6 Hz). ^{13}C NMR (100.6 MHz, C_6D_6): δ=16.3 (CH_3), 16.5 (CH_3), 20.0 (CH_3), 20.1 (CH_3), 31.4 (CH_3, ^{t}Bu), 34.6 (C, ^{t}Bu), 34.7 (C, ^{t}Bu), 38.8 (CH_2), 43.5 (C, ^{t}Bu), 54.0 (d, CH-S, $^3J_{C-P}$ =3.8 Hz), 83.7 (CH-OP), 124.7-145.7 (aromatic carbons). MS HR-ESI [found 627.3026, $C_{37}H_{49}O_3PS$ $(M-Na)^+$ requires 627.3032].

L54b. Yield: 284.8 mg (41%). ^{31}P NMR (161.9 MHz, C_6D_6): δ=135.3 (s). ^{1}H NMR (400 MHz, C_6D_6): δ=1.44 (s, 9H, CH_3, ^{t}Bu), 1.51 (s, 9H, CH_3, ^{t}Bu), 1.69 (s, 3H, CH_3), 1.77 (s, 3H, CH_3), 2.06 (s, 3H, CH_3), 2.07 (s, 3H, CH_3), 2.73 (d, 1H, CH_2, $^2J_{H-H}$ =16.8 Hz), 2.93 (dd, 1H, CH_2, $^2J_{H-H}$ =17.2 Hz, $^3J_{H-H}$ =5.6 Hz), 4.95 (b, 1H, CH-S), 5.03-5.06 (m, 1H, CH-OP), 6.80-6.82 (m, 1H, CH=), 6.90-7.01 (m, 5H, CH=), 7.21 (d, 2H, CH=, $^3J_{H-H}$ =3.6 Hz), 7.27-7,29 (m, 3H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ=16.2 (CH_3), 16.5 (CH_3), 20.0 (CH_3), 20.1 (CH_3), 31.3 (CH_3, ^{t}Bu), 31.4 (CH_3, ^{t}Bu), 34.5 (C, ^{t}Bu), 34.6 (C, ^{t}Bu), 39.2 (d, CH_2, $^3J_{C-P}$ =3.0 Hz), 58.8 (d, CH-S, $^3J_{C-P}$ =3.8 Hz), 81.6 (d, CH-OP, $^2J_{C-P}$ =4.6 Hz), 124.8-145.7 (aromatic carbons). MS HR-ESI [found 647.2737, $C_{39}H_{45}O_3PS$ $(M-Na)^+$ requires 647.2719].

L55b. Yield: 324.6 mg (42%). ^{31}P NMR (161.9 MHz, C_6D_6): δ=135.7 (s). ^{1}H NMR (400 MHz, C_6D_6): δ=1.42 (s, 9H, CH_3, ^{t}Bu), 1.52 (s, 9H, CH_3, ^{t}Bu), 1.68 (s, 3H, CH_3), 1.79 (s, 3H, CH_3), 2.04 (s, 3H, CH_3), 2.08 (s, 3H, CH_3), 2.31 (s, 6H, CH_3), 2.90 (d, 1H, CH_2, $^2J_{H-H}$ =16.8 Hz), 3.38 (dd, 1H, CH_2, $^2J_{H-H}$ =16.8 Hz, $^3J_{H-H}$ =4.8 Hz), 4.80-4.83 (m, 1H, CH-OP), 4.91 (s, 1H, CH-S), 6.67 (d, 1H, CH=, $^3J_{H-H}$ =7.2 Hz), 6.83 (pt, 1H, CH=, $^3J_{H-H}$ =7.2 Hz), 6.88-7.03 (m, 5H, CH=), 719 (d, 1H, CH=, $^4J_{H-H}$ =2.4 Hz). ^{13}C NMR (100.6 MHz, C_6D_6): δ=16.2 (CH_3), 16.5 (CH_3), 20.0 (CH_3), 20.1 (CH_3), 21.7 (CH_3), 31.2 (CH_3, ^{t}Bu), 31.3 (d, CH_3, ^{t}Bu, J_{C-P} =5.4 Hz), 34.5 (C, ^{t}Bu), 34.6 (C, ^{t}Bu), 39.3 (d, CH_2, $^3J_{C-P}$ =3.8 Hz), 58.0 (d, CH-S, $^3J_{C-P}$ =3.8 Hz), 81.3 (d, CH-OP, $^2J_{C-P}$ =4.6 Hz), 124.8-145.6 (aromatic carbons). MS HR-ESI [found 675.3026, $C_{41}H_{49}O_3PS$ $(M-Na)^+$ requires 675.3032].

L55c. Yield: 276.4 mg (36%). ^{31}P NMR (161.9 MHz, C_6D_6): δ=137.5 (s). ^{1}H NMR (400 MHz, C_6D_6): δ=1.44 (s, 9H, CH_3, ^{t}Bu), 1.56 (s, 9H, CH_3, ^{t}Bu), 1.69 (s, 3H, CH_3), 1.74 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 2.06 (s, 3H, CH_3), 2.25 (s, 6H, CH_3), 3.19 (d, 1H, CH_2, $^2J_{H-H}$ =16.8 Hz), 3.50 (dd, 1H, CH_2, $^2J_{H-H}$ =17.2 Hz, $^3J_{H-H}$ =4.8 Hz), 4.60 (b, 1H, CH-S), 4.93 (m, 1H, CH-OP), 6.46 (d, 1H, CH=, $^3J_{H-H}$ =7.2 Hz), 6.79 (m, 1H, CH=), 6.86-7.22 (m, 6H, CH=), 7.22 (s, 1H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ=16.2 (CH_3), 16.4 (CH_3), 20.0 (CH_3), 20.7 (CH_3), 31.3 (CH_3, ^{t}Bu), 34.5 (C, ^{t}Bu), 34.6 (C, ^{t}Bu), 40.2 (d, CH_2, $^3J_{C-P}$ =3.0 Hz), 57.5 (d, CH-S, $^3J_{C-P}$ =3.8 Hz), 81.0 (d, CH-OP, $^3J_{C-P}$ =7.6

Hz), 124.8-145.5 (aromatic carbons). MS HR-ESI [found 675.3041, $C_{41}H_{49}O_3PS$ $(M-Na)^+$ requires 675.3032].

L56b. Yield: 336.1 mg (52%). ^{31}P NMR (161.9 MHz, C_6D_6): δ=135.6 (s). ^1H NMR (400 MHz, C_6D_6): δ=1.41 (s, 9H, CH_3, ^{t}Bu), 1.47 (s, 9H, CH_3, ^{t}Bu), 1.69 (s, 3H, CH_3), 1.74 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 2.06 (s, 3H, CH_3), 2.67 (d, 1H, CH_2, $^2J_{H-H}$ =16.8 Hz), 2.99 (dd, 1H, CH_2, $^2J_{H-H}$ =16.8 Hz, $^3J_{H-H}$ =6.0 Hz), 4.92 (b, 1H, CH-S), 4.96-5.01 (m, 1H, CH-OP), 6.82-6.84 (m, 1H, CH=), 6.99-7.19 (m, 8H, CH=), 7.24-7.26 (m, 1H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ=16.9 (CH_3), 17.1 (CH_3), 20.6 (CH_3), 20.7 (CH_3), 31.9 (d, CH_3, ^{t}Bu, $^3J_{C-P}$ =5.3 Hz), 32.0 (CH_3,^{t}Bu), 35.2 (C,^{t}Bu), 35.3 (C,^{t}Bu), 39.6 (CH_2), 58.3 (d, CH-S, $^3J_{C-P}$ =3.8 Hz), 81.7 (d, CH-OP, $^3J_{C-P}$ =4.6 Hz), 125.7-146.2 (aromatic carbons). MS HR-ESI [found 715.2610, $C_{40}H_{44}F_3O_3PS$ $(M-Na)^+$ requires 715.2593].

L57b. Yield: 321 mg (49%). ^{31}P NMR (161.9 MHz, C_6D_6): δ=135.4 (s). ^1H NMR (400 MHz, C_6D_6): δ=1.47 (s, 9H, CH_3, ^{t}Bu), 1.55 (s, 9H, CH_3, ^{t}Bu), 1.71 (s, 3H, CH_3), 1.82 (s, 3H, CH_3), 2.07 (s, 3H, CH_3), 2.10 (s, 3H, CH_3), 2.78 (d, 1H, CH_2, $^2J_{H-H}$ =16.8 Hz), 2.87 (dd, 1H, CH_2, $^2J_{H-H}$ =16.8 Hz, $^3J_{H-H}$ =5.6 Hz), 3.16 (s, CH_3, *p*-OMe) 4.88 (b, 1H, CH-S), 5.04-5.07 (m, 1H, CH-OP), 6.54 (d, 2H, CH=, $^3J_{H-H}$ =8.8 Hz), 6.82 (d, 1H, CH=, $^3J_{H-H}$ =6.8 Hz), 6.96-7.23 (m, 6H, CH=), 7.31 (d, 1H, CH=, $^3J_{H-H}$ =7.2 Hz). ^{13}C NMR (100.6 MHz, C_6D_6): δ=16.7 (CH_3), 16.9 (CH_3), 20.4 (CH_3), 20.5 (CH_3), 31.7 (CH_3, ^{t}Bu), 31.8 (CH_3,^{t}Bu), 35.0 (C,^{t}Bu), 35.1 (C,^{t}Bu), 39.9 (CH_2), 54.8 (CH_3, *p*-MeO), 60.5 (d, CH-S, $^3J_{C-P}$ =3.8 Hz), 82.4 (d, CH-OP, $^3J_{C-P}$ =4.6 Hz), 114.7-160.4 (aromatic carbons). MS HR-ESI [found 677.2851, $C_{40}H_{47}O_4PS$ $(M-Na)^+$ requires 677.2825].

3.5.4.4. General procedure for the preparation of the phosphinite-thioether ligands L51e, L53e and L55e

The corresponding thioether-hydroxyl compound (0.5 mmol) and DMAP (6.7 mg, 0.055 mmol) were dissolved in toluene (1 ml), and triethylamine was added (0.09 ml, 0.65 mmol) at r.t, followed by the addition of the corresponding chlorophosphine (0.55 mmol) via syringe. The reaction was stirred for 20 min at r.t. The solvent was removed *in vacuo*, and the product was purified by flash chromatography on alumina (toluene/NEt_3 = 100/1) to produce the corresponding ligand as an oil.

L51e. Yield: 257.8 mg (61%). ^{31}P NMR (161.9 MHz, C_6D_6): δ=98.2 (s). ^1H NMR (400 MHz, C_6D_6): δ=1.08 (d, 3H, CH_3, ^{i}Pr, $^3J_{H-H}$ =6.8 Hz), 1.21 (d, 3H, CH_3, ^{i}Pr, $^3J_{H-H}$ =6.4 Hz), 2.37 (s, 3H, CH_3, *o*-Tol), 2.41 (s, 3H, CH_3, *o*-Tol), 2.91-3.01 (m, 2H, CH ^{i}Pr, CH_2), 3.30 (dd, 1H, CH_2, $^2J_{H-H}$ =16.4 Hz, $^3J_{H-H}$ =6.0 Hz), 4.49 (b, 1H, CH-S), 4.82 (m, 1H, CH-OP), 6.91-7.15 (m, 9H, CH=), 7.36 (d, 1H, CH=, $^3J_{H-H}$ =6.8 Hz), 7.52 (m, 2H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ=20.3 (d,CH_3, *o*-Tol, $^3J_{C-P}$ =4.0 Hz), 20.5 (d,CH_3, *o*-Tol, $^3J_{C-P}$ =4.4 Hz), 23.2 (CH_3, ^{i}Pr), 23.8 (CH_3, ^{i}Pr), 35.3 (CH, ^{i}Pr), 39.1 (d, CH_2, $^3J_{C-P}$ =6.1 Hz), 54.7 (d, CH-S, $^3J_{C-P}$ =6.1 Hz), 87.7 (d, CH-OP, $^2J_{C-P}$ =20,7 Hz), 124.8-141.4 (aromatic carbons).

L53e. Yield: 147,6 mg (31%). ^{31}P NMR (161.9 MHz, C_6D_6): δ=97.7 (s). ^1H NMR (400 MHz, C_6D_6): δ=1.24 (s, 9H, CH_3, ^{t}Bu), 2.32 (s, 3H, CH_3, *o*-Tol), 2.41 (s, 3H, CH_3, *o*-Tol), 2.92 (dd, 1H, CH_2, $^2J_{H-H}$ =16.4 Hz, $^3J_{H-H}$ =2.8 Hz), 3.22 (dd, 1H, CH_2, $^2J_{H-H}$ =16.0 Hz, $^3J_{H-H}$ =5.2 Hz), 4.40 (b, 1H, CH-S), 4.82-4.85 (m, 1H, CH-OP), 6.89-7.12 (m, 9H, CH=), 7.39 (d, 1H, CH=, $^3J_{H-H}$ =7.2 Hz), 7.50-7.54 (m, 2H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ=20.2 (d, CH_3, $^3J_{C-P}$ =15.3 Hz), 20.4 (d, CH_3, $^3J_{C-P}$ =16.0 Hz), 31.3 (CH_3, ^{t}Bu), 39.0 (d, CH_2, $^3J_{C-P}$ =6.0 Hz), 43.4 (C, ^{t}Bu), 53.6 (d, CH-S, $^3J_{C-}$

$_P$ =6.8 Hz), 88.5 (d, CH-OP, $^3J_{C-P}$ =20.6 Hz), 124.6-142.3 (aromatic carbons). MS HR-ESI [found 457.1731, $C_{27}H_{31}OPS$ $(M-Na)^+$ requires 457.1725].

L55e. Yield: 260.6 mg (54%). ^{31}P NMR (161.9 MHz, C_6D_6): δ=98.5 (s). ^{1}H NMR (400 MHz, C_6D_6): δ=2.30 (s, 3H, CH_3, *o*-Tol), 2.35 (s, 3H, CH_3, *o*-Tol), 2.44 (s, 6H, CH_3), 3.14 (d, 1H, CH_2, $^2J_{H-H}$ =16.8 Hz), 3.54 (dd, 1H, CH_2, $^2J_{H-H}$ =16.8 Hz, $^3J_{H-H}$ =5.2 Hz), 4.78-4.82 (m, 1H, CH-OP), 4.83 (b, 1H, CH-S), 6.91-7.14 (m, 12H, CH=), 7.23 (s, 1H, CH=), 7.32-7.35 (m, 1H, CH=), 7.40-7.44 (m, 1H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ=20.1 (d, CH_3, $^3J_{C-P}$ =6.1 Hz), 20.3 (d, CH_3, $^3J_{C-P}$ =6.8 Hz), 21.7 (CH_3), 39.4 (d, CH_2, $^3J_{C-P}$ =6.9 Hz), 58.0 (d, CH-S, $^3J_{C-P}$ =6.9 Hz), 85.7 (d, CH-OP, $^3J_{C-P}$ =5.4 Hz), 124.9-143.5 (aromatic carbons).

3.5.4.5. Typical Procedure for the Preparation of [Ir(cod)(L)]BAr_F (L=L51–L57a–e)

The corresponding ligand (0.037 mmol) was dissolved in CH_2Cl_2 (2 mL) and [Ir(μ-Cl)(cod)]$_2$ (12.5 mg, 0.0185 mmol) was added. The reaction mixture was refluxed at 50 °C for 1 hour. After 5 min at room temperature, $NaBAr_F$ (38.6 mg, 0.041 mmol) and water (2 mL) were added and the reaction mixture was stirred vigorously for 30 min at room temperature. The phases were separated and the aqueous phase was extracted twice with CH_2Cl_2. The combined organic phases were dried with $MgSO_4$, filtered through a plug of celite and the solvent was evaporated to give the product as red-orange solids.

[Ir(cod)(L51a)]BAr_F. Yield: 67 mg (92%). ^{31}P NMR (161.9 MHz, C_6D_6): δ=114.1 (s). ^{1}H NMR (400 MHz, C_6D_6): δ=1.36 (s, 9H, CH_3, ^{t}Bu), 1.37 (s, 9H, CH_3, ^{t}Bu), 1.49 (s, 9H, CH_3, ^{t}Bu), 1.55 (s, 9H, CH_3, ^{t}Bu), 1.63 (d, 6H, CH_3, ^{i}Pr, $^3J_{H-H}$ =6.8 Hz), 1.91-2.10 (m, 5H, CH_2, cod), 2.22-2.27 (m, 3H, CH_2, cod), 3.02 (dd, 1H, CH_2, $^2J_{H-H}$ =14.8 Hz, $^3J_{H-H}$ =9.6 Hz), 3.26 (dd, 1H, CH_2, $^2J_{H-H}$ =15.2 Hz, $^3J_{H-H}$ =7.6 Hz), 3.68-3.75 (m, 1H, CH, ^{i}Pr), 4.25 (d, 1H, CH-S, $^3J_{H-H}$ =18.8 Hz), 4.47 (b, 1H, CH=, cod), 4.76 (b, 1H, CH=, cod), 4.98-5.07 (m, 1H, CH-OP), 5.09 (b, 1H, CH= cod), 5.43 (b, 1H, CH=, cod), 7.16-7.71 (m, 20H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ=24.6 (CH_3, ^{i}Pr), 25.6 (CH_3, ^{i}Pr), 28.4 (b, CH_2, cod), 29.9 (CH_2, cod), 30.9 (b, CH_2, cod), 31.3 (CH_3, ^{t}Bu), 31.5 (CH_3, ^{t}Bu), 31.8 (CH_3, ^{t}Bu), 33.6 (b, CH_2, cod), 35.0 (C, ^{t}Bu), 35.5 (C, ^{t}Bu), 35.6 (C, ^{t}Bu), 37.5 (d, CH_2, $^3J_{C-P}$ =7.6 Hz), 48.3 (b, CH, ^{i}Pr), 55.0 (CH-S), 75.7 (b, CH=, cod), 78.4 (b, CH=, cod), 82.5 (CH-OP), 100.8 (b, CH=, cod), 104.3 (b, CH=, cod), 117.6-149.1 (aromatic carbons), 161.9 (q, C-B, BAr_F, $^1J_{C-B}$ =49.7 Hz). MS HR-ESI [found 947.4136 $C_{48}H_{67}IrO_3PS$ $(M)^+$ requires 947.4172].

[Ir(cod)(L51b)]BAr_F. Yield: 60 mg (93%). ^{31}P NMR (161.9 MHz, C_6D_6): δ=108.8 (s). ^{1}H NMR (400 MHz, C_6D_6): δ=1.03 (d, 3H, CH_3, ^{i}Pr, $^3J_{H-H}$ =6.4 Hz), 1.41 (s, 9H, CH_3, ^{t}Bu), 1.50 (d, 3H, CH_3, ^{i}Pr, $^3J_{H-H}$ =6.8 Hz), 1.54 (s, 9H, CH_3, ^{t}Bu), 1.78 (s, 3H, CH_3), 1.79 (s, 3H, CH_3), 1.93-2.15 (m, 6H, CH_2, cod), 2.25 (b, 2H, CH_2, cod), 2.27 (s, 6H, CH_3), 2.89 (dd, 1H, CH_2, $^2J_{H-H}$ =15.2 Hz, $^3J_{H-H}$ =8.8 Hz), 3.35 (dd, 1H, CH_2, $^2J_{H-H}$ =15.6 Hz, $^3J_{H-H}$ =8.4 Hz), 3.61-3.77 (m, 1H, CH, ^{i}Pr), 3.86 (b, 1H, CH=, cod), 4.53 (d, 1H, CH-S, $^3J_{H-H}$ =11.2 Hz), 4.97 (b, 1H, CH=, cod), 5.06-5.13 (m, 2H, CH-OP, CH= cod), 5.37 (b, 1H, CH=, cod), 7.20-7.70 (m, 18H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ=16.5 (CH_3), 16.8 (CH_3), 20.3 (CH_3), 20.4 (CH_3), 24.7 (CH_3, ^{i}Pr), 24.9 (CH_3, ^{i}Pr), 28.9 (CH_2, cod), 30.0 (CH_2, cod), 31.8 (CH_3, ^{t}Bu), 32.1 (CH_3, ^{t}Bu), 32.3 (CH_2, cod), 32.5 (d, CH_2, cod, J_{C-P} =4.6 Hz), 34.7 (C, ^{t}Bu), 34.8 (C, ^{t}Bu), 38.2 (d, CH_2, $^3J_{C-P}$ =6.8 Hz), 44.7 (CH, ^{i}Pr), 55.1 (CH-S), 71.9 (CH=, cod), 79.2 (CH-OP), 81.5 (CH=, cod), 98.0 (CH=, cod, J_{C-P} =16.9 Hz),

106.7 (CH=, cod, $J_{C\text{-}P}$ =13.2 Hz), 117.4-145.0 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^1J_{C\text{-}B}$ =49.7 Hz). MS HR-ESI [found 891.3519, $C_{44}H_{59}IrO_3PS$ $(M)^+$ requires 891.3546].

[Ir(cod)(L51c)]BAr_F. Yield: 62 mg (95%). ^{31}P NMR (161.9 MHz, C_6D_6): δ=111.1 (s). ^{1}H NMR (400 MHz, C_6D_6): δ=1.43 (s, 9H, CH_3, ^{t}Bu), 1.56 (s, 9H, CH_3, ^{t}Bu), 1.60 (d, 3H, CH_3, ^{i}Pr, $^3J_{H\text{-}H}$ =6.8 Hz), 1.63 (d, 3H, CH_3, ^{i}Pr, $^3J_{H\text{-}H}$ =6.8 Hz), 1.77 (s, 3H, CH_3), 1.82 (s, 3H, CH_3), 1.82-1.91 (m, 2H, CH_2, cod), 2.03-2.15 (m, 4H, CH_2, cod), 2.22 (b, 2H, CH_2, cod), 2.28 (s, 6H, CH_3), 3.09 (dd, 1H, CH_2, $^2J_{H\text{-}H}$ =15.2 Hz, $^3J_{H\text{-}H}$ =9.2 Hz), 3.28 (dd, 1H, CH_2, $^2J_{H\text{-}H}$ =15.6 Hz, $^3J_{H\text{-}H}$ =8.0 Hz), 3.63-3.70 (m, 1H, CH, ^{i}Pr), 3.85 (b, 1H, CH=, cod), 4.22 (d, 1H, CH-S, $^3J_{H\text{-}H}$ =8.8 Hz), 4.86 (b, 1H, CH=, cod), 4.92-4.98 (m, 1H, CH-OP), 5.03 (b, 1H, CH= cod), 5.41 (b, 1H, CH=, cod), 7.22-7.72 (m, 18H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ=16.5 (CH_3), 20.3 (CH_3), 24.0 (CH_3, ^{i}Pr), 25.6 (CH_3, ^{i}Pr), 28.1 (CH_2, cod), 29.7 (CH_2, cod), 30.6 (CH_2, cod), 31.2 (CH_3, ^{t}Bu), 32.0 (CH_3, ^{t}Bu), 33.3 (d, CH_2, cod, $J_{C\text{-}P}$ =4.0 Hz), 34.7 (C, ^{t}Bu), 37.4 (d, CH_2, $^3J_{C\text{-}P}$ =8.9 Hz), 48.2 (CH, ^{i}Pr), 54.4 (CH-S), 72.5 (CH=, cod), 79.9 (CH=, cod), 83.0 (d, CH-OP, $^3J_{C\text{-}P}$ =5.5 Hz), 99.3 (CH=, cod, $J_{C\text{-}P}$ =17.2 Hz), 104.6 (CH=, cod, $J_{C\text{-}P}$ =10.8 Hz), 117.4-144.7 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^1J_{C\text{-}B}$ =50.0 Hz). MS HR-ESI [found 891.3518, $C_{44}H_{59}IrO_3PS$ $(M)^+$ requires 891.3546].

[Ir(cod)(L51d)]BAr_F. Yield: 54 mg (93%). ^{31}P NMR (161.9 MHz, C_6D_6): δ=107.7 (s). ^{1}H NMR (400 MHz, C_6D_6): δ=1.37 (d, 6H, CH_3, ^{i}Pr, $^3J_{H\text{-}H}$ =6.8 Hz), 1.95 -2.15 (m, 8H, CH_2, cod), 2.72 (b, 1H, CH, ^{i}Pr), 3.56 (dd, 1H, CH_2, $^2J_{H\text{-}H}$ =14.8 Hz, $^3J_{H\text{-}H}$ =9.2 Hz), 3.53-3.59 (m, 2H, CH_2, CH= cod), 3.85 (b, 1H, CH=, cod), 4.22 (b, 1H, CH-S), 4.99 (b, 1H, CH=, cod), 5.11 (b, 1H, CH-OP), 5.23 (b, 1H, CH=, cod), 7.32-7.74 (m, 26H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ=24.4 (CH_3, ^{i}Pr), 24.8 (CH_3, ^{i}Pr), 29.5 (CH_2, cod), 30.5 (CH_2, cod), 31.9 (CH_2, cod), 32.7 (CH_2, cod), 38.0 (d, CH_2, $^3J_{C\text{-}P}$ =10.6 Hz), 48.5 (b, CH, ^{i}Pr), 57.2 (CH-S), 98.2 (b, CH=, cod), 106.7 (CH=, cod, $J_{C\text{-}P}$ =16.9 Hz), 117.6-136.8 (aromatic carbons), 161.8 (q, C-B, BAr_F, $^1J_{C\text{-}B}$ =49.7 Hz). MS HR-ESI [found 693.1915, $C_{32}H_{37}IrOPS$ $(M)^+$ requires 693.1926].

[Ir(cod)(L51e)]BAr_F. Yield: 54 mg (92%). ^{31}P NMR (161.9 MHz, C_6D_6): δ=116.0 (s). ^{1}H NMR (400 MHz, C_6D_6): δ=1.42 (m, 6H, CH_3 ^{i}Pr, CH_3 *o*-Tol), 1.57 (s, 3H, CH_3, *o*-Tol), 1.63 (d, 3H, CH_3, ^{i}Pr, $^3J_{H\text{-}H}$ =5.2 Hz), 1.78 (b, CH_2, cod), 2.05-2.36 (m, 6H, CH_2, cod), 2.85 (b, 1H, CH=, cod), 2.97 (b, 1H, CH, ^{i}Pr), 3.18-3.24 (m, 1H, CH_2), 3.41-3.44 (m, 1H, CH_2), 3.82 (b, 1H, CH=, cod), 3.92 (b, 1H, CH-S), 3.99 (b, 1H, CH=, cod), 4.62-4.83 (b, 1H, CH=, cod), 5.09 (b, 1H, CH-OP), 5.35 (b, 1H, CH=, cod), 6.52-8.34 (m, 24H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ=21.5 (CH_3, *o*-Tol), 22.2 (CH_3, *o*-Tol), 24.2 (CH_3, ^{i}Pr), 24.4 (CH_3, ^{i}Pr), 27.5 (CH_2, cod), 29.8 (CH_2, cod), 32.2 (CH_2, cod), 34.2 (CH_2, cod), 37.5 (CH_2), 49.8 (b, CH, ^{i}Pr), 57.6 (CH-S), 75.9 (CH=, cod), 77.2 (b, CH-OP), 87.4 (b, CH=, cod), 93.6 (b, CH=, cod), 101.0 (b, CH=, cod), 117.4-143.1 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^1J_{C\text{-}B}$ =49.7 Hz). MS HR-ESI [found 721.2243, $C_{34}H_{41}IrOPS$ $(M)^+$ requires 721.2240].

[Ir(cod)(L52b)]BAr_F. Yield: 62 mg (93%). ^{31}P NMR (161.9 MHz, C_6D_6): δ=107.9 (s). ^{1}H NMR (400 MHz, C_6D_6): δ=0.98 (t, 3H, CH_3, Pr, $^3J_{H\text{-}H}$ =6.8 Hz), 1.42 (s, 9H, CH_3, ^{t}Bu), 1.55 (s, 9H, CH_3, ^{t}Bu), 1.57-1.67 (m, 2H, CH_2, Pr), 1.78 (s, 3H, CH_3), 1.82 (s, 3H, CH_3), 1.94-1.99 (m, 2H, CH_2, cod), 2.04 (m, 2H, CH_2, cod), 2.18 (m, 2H, CH_2, cod), 2.22-2.30 (m, 2H, CH_2, cod), 2.28 (s, 3H, CH_3), 2.29 (s, 3H, CH_3), 2.77-2.81 (m, 2H, CH_2, Pr), 2.95 (dd, 1H, CH_2, $^2J_{H\text{-}H}$ =15.2 Hz, $^3J_{H\text{-}H}$ =9.2 Hz), 3.34 (dd, 1H, CH_2, $^2J_{H\text{-}H}$ =15.6 Hz, $^3J_{H\text{-}H}$ =7.6 Hz), 3.44 (b, 1H, CH=, cod), 4.43 (d, 1H, CH-S, $^3J_{H\text{-}H}$ =8.8 Hz), 4.93-5.01 (m, 2H, CH-OP, CH= cod), 5.05-5.09 (m, 1H, CH= cod), 5.31 (b, 1H, CH=, cod), 7.22-7.70 (m, 18H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ=13.2 (CH_3, Pr),

16.5 (CH_3), 16.7 (CH_3), 20.3 (CH_3), 20.4 (CH_3), 21.8 (CH_2,Pr), 29.2 (CH_2, cod), 29.5 (CH_2, cod), 31.9 (CH_3 ^tBu, CH_2 cod), 32.3 (CH_3, ^tBu), 33.1 (CH_2, cod), 34.9 (C, ^tBu), 37.3 (CH_2, Pr), 38.1 (d, CH_2, $^3J_{C\text{-}P}$ =6.8 Hz), 53.8 (CH-S), 70.9 (CH=, cod), 79.3 (CH-OP), 82.1 (CH=, cod), 98.5 (CH=, cod, $J_{C\text{-}P}$ =17.5 Hz), 108.8 (CH=, cod, $J_{C\text{-}P}$ =14.6 Hz), 117.4-137.0 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^1J_{C\text{-}B}$ =50.5 Hz). MS HR-ESI [found 889.3509, $C_{44}H_{59}IrO_3PS$ $(M)^+$ requires 889.3523].

[Ir(cod)(L54b)]BAr_F. Yield: 61 mg (93%). ^{31}P NMR (161.9 MHz, C_6D_6): δ=104.4 (s). ^1H NMR (400 MHz, C_6D_6): δ=1.49 (s, 9H, CH_3, ^tBu), 1.59 (s, 9H, CH_3, ^tBu), 1.63-1.91 (m, 4H, CH_2, cod), 1.75 (s, 3H, CH_3), 1.85 (s, 3H, CH_3), 2.12-2.35 (m, 4H, CH_2, cod), 2.29 (s, 6H, CH_3), 2.89 (b, 1H, CH=, cod), 3.00 (dd, 1H, CH_2, $^2J_{H\text{-}H}$ =14.8 Hz, $^3J_{H\text{-}H}$ =9.6 Hz), 3.37 (dd, 1H, CH_2, $^2J_{H\text{-}H}$ =15.6 Hz, $^3J_{H\text{-}H}$ =8.0 Hz), 4.19 (m, 1H, CH=, cod), 4.67 (m, 1H, CH=, cod), 4.81-4.91 (m, 1H, CH-OP), 5.17 (b, 1H, CH=, cod), 5.21 (d, 1H, CH-S, $^3J_{H\text{-}H}$ =9.6 Hz), 6.23-7.74 (m, 23H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ=16.4 (CH_3), 16.6 (CH_3), 20.2 (CH_3), 20.5 (CH_3), 26.4 (CH_2, cod), 29.9 (CH_2, cod), 31.1 (CH_2, cod), 31.8 (CH_3 ^tBu), 32.8 (CH_3, ^tBu), 34.7 (CH_2, cod), 35.0 (C, ^tBu), 35.2 (C, ^tBu), 37.8 (d, CH_2, $^3J_{C\text{-}P}$ =7.4 Hz), 55.9 (CH-S), 67.9 (CH=, cod), 78.6 (CH=, cod), 79.4 (CH-OP), 101.2 (CH=, cod, $J_{C\text{-}P}$ =14.5 Hz), 106.0 (CH=, cod, $J_{C\text{-}P}$ =15.3 Hz), 117.4-143.6 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^1J_{C\text{-}B}$ =50.4 Hz). MS HR-ESI [found 923.3367, $C_{47}H_{57}IrO_3PS$ $(M)^+$ requires 923.3366].

[Ir(cod)(L55b)]BAr_F. Yield: 64 mg (95%). ^{31}P NMR (161.9 MHz, C_6D_6): δ=104.1 (s). ^1H NMR (400 MHz, C_6D_6): δ=1.47 (s, 9H, CH_3, ^tBu), 1.60 (s, 9H, CH_3, ^tBu), 1.65-1.84 (m, 4H, CH_2, cod), 1.76 (s, 3H, CH_3), 1.86 (s, 3H, CH_3), 2.13-2.36 (m, 4H, CH_2, cod), 2.29 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 2.56 (s, 3H, CH_3), 2.72 (m, 1H, CH=, cod), 2.95 (dd, 1H, CH_2, $^2J_{H\text{-}H}$ =15.2 Hz, $^3J_{H\text{-}H}$ =9.6 Hz), 3.08 (s, 3H, CH_3), 3.38 (dd, 1H, CH_2, $^2J_{H\text{-}H}$ =15.2 Hz, $^3J_{H\text{-}H}$ =7.6 Hz), 3.92 (m, 1H, CH=, cod), 4.72 (m, 1H, CH=, cod), 4.89 (m, 1H, CH-OP), 5.12 (d, 1H, CH-S, $^3J_{H\text{-}H}$ =8.8 Hz), 5.18 (b, 1H, CH=, cod), 6.08-7.70 (m, 21H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ=16.4 (CH_3), 16.6 (CH_3), 20.3 (CH_3), 20.5 (CH_3), 22.8 (CH_3), 22.9 (CH_3), 25.7 (CH_2, cod), 30.5 (CH_2, cod), 31.0 (CH_2, cod), 31.8 (CH_3 ^tBu), 32.7 (CH_3, ^tBu), 35.0 (CH_2, cod), 35.2 (C, ^tBu), 37.8 (d, CH_2, $^3J_{C\text{-}P}$ =7.6 Hz), 53.7 (CH-S), 66.2 (CH=, cod), 77.7 (CH=, cod), 80.0 (CH-OP), 102.1 (CH=, cod, $J_{C\text{-}P}$ =13.8 Hz), 104.6 (CH=, cod, $J_{C\text{-}P}$ =16.1 Hz), 117.4-143.8 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^1J_{C\text{-}B}$ =49.7 Hz). MS HR-ESI [found 951.3674, $C_{49}H_{61}IrO_3PS$ $(M)^+$ requires 951.3679].

[Ir(cod)(L55c)]BAr_F. Yield: 63 mg (94%). ^{31}P NMR (161.9 MHz, C_6D_6): δ=108.7 (s). ^1H NMR (400 MHz, C_6D_6): δ=1.41 (s, 9H, CH_3, ^tBu), 1.59 (s, 9H, CH_3, ^tBu), 1.71-1.89 (m, 4H, CH_2, cod), 1.71 (s, 3H, CH_3), 1.73 (s, 3H, CH_3), 1.97-2.20 (m, 4H, CH_2, cod), 2.21 (s, 3H, CH_3), 2.22 (s, 3H, CH_3), 2.24 (s, 3H, CH_3), 2.75 (s, 3H, CH_3), 2.99-3.08 (m, 2H, CH_2, CH= cod), 3.31 (dd, 1H, CH_2, $^2J_{H\text{-}H}$ =15.6 Hz, $^3J_{H\text{-}H}$ =8.4 Hz), 4.26 (m, 1H, CH=, cod), 4.67 (m, 1H, CH=, cod), 4.74 (m, 1H, CH=, cod), 4.80 (d, 1H, CH-S, $^3J_{H\text{-}H}$ =8.8 Hz), 5.31-5.35 (m, 1H, CH-OP), 5.88-7.63 (m, 21H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ=16.7 (CH_3), 16.8 (CH_3), 20.5 (CH_3), 20.6 (CH_3), 23.5 (CH_3), 24.3 (CH_3), 27.6 (CH_2, cod), 29.8 (d, CH_2, cod, $J_{C\text{-}P}$ =10.0 Hz), 31.8 (CH_3 ^tBu), 32.1 (CH_2, cod), 32.9 (CH_3, ^tBu), 34.2 (CH_2, cod), 35.0 (C, ^tBu), 35.4 (C, ^tBu), 37.4 (d, CH_2, $^3J_{C\text{-}P}$ =9.2 Hz), 56.4 (CH-S), 67.3 (CH=, cod), 77.4 (CH=, cod), 86.3 (d, CH-OP, $^2J_{C\text{-}P}$ =6.0 Hz), 103.4 (CH=, cod, $J_{C\text{-}P}$ =14.8 Hz), 104.7 (CH=, cod, $J_{C\text{-}P}$ =13.9 Hz), 117.6-144.6 (aromatic carbons), 161.9 (q, C-B, BAr_F, $^1J_{C\text{-}B}$ =50.1 Hz). MS HR-ESI [found 951.3641, $C_{49}H_{61}IrO_3PS$ $(M)^+$ requires 951.3679].

[Ir(cod)(L55d)]BAr_F. Yield: 55 mg (92%). ^{31}P NMR (161.9 MHz, C_6D_6): δ=114.3 (s). ^1H NMR (400 MHz, C_6D_6): δ=1.75-1.86 (m, 2H, CH_2, cod), 1.93-2.01 (m, 2H, CH_2, cod), 2.10-2.19

(m, 1H, CH_2, cod), 2.20-2.40 (m, 3H, CH_2, cod), 2.57 (s, 3H, CH_3), 3.02 (s, 3H, CH_3), 3.07 (dd, 1H, CH_2, $^2J_{H-H}$ =15.6 Hz, $^3J_{H-H}$ =9.6 Hz), 3.19 (dd, 1H, CH_2, $^2J_{H-H}$ =15.6 Hz, $^3J_{H-H}$ =8.0 Hz), 3.27 (m, 1H, CH=, cod), 3.41 (m, 1H, CH=, cod), 3.97 (m, 1H, CH=, cod), 4.49-4.58 (m, 1H, CH-OP), 5.05 (d, 1H, CH-S, $^3J_{H-H}$ =8.4 Hz), 5.11 (m, 1H, CH=, cod), 6.09-7.94 (m, 29H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ=23.2 (CH_3), 23.6 (CH_3), 27.3 (CH_2, cod), 30.7 (CH_2, cod), 31.0 (CH_2, cod), 33.6 (CH_2, cod), 38.3 (d, CH_2, $^3J_{C-P}$ =7.6 Hz), 52.9 (CH-S), 69.3 (CH=, cod), 74.9 (CH=, cod), 82.5 (CH-OP), 97.2 (CH=, cod, J_{C-P} =10.0 Hz), 98.6 (CH=, cod, J_{C-P} =13.0 Hz), 117.4-144.7 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^1J_{C-B}$ =49.7 Hz).

[Ir(cod)(L55e)]BAr_F. Yield: 56 mg (96%). ^{31}P NMR (161.9 MHz, C_6D_6): δ=118.2 (s). ^{1}H NMR (400 MHz, C_6D_6): δ=1.68-1.85 (m, 2H, CH_2, cod), 1.95-2.19 (m, 2H, CH_2, cod), 2.23 (s, 3H, CH_3), 2.25-2.47 (m, 4H, CH_2, cod), 2.53 (s, 3H, CH_3), 2.92 (s, 4H, CH= cod, CH_3), 3.03 (dd, 1H, CH_2, $^2J_{H-H}$ =15.6 Hz, $^3J_{H-H}$ =9.6 Hz), 3.15 (s, 3H, CH_3), 3.15-3.20 (m, 2H, CH= cod, CH_2), 3.75 (m, 1H, CH=, cod), 4.32-4.41 (m, 1H, CH-OP), 5.08 (b, 1H, CH=, cod), 5.24 (d, 1H, CH-S, $^3J_{H-H}$ =8.4 Hz), 5.89-9.06 (m, 27H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ=21.8 (CH_3), 22.3 (d, CH_3, $^3J_{C-P}$ =6.9 Hz), 23.1 (CH_3), 26.7 (CH_2, cod), 29.9 (CH_2, cod), 31.7 (CH_2, cod), 34.3 (CH_2, cod), 38.3 (d, CH_2, $^3J_{C-P}$ =7.6 Hz), 52.0 (CH-S), 67.9 (CH=, cod), 77.2 (CH=, cod), 81.4 (CH-OP), 96.5 (CH=, cod, J_{C-P} =9.2 Hz), 96.8 (CH=, cod, J_{C-P} =13.8 Hz), 117.4-143.5 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^1J_{C-B}$ =49.7 Hz).

[Ir(cod)(L56b)]BAr_F. Yield: 69 mg (97%). ^{31}P NMR (161.9 MHz, C_6D_6): δ=104.1 (s). ^{1}H NMR (400 MHz, C_6D_6): δ=1.49 (s, 9H, CH_3, ^{t}Bu), 1.58 (s, 9H, CH_3, ^{t}Bu), 1.61-1.91 (m, 4H, CH_2, cod), 1.76 (s, 3H, CH_3), 1.85 (s, 3H, CH_3), 2.08-2.38 (m, 4H, CH_2, cod), 2.29 (s, 6H, CH_3), 2.99-3.05 (m, 2H, CH_2, CH= cod), 3.39 (dd, 1H, CH_2, $^2J_{H-H}$ =15.2 Hz, $^3J_{H-H}$ =7.6 Hz), 4.10 (m, 1H, CH=, cod), 4.76 (b, 1H, CH=, cod), 4.84-4.92 (m, 1H, CH-OP), 5.13 (b, 1H, CH=, cod), 5.23 (d, 1H, CH-S, $^3J_{H-H}$ =9.2 Hz), 6.23-7.89 (m, 22H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ=16.4 (CH_3), 16.6 (CH_3), 20.2 (CH_3), 20.4 (CH_3), 26.6 (CH_2, cod), 29.8 (CH_2, cod), 31.2 (CH_2, cod), 31.8 (CH_3 ^{t}Bu), 32.8 (CH_3, ^{t}Bu), 34.5 (CH_2, cod), 35.0 (C, ^{t}Bu), 35.2 (C, ^{t}Bu), 37.7 (CH_2), 56.1 (CH-S), 68.9 (CH=, cod), 79.3 (CH=, cod), 79.7 (CH-OP), 100.9 (CH=, cod, J_{C-P} =13.7 Hz), 105.4 (CH=, cod, J_{C-P} =15.3 Hz), 117.4-143.5 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^1J_{C-B}$ =49.7 Hz). MS HR-ESI [found 991.3222, $C_{48}H_{56}F_3IrO_3PS$ $(M)^+$ requires 991.3240].

[Ir(cod)(L57b)]BAr_F. Yield: 64 mg (95%). ^{31}P NMR (161.9 MHz, C_6D_6): δ=104.7 (s). ^{1}H NMR (400 MHz, C_6D_6): δ=1.49 (s, 9H, CH_3, ^{t}Bu), 1.58 (s, 9H, CH_3, ^{t}Bu), 1.65-1.94 (m, 4H, CH_2, cod), 1.75 (s, 3H, CH_3), 1.85 (s, 3H, CH_3), 2.06-2.37 (m, 4H, CH_2, cod), 2.29 (s, 6H, CH_3), 2.86 (m, 1H, CH= cod), 2.98 (dd, 1H, CH_2, $^2J_{H-H}$ =15.2 Hz, $^3J_{H-H}$ =9.6 Hz), 3.36 (dd, 1H, CH_2, $^2J_{H-H}$ =15.2 Hz, $^3J_{H-H}$ =8.0 Hz), 3.84 (s, 3H, CH_3, MeO), 4.28-4.36 (m, 1H, CH=, cod), 4.67 (b, 1H, CH=, cod), 4.79-4.88 (m, 1H, CH-OP), 5.12 (d, 1H, CH-S, $^3J_{H-H}$ =9.2 Hz), 5.16 (b, 1H, CH=, cod), 6.31-7.70 (m, 22H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ=16.4 (CH_3), 16.6 (CH_3), 20.2 (CH_3), 20.5 (CH_3), 26.3 (CH_2, cod), 30.0 (CH_2, cod), 31.0 (CH_2, cod), 31.8 (CH_3 ^{t}Bu), 32.8 (CH_3, ^{t}Bu), 34.9 (CH_2, cod), 35.0 (C, ^{t}Bu), 35.2 (C, ^{t}Bu), 37.8 (d, CH_2, $^3J_{C-P}$ =8.1 Hz), 55.6 (CH_3, MeO), 56.2 (CH-S), 67.7 (CH=, cod), 78.5 (CH=, cod), 79.4 (CH-OP), 101.3 (CH=, cod, J_{C-P} =14.4 Hz), 106.0 (CH=, cod, J_{C-P} =16.3 Hz), 116.2-163.4 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^1J_{C-B}$ =50.5 Hz). MS HR-ESI [found 955.3512, $C_{48}H_{56}F_3IrO_3PS$ $(M)^+$ requires 955.3501].

3.5.5. Acknowledgements

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3.5.6. References

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3.6. The application of pyranoside phosphite-pyridine ligands to enantioselective Ir-catalyzed hydrogenations of highly unfunctionalized olefins

Jèssica Margalef, Matteo Lega, Francesco Ruffo, Oscar Pàmies and Montserrat Diéguez in *Tetrahedron: Asymmetry* **2012**, *23*, 945.

Abstratct*: Eight (biaryl)phosphite/pyridine ligands (**L59**-**60a**-**d**) have been prepared by modular functionalization of positions C-2 and C-3 of two D-glucopyranoside backbones. The chiral auxiliaries have been examined in the iridium-catalyzed asymmetric hydrogenation of poorly functionalized alkenes, as a function of the relative position of the coordinating groups and the geometric properties of the biaryl phosphite moieties. Ee's up to 90% were achieved in the hydrogenation of (E)-2-(4-methoxyphenyl)-2-butene by using **L59a** and **L59c**, which seemingly combine the beneficial effect of the phosphite in position 2 with the matching (R)-configuration of their encumbered biaryl susbstituents. The results of the hydrogenation of more challenging substrates (i.e. (Z)-trisubstituted alkenes, alkenes with a neighboring polar group or demanding 1,1-di-substituted alkenes) generally confirmed this trend, and, in some significant cases, the chiral hydrogenated products were isolated with ee's within 65-79%.*

3.6.1. Introduction

The increasing demand for enantiomerically pure pharmaceuticals, agrochemicals, flavors and other fine chemicals has advanced the field of asymmetric catalytic technologies. Asymmetric hydrogenation utilizing molecular hydrogen to reduce prochiral olefins has become one of the most reliable catalytic methods for the preparation of optically active compounds.[1] Over many years the scope of this reaction has gradually extended in terms of reactant structure and catalyst efficiency. Nowadays, an impressive number of chiral phosphine ligands have been developed and successfully applied in Rh- and Ru-catalyzed hydrogenation.[1] However, the range of olefins that can be hydrogenated with high enantiomeric excess is limited, because rhodium and ruthenium catalysts require the presence of a coordinating group next to the C=C bond.[1] With minimally funtionalized olefins these catalysts generally show low reactivity and unsatisfactory enantioselectivity.[1] In this context, Pfaltz introduced a new class of hydrogenation catalysts, iridium complexes with chiral N,P ligands, which overcome these limitations.[2-4] The first successful P,N ligands[5] contained a phosphine or phosphinite moiety as P-donor group and either an oxazoline,[5b,g,j] oxazole,[5d] thiazole[5i] or pyridine[5c] as N-donor group. However, these iridium-phosphine/phosphinite,N catalysts were still highly substrate-dependent and the development of efficient chiral ligands that tolerate a broader range of substrates remained a challenge. Some years ago we discovered that the presence of biaryl-phosphite moieties in these P,N-ligands provides greater substrate versatility than previous Ir-phosphine/phosphinite,N catalyst systems.[6]

In our efforts to expand the range of ligands and improve performance, we herein report the first application of phosphite-pyridine ligands in the Ir-catalyzed asymmetric hydrogenation of minimally funtionalized olefins (Figure 3.6.1). These ligands combine a priori the advantages of both types of successful ligands for this process (phosphite and pyridine). Ligands **L59**-**60a**-**d** have also the advantage of carbohydrates and phosphite ligands, such as availability at low price from readily available alcohols, facile modular constructions and high resistance to oxidation.[7] Therefore, with these ligands we fully investigated the effects of systematically varying the position of the phosphite group at both C-2 (ligands **59**) or C-3 (ligands **60**) of the pyranoside backbone, as well as the effects of different substituents and configurations in the biaryl phosphite moiety (**a**-**d**) with the aim to maximize catalyst performance.

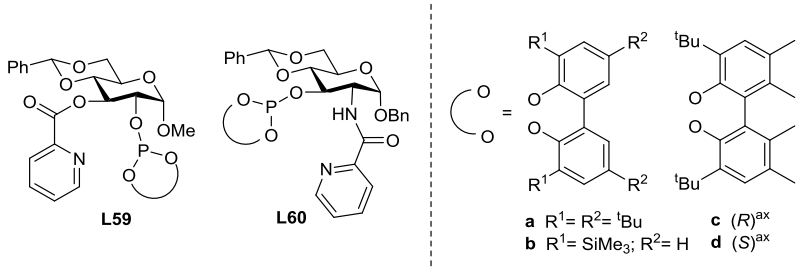
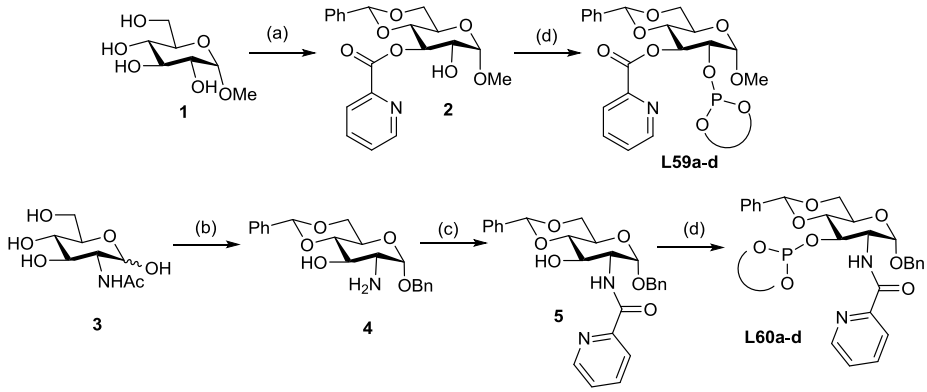


Figure 3.6.1. Carbohydrate-based phosphite-pyridine ligands **L59**-**60a**-**d**.

3.6.2. Results and discussion

3.6.2.1. Synthesis of phosphite-pyridine ligands

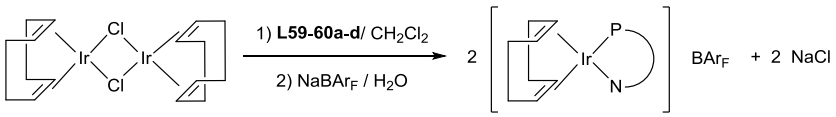
The new ligands **L59**-**L60a-d** were synthesized efficiently in one step from the corresponding pyridil-alcohols **2** and **5**, which are easily prepared on a large scale from methyl-α-D-glucopyranoside (**1**) and *N*-acetyl-D-glucosamine (**3**), respectively, using standard procedures (Scheme 3.6.1).[8] Reaction of **2** and **5** with one equivalent of the corresponding phosphorochloridite in dry toluene, under argon and in the presence of pyridine, provided the desired ligands **L59**-**60a**-**d**. All of the ligands were stable during purification on neutral alumina under an argon atmosphere and could be isolated in moderate yields as white solids. Rapid ring inversions (tropoisomerization) in the biphenyl-phosphorus moieties (**a**-**b**) occurred on the NMR time scale since the expected diastereoisomers were not detected by low-temperature ^{31}P NMR.[9]



Scheme 3.6.1. Synthesis of phosphite-pyridine ligands **L59**-**60a**-**d**. a) ref 8a. b) ref 8b. c) DMAP, picolinic acid, DCC. d) ClP(OR)2; (OR)2 = a-d / Py / Toluene.

3.6.2.2. Synthesis of the Ir-catalyst precursors

The catalyst precursors were made by refluxing a dichloromethane solution of the appropriate ligand in the presence of 0.5 equivalent of $[Ir(\mu\text{-}Cl)cod]_2$ for 1 h and then exchanging the counterion with sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate ($NaBAr_F$) (1 equiv), in the presence of water (Scheme 3.6.2Scheme 3.6.2).



Scheme 3.6.2. Synthesis of catalyst precursors [Ir(cod)(**L59**-**60a**-**d**)]BAr_F.

All complexes were isolated as air-stable orange solids and were used without further purification. The complexes were characterized by elemental analysis and ^{1}H, ^{13}C, and ^{31}P NMR spectroscopy. The spectral assignments were based on data from ^{1}H-^{1}H and ^{13}C-^{1}H correlation measurements and were as expected for these C_1 iridium complexes. The elemental analysis of C, H, N matched the stoichiometry $[Ir(cod)(P\text{-}N)]_n(BAr_F)_n$.

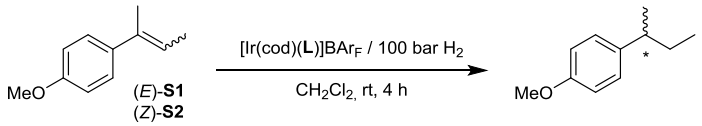
For all complexes, variable temperature NMR measurements (from +40 °C to -80 °C) indicate that only one isomer was present in solution. In this context, the ^{31}P- NMR spectra showed one sharp signal. The ^{1}H and ^{13}C NMR showed four signals for the olefinic protons and four signals for the olefinic carbon atoms of the coordinated cyclooctadiene, as expected for C_1-symmetrical complexes. Two of the four signals, those located *trans* to the phosphorus atom, appeared shifted to a lower field. The ^{13}C NMR spectra also showed the expected four signals of the methylenic carbons of the cyclooctadiene, except for complexes containing ligands **L59c** and **L60c** in which only three signals were observed. This is probably due to an overlap of the signals. The signals from the phosphite-pyridine ligands in these complexes produced the expected ^{1}H and ^{13}C NMR pattern for the gluco-pyranoside nucleus.

3.6.2.3. Asymmetric hydrogenation

In a first set of experiments we used the Ir-catalyzed hydrogenation of substrate (*E*)-2-(4-methoxyphenyl)-2-butene **S1** to study the potential of phosphite-pyridine ligands **L59**-**L60a**-**d**. Substrate **S1** was chosen as a model for the hydrogenation of trisubstituted olefins because it has been reduced with a wide range of ligands, which enable the efficiency of the various ligand systems to be compared directly.[2] The results, which are summarized in Table 3.6.1, indicate that enantioselectivities are highly affected by the position of the phosphite moiety at either C-2 (ligands **L59**) or C-3 (ligands **L60**) of the pyranoside backbone as well as the substituents/configuration of the biaryl phosphite moiety.

With ligands **L59** and **L60**, we studied how the position of the phosphite moiety affects the product outcome. The results indicate an important effect at both activity and enantioselectivity. Therefore, ligands **L59** with the phosphite group attached at C-2 provided in general higher activities and enantioselectivities than when ligands **L60** were used (Table 3.6.1, entries 1-4 *vs* 5-7).

Table 3.6.1. Results for the Ir-catalyzed hydrogenation of **S1** using ligands **L59**-**L60a**-**d**.[a]



Entry	L	Substrate	% Conv	%ee[b]	Entry	L	Substrate	% Conv	%ee[b]
1	**L59a**	**S1**	100	88 (*S*)	9[d]	**L59a**	**S1**	89	90 (*S*)
2	**L59b**	**S1**	100	15 (*S*)	10	**L59a**	**S2**	100	0
3	**L59c**	**S1**	100	79 (*S*)	11	**L59b**	**S2**	100	0
4	**L59d**	**S1**	100	11 (*R*)	12	**L59c**	**S2**	84	23 (*S*)
5	**L60a**	**S1**	82	2 (*R*)	13	**L59d**	**S2**	69[e]	38 (*R*)
6	**L60c**	**S1**	75	15 (*R*)	14	**L60a**	**S2**	28	2 (*S*)
7	**L60d**	**S1**	62	3 (*S*)	15	**L60c**	**S2**	85[f]	0
8[c]	**L59a**	**S1**	100	88 (*S*)	16	**L60d**	**S2**	43[g]	0

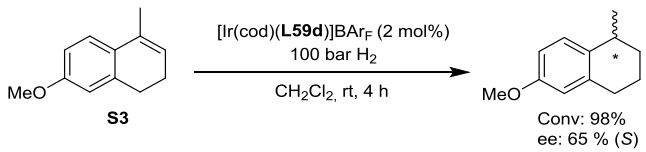
[a] Reactions carried out using 0.5 mmol of substrate and 2 mol% of Ir-catalyst precursor. [b] Conversion and enantiomeric excesses determined by chiral GC. [c] Reaction carried out at 0.5 mol% of Ir-catalyst precursor. [d] Reaction carried out at 5 °C. [e] 9% of **S1** observed. [f] 15% of **S1** observed. [g] 23% of **S1** observed.

We next investigated the effect of the substituents/configuration at the biaryl phosphite moiety. We found that for ligands **L59**, in which the phosphite moiety is attached to C-2, the presence of bulky *tert*-butyl groups at the *para* positions of the biphenyl phosphite moiety are crucial for high enantioselectivity (Table 3.6.1, entry 1 vs 2). We also observed a cooperative effect between the position of the phosphite moiety (at either C-3 or C-2) and the configuration of the biaryl phosphite group (Table 3.6.1, entries 3, 4, 6 and 7). This effect was seen for ligand **L59c**, which contains an (*R*)-biaryl phosphite moiety attached to C-2 (Table 3.6.1, entry 3). Moreover, by comparing the results of tropoisomeric ligands (**a**-**b**) with those of enantiopure ones (**c**-**d**) we can conclude that if enantioselectivity has to be high, tropoisomerization has to be avoided upon coordination in the active species. For instance, ligands **L59** efficiently control the tropoisomerization of the biaryl phosphite moiety when bulky *tert*-butyl substituents at both *ortho* and *para* positions of the biaryl phosphite moiety are present. The biphenyl moiety adopts an (*R*)-configuration

in the active species (Table 3.6.1, entries 1 *vs* 3 and 4). In a similar way, the low enantioselectivity obtained when using ligand **L59b** (Table 3.6.1, entry 2) can be explained by the lack of appropriate substituents at the *para* position of the biphenyl moiety to prevent the tropoisomerization of the biphenyl unit.

The best enantioselectivities (ee's up to 88%; Table 3.6.1, entry 1) were obtained when using ligand **L59a**, which has the appropriate combination of ligand parameters. The enantioselectivity can also be improved by controlling not only the structural but also the reaction parameters. In this case, enantioselectivity was further improved (ee's up to 90%) with Ir- **L59a** catalyst precursor by lowering the reaction temperature to 5 °C (Table 3.6.1, entry 9). We also performed the reaction at low catalyst loading (0.5 mol%) using Ir- **L59a** catalyst precursor (entry 8) and the high enantioselectivity and activity were maintained.

In order to assess the potential of ligands **L59**-**60a**-**d** for the more demanding (*Z*)-isomers, which are usually hydrogenated less enantioselectively than the corresponding (*E*)-isomers, we chose (*Z*)-2-(4-methoxyphenyl)-2-butene **S2** as the model substrate. However, low enantioselectivities were obtained (Table 3.6.1, entries 10-16). A plausible explanation for this could be the competition between direct hydrogenation *vs* (*Z*)/(*E*)-isomerisation of the substrate. The hydrogenation of the (*E*)-isomer produces the opposite configuration of the hydrogenated product to that when (*Z*)-isomer is hydrogenated,[2] which results in low enantioselectivity. This is supported by the presence of high amounts of **S1** in the reaction mixture (i.e. 23% of **S1** was observed using Ir-**60d** catalytic system after 4 hours). In this respect we next decided to evaluate these ligands in the hydrogenation of 7-methoxy-4-methyl-1,2-dihydronaphthalene **S3** (Scheme 3.6.3), which has a (*Z*)-configuration and for which (*Z*)/(*E*)-isomerization is not possible. Enantioselectivities up to 65% were obtained when using the Ir-**L59d** catalyst precursor.



Scheme 3.6.3. Asymmetric hydrogenation of **S3**.

We next studied the asymmetric hydrogenation of trisubstituted olefins **S4**-**S6** containing a neighbouring polar group. These substrates are interesting because they allow for further functionalization and are therefore important synthons for the synthesis of more complex chiral molecules. The results are summarized in Figure 3.6.2. The reduction of these substrates follows the same trend as those observed for the previous (*E*)-trisubstituted substrate **S1**. Again the highest enantioselectivities were obtained using the Ir-**L59a** catalyst precursor. High enantioselectivities were obtained in the hydrogenation of α,β-unsaturated ester **S4** (ee's up to 79%). Conversely, the reduction of allylic alcohol **S5** and allylic acetate **S6** provided lower enantioselectivity (ee's up to 48%).

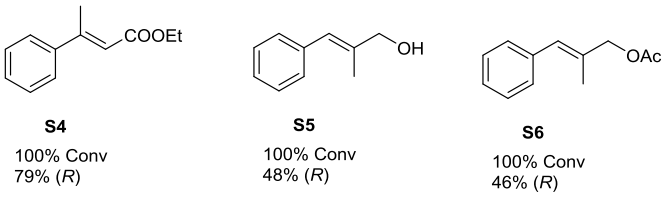


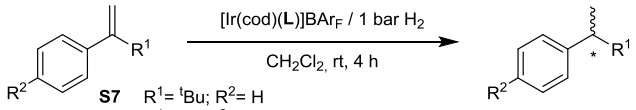
Figure 3.6.2. Selected hydrogenation results of other trisubstituted olefins using [Ir(cod)(**L59a**)]BAr_F catalyst precursor. Reaction conditions: 2 mol % catalyst precursor, CH_2Cl_2 as solvent, 100 bar H_2, 4 h.

Next, we screened ligands **L59**-**60a**-**d** in the asymmetric hydrogenation of more demanding terminal olefins. Enantioselectivity was more difficult to control in these substrates than in trisubstituted olefins. There are two main reasons for this:[2d,e] a) the two substituents in the substrate can easily exchange positions in the chiral environment formed by the catalysts, thus reversing the face selectivity; and b) the terminal double bond can isomerize to form the more stable internal alkene, which usually leads to the predominant formation of the opposite enantiomer of the hydrogenated product.

Initially we used the Ir-catalyzed hydrogenation of 3,3-dimethyl-2-phenyl-1-butene **S7**. The results using ligands **L59**-**60a**-**d** are shown in Table 3.6.2. Enantioselectivities were again affected by the position of the phosphite moietiy at either C-2 or C-3 of the pyranoside backbone as well as the substituents/configuration of the biaryl phosphite moiety. However the effect of these ligand parameters was different from the effect observed in the reduction of trisubstituted olefins. Thus, the presence of enantiopure biaryl phosphite moiety has a very positive effect on the enantioselectivity (ee's increased from 38% for Ir-**L59a** to 65% for Ir-**L59c**; Table 3.6.2, entries 1 *vs* 3). The cooperative effect between the position of the phosphite and the configuration of the biaryl group is also present, but in this case, both enantiomers of the hydrogenated product can be obtained in good enantioselectivities (ligand **L59c** affords 65% (*S*) and ligand **L60d** affords 72% (*R*)). The best enantioselectivities were therefore obtained using catalyst precursor Ir-**L60d** (ee's up to 72%, Table 3.6.2, entry 7).

Finally, we investigated the asymmetric hydrogenation of other 1,1-disubstituted aryl-alkyl substrates with the ligands containing the enantiopure biphenyl moieties (**L59**-**60c**-**d**). The results indicated that enantioselectivity is highly affected by the nature of the alkyl chain (ee's ranging from 16% to 72%, Table 3.6.2, entry 7 *vs* 12) and less affected by the electronic nature of the aryl ring (Table 3.6.2, entry 9 *vs* 12). One plausible explanation can be found in the competition between direct hydrogenation *vs* isomerization for the different substrates. This is supported by the high amounts of isomerized internal olefin observed in all cases for substrates **S8**-**S11**.

Table 3.6.2. Results for the Ir-catalyzed hydrogenation of **S7**-**S11** using phosphite-pyridine ligands **L59**-**60a**-**d**.[a]



S7 R^1= ^{t}Bu; R^2= H
S8 R^1= Et; R^2= 4-OMe
S9 R^1= Et; R^2= 4-CF_3
S10 R^1= ^{t}Bu; R^2= H
S11 R^1= Bu; R^2= H

Entry	Ligands	Substrate	% Conv[b]	%ee[b]
1	**L59a**	**S7**	100	38 (S)
2	**L59b**	**S7**	100	31 (S)
3	**L59c**	**S7**	100	65 (S)
4	**L59d**	**S7**	100	15 (R)
5	**L60a**	**S7**	100	33 (S)
6	**L60c**	**S7**	100	38 (S)
7	**L60d**	**S7**	100	72 (R)
8	**L59c**	**S8**	99[c]	16 (R)
9	**L59d**	**S8**	98[d]	20 (S)
10	**L60c**	**S8**	78[e]	3 (R)
11	**L60d**	**S8**	96[f]	3 (R)
12	**L59d**	**S9**	100[g]	16 (S)
13	**L59d**	**S10**	99[h]	20 (S)
14	**L59d**	**S11**	100[i]	23 (S)

[a] Reactions carried out using 0.5 mmol of substrate and 2 mol% of Ir-catalyst precursor.[b] Conversion and enantiomeric excesses determined by chiral GC. [c] 60% of **S1** observed. [d] 60% of **S1** observed. [e] 64% of **S1** observed. [f] 67% of **S1** observed. [g] 59% of internal olefin observed. [h] 41% of internal olefin observed. [i] 48% of internal olefin observed.

3.6.3. Conclusions

This work substantiates the versatile strategy aimed at preparing chiral ligands through immediate functionalization of common carbohydrates. Eight ligands (**L59**-**60a**-**d**) were prepared, whose ready availability along with an intrinsic modular nature allowed us refinine the structures by switching the coordinating functions between C-2 and C-3, and by introducing biaryl-phosphite moieties with different geometric properties. Application of the ligands in the enantioselective Ir-catalyzed hydrogenation of minimally functionalized alkenes disclosed a well-balanced combination in **L59a** and **L60c**, which seemingly couple the beneficial effect of the phosphite in position 2 with the matching (*R*)-configuration of their encumbered biaryl susbstituents. In this case, hydrogenation of (*E*)-2-(4-methoxyphenyl)-2-butene yielded the chiral product in 90% ee, and analogous beneficial synergy was generally recognised in the hydrogenation of more challenging substrates. Use of these ligands will be assessed also in other asymmetric reactions of relevant synthetic interest.

3.6.4. Experimental section

3.6.4.1. General considerations

All reactions were carried out using standard Schlenk techniques under an argon atmosphere. Solvents were purified and dried by standard procedures. Compounds **2** and **4** were prepared as previously described.[8] ^{1}H, ^{13}C{^{1}H}, and ^{31}P{^{1}H} NMR spectra were recorded using a 400 MHz spectrometer. Chemical shifts are relative to that of $SiMe_4$ (^{1}H and ^{13}C) as internal standard or H_3PO_4 (^{31}P) as external standard. ^{1}H and ^{13}C assignments were made on the basis of ^{1}H-^{1}H gCOSY and ^{1}H-^{13}C gHSQC experiments. All catalytic experiments were performed three times.

3.6.4.2. Synthesis of the intermediate 5

Intermediate **4** (0.715 g, 2.00 mmol) was dissolved in dry DCM, then DMAP (0.024 g, 0.20 mmol), picolinic acid (0.234 g, 1.90 mmol) and DCC (0.516 g, 2.50 mmol) were added. The system was stirred at RT overnight, then the mixture was filtrated. The product was purified by chromatography (EtOAc/PE=3/2) and precipitation (DCM/PE). Yield: 647 mg (70%). ^{1}H NMR ($CDCl_3$), δ: 8.60 (dd, 1H, CH=, $^{3}J_{H\text{-}H}$= 4.7 Hz, $^{3}J_{H\text{-}H}$= 0.8 Hz), 8.49 (d, 1H, NH, $^{3}J_{NH\text{-}2}$= 10.0 Hz), 8.17 (d, 1H, CH=, $^{3}J_{H\text{-}H}$= 7.8 Hz), 7.84 (td, 1H, CH=, $^{3}J_{H\text{-}H}$= 7.7Hz, $^{3}J_{H\text{-}H}$= 1.6 Hz), 7.55-7.20 (m, 10H, CH=), 5.58 (s, 1H, H-7), 4.99 (d, 1H, H-1, $^{3}J_{1\text{-}2}$ = 3.9 Hz), 4.78 (d, 1H, CH_2-Ph, $^{2}J_{H\text{-}H}$= 12.1 Hz), 4.57 (d, 1H, CH_2-Ph, $^{2}J_{H\text{-}H}$= 12.1 Hz), 4.42 (td, 1H, H-2, $^{3}J_{2\text{-}1}$= 3.9 Hz, $^{3}J_{2\text{-}3}$= $^{3}J_{2\text{-}NH}$= 10.0 Hz), 4.27 (dd, 1H, H-6, $^{2}J_{6\text{-}6'}$= 10.2 Hz, $^{3}J_{6\text{-}5}$= 4.9 Hz), 3.79 (t, 1H, H-3, $^{3}J_{3\text{-}4}$= $^{3}J_{3\text{-}2}$= 10.0 Hz), 3.96 (td, 1H, H-5, $^{3}J_{5\text{-}6}$= 4.9 Hz, $^{3}J_{5\text{-}4}$= $^{3}J_{6\text{-}6'}$= 10.2 Hz), 3.79 (t, 1H, H-6', $^{2}J_{6'\text{-}6}$= $^{3}J_{6'\text{-}5}$= 10.2 Hz), 3.68 (m, 1H, H-4); ^{13}C NMR ($CDCl_3$), δ: 165.1 (C=O), 149.1-122.6 (17 C, aromatics), 102.0 (C-7), 97.3 (C-1), 82.1 (C-4),70.5 (C-3), 69.9 (CH_2Ph), 68.9 (C-6), 62.7 (C-5), 54.2 (C-2).

3.6.4.3. Typical procedure for the preparation of ligands L59-60a-d

The corresponding phosphorochloridite (1.1 mmol) produced *in situ*[1] was dissolved in toluene (5 mL) and pyridine (0.3 mL, 3.9 mmol) was added. The corresponding pyridine-hydroxyl compound (1 mmol) was azeotropically dried with toluene (3 x 2 mL) and then dissolved in toluene (5 mL) to which pyridine (0.3 mL, 3.9 mmol) was added. The alcohol solution was transferred slowly to the solution of phosphorochloridite. The reaction mixture was stirred at 80 ºC for 90 min, and the pyridine salts were removed by filtration. Evaporation of the solvent gave a white foam, which was purified by flash chromatography in alumina (toluene/NEt3= 100/1) to produce the corresponding ligand as a white solid.

L59a. Yield: 489 mg (59%). ^{31}P NMR (C_6D_6), δ: 144.7. ^{1}H NMR (C_6D_6), δ: 1.25 (s, 9H, CH_3, ^{t}Bu), 1.29 (s, 9H, CH_3, ^{t}Bu), 1.57 (s, 9H, CH_3, ^{t}Bu), 1.63 (s, 9H, CH_3, tBu), 2.89 (s, 3H, CH_3, CH_3-O), 3.41 (m, 1H, H-6), 3.66 (m, 1H, H-4), 3.95 (m, 1H, H-5), 4.04 (dd, 1H, H-6', $^{3}J_{6'\text{-}6}$ = 10.0 Hz, $^{3}J_{6'\text{-}5}$ = 4.8 Hz), 4.13 (d, 1H, H-1, $^{3}J_{1\text{-}2}$ = 3.1 Hz), 5.02 (m, 1H, H-2), 5.05 (s, 1H, H-7), 6.43 (m, 1H, H-3), 6.5-8.4 (m, 13H, CH=). ^{13}C NMR (C_6D_6), δ: 31.0 (CH_3, ^{t}Bu), 31.1 (CH_3, ^{t}Bu), 31.1 (CH_3, ^{t}Bu), 31.2 (CH_3, ^{t}Bu), 34.3 (C, ^{t}Bu), 34.4 (C, ^{t}Bu), 35.3 (C, ^{t}Bu), 35.3 (C, ^{t}Bu), 54.3 (CH_3-O), 62.6 (C-5), 68.7 (C-6), 71.5 (d, C-3, $^{3}J_{C\text{-}P}$ = 4.2 Hz), 72.7 (C-2), 79.7 (C-4), 99.5 (C-1), 101.3 (C-7), 124-164 (aromatic carbons). Anal. calcd. (%) for $C_{48}H_{60}NO_9P$: C 69.80, H 7.32, N 1.70; found: C 69.78, H 7.30, N 1.69.

L59b. Yield: 265 mg (36%). ^{31}P NMR (C_6D_6), δ: 146.6. ^{1}H NMR (C_6D_6), δ: 0.48 (s, 9H, CH_3-Si), 0.50 (s, 9H, CH_3-Si), 2.82 (s, 3H, CH_3-O), 3.37 (m, 1H, H-6), 3.72 (m, 1H, H-4), 3.94 (m, 1H, H-5), 4.03 (dd, 1H, H-6', $^{3}J_{6'-6}$ = 10.0 Hz, $^{3}J_{6'-5}$ = 4.8 Hz), 4.24 (d, 1H, H-1, $^{3}J_{1-2}$ = 3.5 Hz), 4.88 (m, 1H, H-2), 5.05 (s, 1H, H-7), 6.40 (m, 1H, H-3), 6.5-8.4 (m, 13H, CH=). ^{13}C NMR (C_6D_6), δ: -0.1 (CH_3-Si), -0.2 (CH_3-Si), 54.5 (CH_3-O), 62.6 (C-5), 68.6 (C-6), 71.3 (d, C-3, $^{3}J_{C-P}$ = 4.3 Hz), 72.6 (d, C-2, $^{2}J_{C-P}$ = 3.7 Hz), 79.7 (C-4), 99.7 (C-1), 101.3 (C-7), 124-165 (aromatic carbons). Anal. calcd. (%) for $C_{38}H_{44}NO_9PSi_2$: C 61.19, H 5.95, N 1.88; found: C 61.21, H 5.98, N 1.86.

L59c. Yield: 261 mg (34%). ^{31}P NMR (C_6D_6), δ: 138.6. ^{1}H NMR (C_6D_6), δ: 1.56 (s, 9H, CH_3, ^{t}Bu), 1.62 (s, 9H, CH_3, ^{t}Bu), 1.65 (s, 3H, CH_3), 1.70 (s, 3H, CH_3), 2.01 (s, 3H, CH_3), 2.04 (s, 3H, CH_3), 2.84 (s, 3H, CH_3, CH_3-O), 3.35 (m, 1H, H-6), 3.62 (m, 1H, H-4), 3.91 (m, 1H, CH, H-5), 4.01 (dd, 1H, H-6', $^{3}J_{6'-6}$ = 10.4 Hz, $^{3}J_{6'-5}$ = 4.8 Hz), 4.38 (d, 1H, H-1, $^{3}J_{1-2}$ = 3.2 Hz), 4.89 (m, 1H, H-2), 5.09 (s, 1H, H-7), 6.34 (m, 1H, H-3), 6.5-8.4 (m, 11H, CH=). ^{13}C NMR (C_6D_6), δ: 16.9 (CH_3), 17.0 (CH_3), 20.6 (CH_3), 20.7 (CH_3), 32.0 (CH_3, ^{t}Bu), 32.1 (CH_3, ^{t}Bu), 35.3 (C, ^{t}Bu), 35.4 (C, ^{t}Bu), 55.1 (CH_3-O), 63.2 (C-5), 69.3 (C-6), 72.2 (C-3), 73.3 (C-2), 80.4 (C-4), 100.4 (C-1), 101.9 (C-7), 125-165 (aromatic carbons). Anal. calcd. (%) for $C_{44}H_{52}NO_9P$: C 68.65, H 6.81, N 1.82; found: C 68.68, H 6.82, N 1.80.

L59d. Yield: 315 mg (41%). ^{31}P NMR (C_6D_6), δ: 137.7. ^{1}H NMR (C_6D_6), δ: 1.54 (s, 3H, CH_3), 1.62 (s, 9H, CH_3, ^{t}Bu), 1.65 (s, 3H, CH_3), 1.67 (s, 9H, CH_3, ^{t}Bu), 2.02 (s, 6H, CH_3), 3.03 (s, 3H, CH_3, CH_3-O), 3.35 (m, 1H, H-6), 3.56 (m, 1H, H-4), 3.89 (m, 1H, CH, H-5), 4.02 (dd, 1H, H-6', $^{3}J_{6'-6}$ = 10.0 Hz, $^{3}J_{6'-5}$ = 4.8 Hz), 4.55 (m, 1H, H-2), 4.91 (d, 1H, H-1, $^{3}J_{1-2}$ = 3.6 Hz), 5.09 (s, 1H, H-7), 6.34 (m, 1H, H-3), 6.5-8.4 (m, 11H, CH=). ^{13}C NMR (C_6D_6), δ: 16.9 (CH_3), 20.7 (CH_3), 20.8 (CH_3), 31.9 (d, CH_3, ^{t}Bu, J_{C-P}= 8.5 Hz), 32.4 (CH_3, ^{t}Bu), 35.3 (C, ^{t}Bu), 35.7 (C, ^{t}Bu), 55.4 (CH_3-O), 63.2 (C-5), 69.2 (C-6), 71.2 (d, C-3, J_{C-P}= 9.8 Hz), 75.0 (d, C-2, J_{C-P}= 11.2 Hz), 80.3 (C-4), 100.0 (C-1), 101.9 (C-7), 125-165 (aromatic carbons). Anal. calcd. (%) for $C_{44}H_{52}NO_9P$: C 68.65, H 6.81, N 1.82; found: C 68.69, H 6.82, N 1.79.

L60a. Yield: 156 mg (18%). ^{31}P NMR (C_6D_6), δ: 147.7. ^{1}H NMR (C_6D_6), δ: 1.21 (s, 9H, CH_3, ^{t}Bu), 1.23 (s, 9H, CH_3, ^{t}Bu), 1.54 (s, 9H, CH_3, ^{t}Bu), 1.56 (s, 9H, CH_3, tBu), 3.53 (m, 1H, H-6), 3.79 (m, 1H, H-4), 4.07 (m, 2H, H-5 and H-6'), 4.15 (d, 1H, CH_2-Ph, $^{2}J_{H-H}$ = 12.0 Hz), 4.41 (d, 1H, CH_2-Ph, $^{2}J_{H-H}$ = 12.0 Hz), 4.79 (m, 1H, H-3), 5.13 (m, 1H, H-2), 5.31 (d, 1H, H-1, $^{3}J_{1-2}$ = 3.6 Hz), 5.42 (s, 1H, H-7), 6.53 (m, 1H, CH=), 6.9-7.1 (m, 10 H, CH=), 7.22 (d, 1H, CH=, J = 2.4 Hz), 7.54 (dd, 1H, CH=, J = 10.8 Hz, J = 2.8 Hz), 7.69 (d, 1H, CH=, $^{3}J_{H-H}$ = 7.2 Hz), 7.88 (m, 1H, NH), 8.01 (d, 1H, CH=, $^{3}J_{H-H}$ = 8.0 Hz), 8.82 (d, 1H, CH=, $^{3}J_{H-H}$ = 8.4 Hz). ^{13}C NMR (C_6D_6), δ: 31.6 (CH_3, ^{t}Bu), 31.7 (CH_3, ^{t}Bu), 31.8 (CH_3, ^{t}Bu), 31.9 (CH_3, ^{t}Bu), 34.8 (C, ^{t}Bu), 34.9 (C, ^{t}Bu), 36.0 (C, ^{t}Bu), 54.9 (C-3), 64.2 (C-4), 69.3 (C-6), 70.4 (CH_2-Ph), 72.8 (d, C-2, J_{C-P}= 16.8 Hz), 81.5 (C-5), 99.3 (C-1), 102.1 (C-7), 122-165 (aromatic carbons). Anal. calcd. (%) for $C_{54}H_{65}N_2O_8P$: C 71.98, H 7.27, N 3.11; found: C 72.03, H 7.29, N 3.08.

L60c. Yield: 144 mg (18%). ^{31}P NMR (C_6D_6), δ: 140.1. ^{1}H NMR (C_6D_6), δ: 1.44 (s, 9H, CH_3, ^{t}Bu), 1.59 (s, 9H, CH_3, ^{t}Bu), 1.61 (s, 3H, CH_3), 1.66 (s, 3H, CH_3), 1.91 (s, 3H, CH_3), 2.02 (s, 3H, CH_3), 3.44 (m, 1H, H-6), 3.83 (m, 1H, H-4), 4.08 (m, 2H, H-5 and H-6'), 4.17 (d, 1H, CH_2-Ph, $^{2}J_{H-H}$ = 12.4 Hz), 4.35 (d, 1H, CH_2-Ph, $^{2}J_{H-H}$ = 12.4 Hz), 4.92 (m, 1H, H-3), 5.08 (m, 1H, H-2), 5.12 (s, 1H, H-7), 5.29 (d, 1H, H-1, $^{3}J_{1-2}$ = 3.2 Hz), 6.53 (m, 1H, CH=), 6.9-7.2 (m, 11H, CH=), 7.53 (m, 2H, CH=), 8.04 (m, 1H, NH), 8.23 (d, 1H, CH=, $^{3}J_{H-H}$ = 8.0 Hz), 8.82 (d, 1H, CH=, $^{3}J_{H-H}$ = 8.4 Hz). ^{13}C NMR (C_6D_6), δ: 16.2 (CH_3), 16.5 (CH_3), 19.9 (CH_3), 20.0 (CH_3), 31.2 (CH_3, ^{t}Bu), 31.3

(CH_3, ^{t}Bu), 34.6 (C, ^{t}Bu), 34.7 (C, ^{t}Bu), 54.7 (C-3), 63.7 (C-4), 68.5 (C-6), 69.5 (CH_2-Ph), 72.6 (d, C-2, $J_{C\text{-}P}$= 19.1 Hz), 80.3 (C-5), 97.3 (C-1), 101.5 (C-7), 121-165 (aromatic carbons). Anal. calcd. (%) for $C_{50}H_{57}N_2O_8P$: C 71.07, H 6.80, N 3.32; found: C 71.12, H 6.83, N 3.28.

L60d. Yield: 109 mg (13%). ^{31}P NMR (C_6D_6), δ: 140.8. ^{1}H NMR (C_6D_6), δ: 1.45 (s, 3H, CH_3), 1.52 (s, 9H, CH_3, ^{t}Bu), 1.66 (s, 3H, CH_3), 1.67 (s, 9H, CH_3, ^{t}Bu), 1.83 (s, 3H, CH_3), 2.01 (s, 3H, CH_3), 3.55 (m, 1H, H-6), 3.80 (m, 1H, H-4), 4.03 (m, 1H, H-5), 4.08 (m, 1H, H-6'), 4.13 (d, 1H, CH_2-Ph, $^2J_{H\text{-}H}$ = 12.4 Hz), 4.37 (d, 1H, CH_2-Ph, $^2J_{H\text{-}H}$ = 12.4 Hz), 4.85 (m, 1H, H-3), 5.07 (m, 1H, H-2), 5.14 (d, 1H, H-1, $^3J_{1\text{-}2}$ = 3.6 Hz), 5.49 (s, 1H, H-7), 6.52 (m, 1H, CH=), 6.9-7.2 (m, 11H, CH=), 7.78 (m, 2H, CH=), 7.94 (d, 1H, CH=, $^3J_{H\text{-}H}$ = 8.0 Hz), 8.05 (m, 1H, NH), 8.56 (d, 1H, CH=, $^3J_{H\text{-}H}$ = 8.8 Hz). ^{13}C NMR (C_6D_6), δ: 16.2 (CH_3), 16.3 (CH_3), 19.9 (CH_3), 20.0 (CH_3), 31.3 (d, CH_3, ^{t}Bu, $J_{C\text{-}P}$= 5.0 Hz), 31.5 (CH_3, ^{t}Bu), 34.6 (C, ^{t}Bu), 34.8 (C, ^{t}Bu), 53.5 (C-3), 63.4 (C-4), 68.5 (C-6), 69.4 (CH_2-Ph), 71.8 (d, C-2, $J_{C\text{-}P}$= 10.9 Hz), 81.2 (C-5), 97.8 (C-1), 101.2 (C-7), 125-165 (aromatic carbons). Anal. calcd. (%) for $C_{50}H_{57}N_2O_8P$: C 71.07, H 6.80, N 3.32; found: C 71.13, H 6.83, N 3.29

3.6.4.4. Typical procedure for the preparation of [Ir(cod)(L)]BAr$_F$

The corresponding ligand (0.037 mmol) was dissolved in CH_2Cl_2 (2.5 mL) and [Ir(μ-Cl)cod]$_2$ (12.5 mg, 0.0185 mmol) was added. The reaction was refluxed at 45 °C for 1 hour. After 5 min at room temperature, $NaBAr_F$ (38.6 mg, 0.041 mmol) and water (2.5 mL) were added and the reaction mixture was stirred vigorously for 30 min at room temperature. The phases were separated and the aqueous phase was extracted twice with CH_2Cl_2. The combined organic phases were filtered through a celite plug, dried with $MgSO_4$ and the solvent was evaporated to give the product as an orange solid.

[Ir(cod)(L59a)]BAr$_F$. Yield: 71 mg (96%). ^{31}P NMR (CD_2Cl_2), δ: 96.0. ^{1}H NMR (CD_2Cl_2), δ: 1.32 (s, 9H, CH_3, ^{t}Bu), 1.36 (s, 9H, CH_3, ^{t}Bu), 1.52 (s, 9H, CH_3, ^{t}Bu), 1.64 (s, 9H, CH_3, tBu), 1.71 (b, 4H, CH_2, cod), 1.98 (b, 2H, CH_2, cod), 2.16 (b, 2H, CH_2, cod), 2.72 (s, 3H, CH_3-O), 3.39 (m, 2H, H-6 and CH= cod), 3.43 (m, 1H, H-4), 3.48 (m, 1H, H-2), 3.62 (m, 1H, CH=, cod), 3.91 (d, 1H, H-1, $^3J_{1\text{-}2}$ = 3.6 Hz), 4.19 (m, 1H, H-5), 4.47 (m, 2H, H-6' and CH= cod), 5.08 (s, 1H, H-7), 5.24 (m, 1H, H-3), 5.71 (m, 1H, CH= cod), 6.9-7.5 (m, 23H, CH=), 7.81 (m, 1H, CH=), 8.72 (m, 1H, CH=). ^{13}C NMR (CD_2Cl_2), δ: 24.8 (b, CH_2, cod), 28.7 (b, CH_2, cod), 31.0 (CH_3, ^{t}Bu), 31.1 (CH_3, ^{t}Bu), 31.1 (CH_3, ^{t}Bu), 31.2 (CH_3, ^{t}Bu), 32.0 (b, CH_2, cod), 34.3 (C, ^{t}Bu), 34.4 (C, ^{t}Bu), 34.8 (b, CH_2 cod), 35.3 (C, ^{t}Bu), 54.1 (CH_3-O), 62.2 (C-5), 63.7 (CH=, cod), 68.6 (C-6), 68.9 (CH=, cod), 73.2 (b, C-3), 76.9 (b, C-2), 80.3 (C-4), 98.2 (C-1), 101.3 (C-7), 102.4 (b, CH=, cod), 106.5 (b CH=, cod), 117.6 (b, CH=, BAr_F), 120-134 (aromatic carbons), 135.0 (b, CH=, BAr_F), 136-158 (aromatic carbons), 161.9 (q, C-B, BAr_F, $^1J_{C\text{-}B}$= 49.5 Hz), 166.7 (C=O). Anal. calcd. (%) for $C_{88}H_{84}BF_{24}IrNO_9P$: C 53.12, H 4.26, N 0.70; found: C 53.09, H 4.24, N 0.67.

[Ir(cod)(L59b)]BAr$_F$. Yield: 69 mg (98%). ^{31}P NMR (CD_2Cl_2), δ: 96.5. ^{1}H NMR (CD_2Cl_2), δ: 0.01 (s, 9H, CH_3-Si), 0.35 (s, 9H, CH_3-Si), 1.68 (b, 4H, CH_2, cod), 1.95 (b, 2H, CH_2, cod), 2.29 (b, 2H, CH_2, cod), 2.65 (s, 3H, CH_3-O), 3.45 (m, 4H, H-6, H-4, H-2 and CH= cod)), 3.59 (m, 1H, CH=, cod), 3.94 (d, 1H, H-1, $^3J_{1\text{-}2}$ = 3.2 Hz), 4.21 (m, 1H, H-5), 4.44 (m, 2H, H-6' and CH= cod), 5.06 (s, 1H, H-7), 5.19 (m, 1H, H-3), 5.66 (m, 1H, CH= cod), 6.8-7.5 (m, 25H, CH=), 7.82 (m, 1H, CH=), 8.71 (m, 1H, CH=). ^{13}C NMR (CD_2Cl_2), δ: -0.7 (CH_3-Si), 0.6 (CH_3-Si), 24.9 (b, CH_2, cod), 29.4 (b, CH_2, cod), 32.1 (b, CH_2, cod), 37.5 (b, CH_2, cod), 54.3 (CH_3-O), 62.0 (C-5), 63.2 (CH=, cod), 68.5 (C-6), 69.9 (CH=, cod), 75.0 (b, C-3), 77.8 (b, C-2), 80.8 (C-4), 97.3 (C-1),

101.8 (C-7), 107.2 (b, CH=, cod), 109.7 (b CH=, cod), 117.6 (b, CH=, BAr_F), 120.5-132.8 (aromatic carbons), 135.0 (b, CH=, BAr_F), 136-156 (aromatic carbons), 161.9 (q, C-B, BAr_F, $^1J_{C\text{-}B}$= 49.5 Hz), 166.4 (C=O). Anal. calcd. (%) for $C_{78}H_{68}BF_{24}IrNO_9PSi_2$: C 49.06, H 3.59, N 0.73; found: C 49.02, H 3.58, N 0.72.

[Ir(cod)(L59c)]BAr_F. Yield: 66 mg (93%). ^{31}P NMR (CD_2Cl_2), δ: 92.5. ^{1}H NMR (CD_2Cl_2), δ: 1.56 (s, 9H, CH_3, ^{t}Bu), 1.62 (s, 9H, CH_3, ^{t}Bu), 1.68 (s, 3H, CH_3), 1.78 (b, 7H, CH_3 and CH_2, cod), 1.99 (b, 2H, CH_2, cod), 2.03 (s, 3H, CH_3), 2.09 (s, 3H, CH_3), 2.14 (b, 2H, CH_2, cod), 2.76 (s, 3H, CH_3-O), 3.34 (m, 1H, H-6), 3.41 (m, H, CH=, cod), 3.52 (m, 1H, H-4), 3.56 (m, 2H, H-2 and CH=, cod), 4.02 (d, 1H, H-1, $^3J_{1\text{-}2}$ = 3.6 Hz), 4.32 (m, 1H, H-5), 4.46 (m, 2H, H-6' and CH= cod), 5.02 (s, 1H, H-7), 5.23 (m, 1H, H-3), 5.86 (m, 1H, CH= cod), 6.9-7.5 (m, 21H, CH=), 7.82 (m, 1H, CH=), 8.72 (m, 1H, CH=). ^{13}C NMR (CD_2Cl_2), δ: 16.9 (CH_3), 17.0 (CH_3), 20.6 (CH_3), 20.7 (CH_3), 23.9 (b, CH_2, cod), 26.4 (b, CH_2, cod), 29.9 (b, CH_2, cod), 32.3 (CH_3, ^{t}Bu), 32.5 (CH_3, ^{t}Bu), 32.8 (b, CH_2, cod), 35.3 (C, ^{t}Bu), 35.4 (C, ^{t}Bu), 54.8 (CH_3-O), 62.3 (C-5), 63.9 (CH=, cod), 68.3 (C-6), 69.2 (CH=, cod), 72.3 (C-3), 77.8 (b, C-2), 80.1 (C-4), 99.9 (C-1), 101.4 (C-7), 101.9 (b, CH=, cod), 103.9 (b CH=, cod), 117.6 (b, CH=, BAr_F), 120-134 (aromatic carbons), 135.0 (b, CH=, BAr_F), 136-158 (aromatic carbons), 161.9 (q, C-B, BAr_F, $^1J_{C\text{-}B}$= 49.5 Hz), 166.7 (C=O). Anal. calcd. (%) for $C_{84}H_{76}BF_{24}IrNO_9P$: C 52.18, H 3.96, N 0.72; found: C 52.17, H 3.92, N 0.71.

[Ir(cod)(L59d)]BAr_F. Yield: 68 mg (96%). ^{31}P NMR (CD_2Cl_2), δ: 93.6. ^{1}H NMR (CD_2Cl_2), δ: 1.53 (s, 9H, CH_3, ^{t}Bu), 1.58 (s, 3H, CH_3), 1.65 (s, 9H, CH_3, ^{t}Bu),), 1.69 (s, 3H, CH_3), 1.86 (b, 4H, CH_2, cod), 1.95 (b, 2H, CH_2, cod), 1.99 (s, 6H, CH_3), 2.08 (b, 2H, CH_2, cod), 2.79 (s, 3H, CH_3-O), 3.34 (m, H, CH=, cod), 3.38 (m, 1H, H-6), 3.48 (m, 1H, H-4), 3.53 (m, 2H, H-2 and CH=, cod), 4.09 (d, 1H, H-1, $^3J_{1\text{-}2}$ = 3.6 Hz), 4.46 (m, 2H, H-5 and CH= cod), 4.49 (m, 1H, H-6'), 5.02 (s, 1H, H-7), 5.19 (m, 1H, H-3), 5.68 (m, 1H, CH= cod), 6.9-7.5 (m, 21H, CH=), 7.82 (m, 1H, CH=), 8.70 (m, 1H, CH=). ^{13}C NMR (CD_2Cl_2), δ: 16.9 (CH_3), 17.0 (CH_3), 20.7 (CH_3), 22.9 (b, CH_2, cod), 24.6 (b, CH_2, cod), 28.8 (b, CH_2, cod), 30.7 (b, CH_2, cod), 32.1 (CH_3, ^{t}Bu), 32.2 (CH_3, ^{t}Bu), 35.3 (C, ^{t}Bu), 35.4 (C, ^{t}Bu), 54.7 (CH_3-O), 62.5 (C-5), 64.2 (CH=, cod), 68.6 (C-6), 69.3 (CH=, cod), 72.9 (C-3), 77.1 (b, C-2), 80.0 (C-4), 99.6 (C-1), 101.3 (C-7), 102.4 (b, CH=, cod), 103.5 (b CH=, cod), 117.6 (b, CH=, BAr_F), 120-134 (aromatic carbons), 135.0 (b, CH=, BAr_F), 136-158 (aromatic carbons), 161.9 (q, C-B, BAr_F, $^1J_{C\text{-}B}$= 49.5 Hz), 166.7 (C=O). Anal. calcd. (%) for $C_{84}H_{76}BF_{24}IrNO_9P$: C 52.18, H 3.96, N 0.72; found: C 52.16, H 3.94, N 0.70.

[Ir(cod)(L60a)]BAr_F. Yield: 71 mg (93%). ^{31}P NMR (CD_2Cl_2), δ: 92.4. ^{1}H NMR (CD_2Cl_2), δ: 1.23 (s, 9H, CH_3, 1.29 (s, 9H, CH_3, ^{t}Bu), 1.46 (s, 9H, CH_3, ^{t}Bu), 1.51 (s, 9H, CH_3, tBu), 1.87 (b, 2H, CH_2, cod), 2.21 (b, 2H, CH_2, cod), 2.29 (b, 4H, CH_2, cod), 3.09 (m, H, CH=, cod), 3.24 (m, 3H, H-5, H4 and H-6), 3.77 (m, 1H, H-2), 3.89 (m, 1H, CH= cod), 4.24 (m, 2H, H-6' and CH= cod), 4.61 (d, 1H, CH_2-Ph, $^2J_{H\text{-}H}$ = 12.4 Hz), 4.76 (d, 1H, CH_2-Ph, $^2J_{H\text{-}H}$ = 12.4 Hz), 4.91 (m, H-3), 4.98 (d, 1H, H-1, $^3J_{1\text{-}2}$ = 3.6 Hz), 5.09 (s, 1H, H-7), 5.34 (m, 1H, CH= cod), 6.19 (m, 1H, NH), 6.87 (m, 1H, CH=), 7.0-7.9 (m, 25H, CH=), 8.81 (m, 2H, CH=). ^{13}C NMR (CD_2Cl_2), δ: 16.5 (CH_3), 16.7 (CH_3), 20.2 (CH_3), 20.9 (CH_3), 25.2 (b, CH_2, cod), 28.7 (b, CH_2, cod), 29.9 (b, CH_2, cod), 30.9 (CH_3, ^{t}Bu), 31.2 (b, CH_2, cod), 32.1 (CH_3, ^{t}Bu), 34.3 (C, ^{t}Bu), 34.8 (C, ^{t}Bu), 59.0 (C-3), 63.8 (C-4), 68.6 (b, CH=, cod), 68.8 (C-6), 71.2 (CH_2-Ph), 75.1 (b, CH=, cod), 77.6 (C-2), 79.9 (C-5), 98.6 (C-1), 102.8 (b, CH=, cod), 103.1 (C-7), 106.2 (b, CH=, cod), 117.6 (b, CH=, BAr_F), 120-134 (aromatic carbons), 135.0 (b, CH=, BAr_F), 136-158 (aromatic carbons), 161.9 (q, C-B,

BAr_F, $^1J_{C-B}$= 49.5 Hz), 166.6 (C=O). Anal. calcd. (%) for $C_{94}H_{89}BF_{24}IrN_2O_8P$: C 54.68, H 4.34, N 1.36; found: C 54.61, H 4.32, N 1.33.

[Ir(cod)(L60c)]BAr_F. Yield: 73 mg (94%). ^{31}P NMR (CD_2Cl_2), δ: 91.6. ^{1}H NMR (CD_2Cl_2), δ: 1.20 (s, 9H, CH_3, ^{t}Bu), 1.26 (s, 3H, CH_3), 1.50 (s, 3H, CH_3), 1.54 (s, 9H, CH_3, ^{t}Bu), 1.69 (s, 3H, CH_3), 1.83 (s, 3H, CH_3), 1.92 (b, 2H, CH_2, cod), 2.23 (b, 2H, CH_2, cod), 2.35 (b, 4H, CH_2, cod), 2.83 (m, H, CH=, cod), 2.92 (m, 1H, H-4), 3.11 (m, 1H, H-6), 3.48 (m, 1H, H-5), 3.69 (m, 1H, H-2), 3.95 (m, 1H, CH= cod), 4.05 (m, 1H, H-6'), 4.32 (m, 1H, CH= cod), 4.60 (d, 1H, CH_2-Ph, $^2J_{H-H}$ = 12.4 Hz), 4.73 (d, 1H, CH_2-Ph, $^2J_{H-H}$ = 12.4 Hz), 4.89 (m, H-3), 5.01 (d, 1H, H-1, $^3J_{1-2}$ = 3.2 Hz), 5.05 (s, 1H, H-7), 5.28 (m, 1H, CH= cod), 6.22 (m, 1H, NH), 6.28 (s, 1H, CH=), 7.0-7.9 (m, 25H, CH=), 8.81 (m, 2H, CH=). ^{13}C NMR (CD_2Cl_2), δ: 16.8 (CH_3), 20.5 (CH_3), 21.4 (CH_3), 25.5 (b, CH_2, cod), 29.1 (b, CH_2, cod), 29.9 (b, CH_2, cod), 30.5 (CH_3, ^{t}Bu), 31.9 (CH_3, ^{t}Bu), 34.3 (C, ^{t}Bu), 35.0 (C, ^{t}Bu), 59.1 (C-3), 63.3 (C-4), 68.4 (C-6), 68.9 (b, CH=, cod), 71.1 (CH_2-Ph), 75.3 (b, CH=, cod), 77.4 (C-2), 79.8 (C-5), 97.3 (C-1), 102.2 (b, CH=, cod), 103.4 (C-7), 107.0 (b, CH=, cod), 117.6 (b, CH=, BAr_F), 120-134 (aromatic carbons), 135.0 (b, CH=, BAr_F), 136-158 (aromatic carbons), 161.9 (q, C-B, BAr_F, $^1J_{C-B}$= 49.5 Hz), 166.2 (C=O). Anal. calcd. (%) for $C_{90}H_{81}BF_{24}IrN_2O_8P$: C 53.82, H 4.06, N 1.39; found: C 53.79, H 4.05, N 1.35.

[Ir(cod)(L60d)]BAr_F. Yield: 75 mg (97%). ^{31}P NMR (CD_2Cl_2), δ: 90.9. ^{1}H NMR (CD_2Cl_2), δ: 1.23 (s, 9H, CH_3, ^{t}Bu), 1.32 (s, 3H, CH_3), 1.49 (s, 3H, CH_3), 1.53 (s, 9H, CH_3, ^{t}Bu), 1.71 (s, 3H, CH_3), 1.83 (s, 3H, CH_3), 1.92 (b, 2H, CH_2, cod), 2.26 (b, 2H, CH_2, cod), 2.33 (b, 4H, CH_2, cod), 3.01 (m, 1H, CH=, cod), 3.24 (m, 1H, H-4), 3.29 (m, 1H, H-6), 3.47 (m, 1H, H-5), 3.69 (m, 1H, H-2), 3.97 (m, 2H, CH= cod and H-6'), 4.39 (m, 1H, CH= cod), 4.61 (d, 1H, CH_2-Ph, $^2J_{H-H}$ = 12.4 Hz), 4.70 (d, 1H, CH_2-Ph, $^2J_{H-H}$ = 12.4 Hz), 4.92 (m, H-3), 5.03 (d, 1H, H-1, $^3J_{1-2}$ = 3.2 Hz), 5.07 (s, 1H, H-7), 5.57 (m, 1H, CH= cod), 6.02 (m, 1H, NH), 6.7-7.7 (m, 26H, CH=), 8.81 (m, 2H, CH=). ^{13}C NMR (CD_2Cl_2), δ: 16.8 (CH_3), 16.9 (CH_3), 20.4 (CH_3), 20.9 (CH_3), 25.1 (b, CH_2, cod), 26.3 (b, CH_2, cod), 28.9 (b, CH_2, cod), 29.3 (b, CH_2, cod), 32.2 (CH_3, ^{t}Bu), 32.5 (CH_3, ^{t}Bu), 34.4 (C, ^{t}Bu), 34.6 (C, ^{t}Bu), 59.0 (C-3), 63.5 (C-4), 68.4 (C-6), 69.7(b, CH=, cod), 71.0 (CH_2-Ph), 75.9 (b, CH=, cod), 77.1 (C-2), 79.6 (C-5), 98.3 (C-1), 102.9 (C-7), 103.4 (b, CH=, cod), 106.8 (b, CH=, cod), 117.6 (b, CH=, BAr_F), 120-134 (aromatic carbons), 135.0 (b, CH=, BAr_F), 136-158 (aromatic carbons), 161.9 (q, C-B, BAr_F, $^1J_{C-B}$= 49.5 Hz), 166.2 (C=O). Anal. calcd. (%) for $C_{90}H_{81}BF_{24}IrN_2O_8P$: C 53.82, H 4.06, N 1.39; found: C 53.77, H 4.03, N 1.36.

3.6.4.5. Typical procedure for the hydrogenation of olefins

The alkene (0.5 mmol) and Ir complex (2 mol%) were dissolved in CH_2Cl_2 (2 mL) in a high-pressure autoclave, which was purged four times with hydrogen. Then, it was pressurized at the desired pressure. After the desired reaction time, the autoclave was depressurized and the solvent evaporated off. The residue was dissolved in Et_2O (1.5 ml) and filtered through a short celite plug. The enantiomeric excess was determined by chiral GC or chiral HPLC and conversions were determined by ^{1}H NMR. The enantiomeric excesses of hydrogenated products were determined using the conditions previously described.[5]

3.6.5. Acknowledgements

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[9] Pàmies, O.; Diéguez, M.; Net, G. ; Ruiz, A. ; Claver, C. *Organometallics* **2000,** *19,* 1488.

[10] Jongsma, T.; Fossen, D.; Challa, G.; van Leeuwen, P. W. N. M. *J. Mol. Catal.* **1993**, *83*, 17.

3.7. The development of readily accessible phoshite-triazole ligands and their application in the Ir-catalyzed hydrogenation of minimally functionalized olefins

Jèssica Margalef, Erik A. Karlsson, Xisco Caldentey, Oscar Pàmies, Montserrat Diéguez, and Miquel A. Pericàs (preliminary results)

***Abstract**: We have successfully developed a new readily available chiral phosphite-triazole ligand library by using the environmentally friendly CuAAC in one of the steps of the ligand synthesis. Ir-complexes made from these ligands were found in some cases as a mixture of two isomers. DFT calculations of [Ir(cod)(**L61b-c**)]BAr$_F$ have been performed in order to know more about the nature of these two isomers. All ligands led to active Ir-complexes for the hydrogenation of minimally functionalized (E)- and (Z)-trisubstituted olefins **S1** and **S2** and disubstituted olefin **S3**. Although moderate enantioselectivities were achieved in the hydrogenation of trisubstituted substrates (ee's up to 73%), the hydrogenation of the more challenging disubstituted substrate **S3** proceeded in promising enantioselectivities (ee's up to 87%). In addition, by simply changing the configuration of the biaryl phosphite group both product eantiomers could be achieved in good enantiocontrol.*

3.7.1. Introduction

Asymmetric hydrogenation has become one of the most powerful tools for organic chemists to build optically active compounds. High enantioselectivity, low catalyst loadings, essentially quantitative yields, perfect atom economy, and mild conditions are attractive features of this transformation.[1]

A great number of chiral diphosphine ligands have been reported as efficient catalysts when combined with Rh or Ru catalysts precursors. However, the range of olefins that can be hydrogenated is limited because of the requirement of these catalysts to contain a coordinating functional group adjacent to the C=C bond.[1] Some years ago, Pfaltz and coworkers discovered a new class of chiral Ir P,N-ligand complexes that overcame the limitations of Rh- and Ru-based systems.[2] Since then, several P,N-ligands (mainly phosphine-oxazoline, *N*-phosphine-oxazoline, and phosphinite-oxazoline ligands) have emerged as efficient ligands for hydrogenation of weakly functionalized alkenes.[3] More recently, our group showed that the substrate versatility of this process could be improved by the replacement of the phosphine/phosphinite moiety by a biaryl phosphite group.[3e,4] Since this discovery, our group has contributed to the Ir-hydrogenation of minimally functionalized olefins with an improved series of ligands.[5]

Despite all developments made in this field, the activity and enantioselectivity of some relevant minimally functionalized olefins has to be still improved.[3] In addition, the design of new chiral ligands that can be easily prepared in few steps from available and cheap feedstock is still a challenge.

In this respect, click chemistry[6] protocols can be useful tools for synthesizing highly modular ligands in high yields and regioselectivities under mild conditions, and with simple reaction and work-up procedures. Particularly, the Cu(I)-Catalyzed Azide-Alkyne Cycloaddition (CuAAC)[7] allows the obtention of 1,2,3-triazoles which can be part of N-containing ligand scaffolds. There are only few examples of the application of triazole containing P,N-ligands applied in asymmetric metal-catalyzed reactions.[8] To our knowledge, only one triazole-*N*-phosphine ligand family has been applied in the Ir-catalyzed hydrogenation of minimally functionalized olefins.[9] More research is therefore needed to study the possibilities of triazole-based ligands for this transformation. For this purpose, we herein present the synthesis of the ligand library **L61**-**L67a**-**c** and their corresponding Ir-complexes, and the preliminary results of their application in the Ir-catalyzed hydrogenation of (*E*)- and (*Z*)-trisubstituted model olefins (**S1** and **S2**) and disubstituted olefin **S3**.

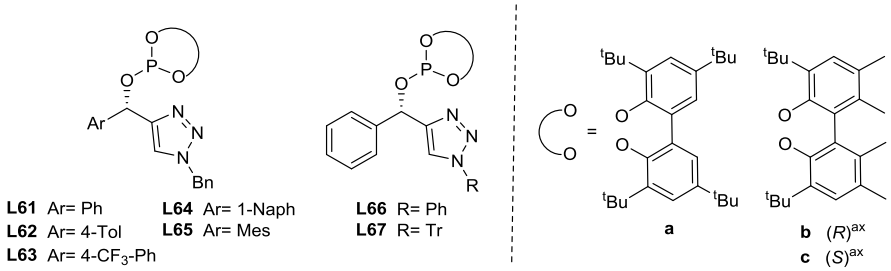
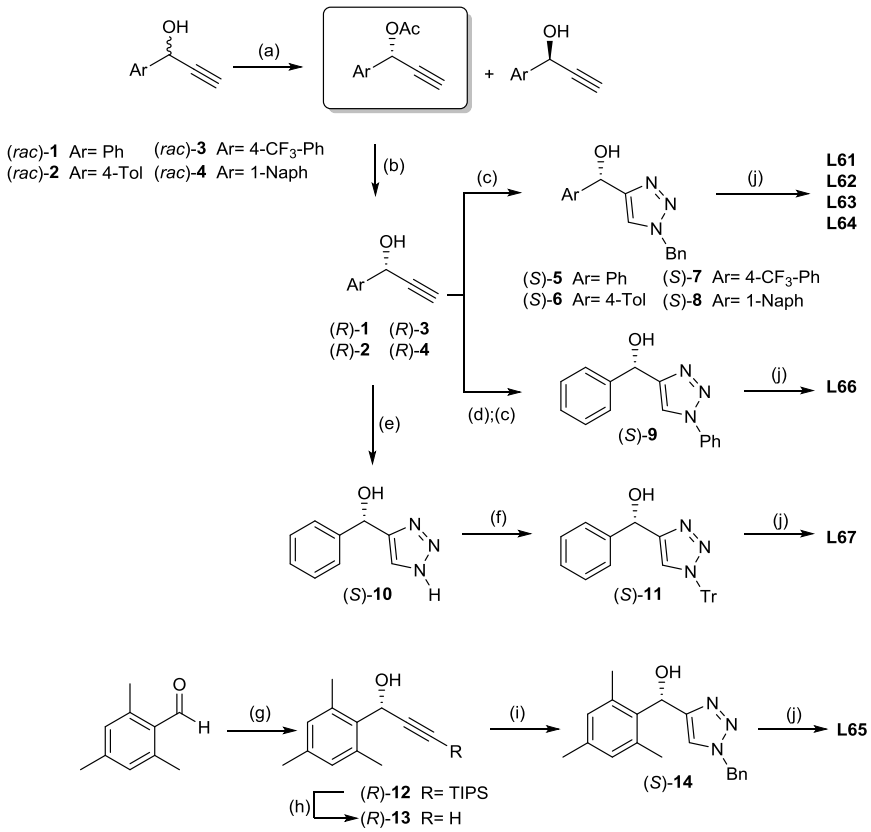


Figure 3.7.1. Phosphite-triazole ligand library **L61**-**L67a**-**c**.

3.7.2. Results and Discussion

3.7.2.1. Synthesis of ligands

New chiral phosphite-triazole ligands **L61**-**L67a**-**c** were efficiently synthesized from readily accessible racemic propargylic alcohols (*rac*)-**1**-**4** or enantiomerically pure (*R*)-**12**. Racemic alcohols **1**-**4** are easily obtained from the corresponding aldehyde and ethynyl magnesium bromide. Enzymatic kinetic resolution of racemic propargylic alcohols using *Candida antarctica lipase B* (CALB) gave access to enantiomerically pure propargylic acetates (ee >99%) (Scheme 3.7.1, step (a)),[10] which after basic hydrolysis yielded alcohols (*R*)-**1**-**4** (Scheme 3.7.1, step (b)). Nevertheless, alcohol (*R*)-**13**, bearing a bulky mesityl substituent, could not be achieved by using this strategy. Alternatively, (*R*)-**BINOL** in combination with $Ti(^{i}PrO)_4$ was used to enantioselectively catalyze the addition of triisopropylsilylacetylene to mesitaldehyde (Scheme 3.7.1, step (g)).[11] Subsequent standard deprotection of (*R*)-**12** with TBAF easily afforded compound (*R*)-**13** (Scheme 3.7.1, step (h)), which was obtained in 93% ee. After recrystallization, enantioselectivity was improved to >99% ee.



Scheme 3.7.1. Synthesis of traizole-phosphite ligands **L61**-**L67a**-**c**. (a) CALB/vinyl acetate; (b) K_2CO_3/MeOH/H_2O; (c) RN_3/$CuSO_4$/^tBuOH/H_2O; (d) $PhNH_2$/HCl/$NaNO_2$/H_2O; (e) $SiMe_3N_3$/CuBr/NEt_3/H_2O/DMF; (f) TrCl/Py; (g) CH≡CTIPS/$ZnEt_2$/(*R*)-BINOL/Ti(O^iPr)$_4$/DCM/Tol; (h)TBAF/THF; (i) BnN_3/L.CuCl/^tBuOH/H_2O; (j) $ClP(OR)_2$; $(OR)_2$= **a**-**c**/Py/Tol.

Subsequent reaction of enantiopure propargylic alcohols (*R*)-**1**-**4** with benzyl azide in presence of $CuSO_4$/Na-ascorbate,[12] provided the corresponding triazole-hydroxyl compounds (*S*)-**5**-**8** in high yields (71-91%) (Scheme 3.7.1, step (c)). Triazole compound (*S*)-**9** was also obtained through typical reaction conditions of CuAAC ($CuSO_4$/Na-ascorbate), but phenyl azide was *in situ* generated from aniline and sodium azide (49% yield) (Scheme 3.7.1, step (d)).[13] In contrast, triazole (*S*)-**14**, containing a bulkier aromatic ring, could not be obtained under standard CuAAC conditions. However, the use of Cu-catalyst (**15**.CuCl) (Figure 3.7.2), developed by Pericàs and coworkers,[14] resulted in the desired triazole in 82% yield (Scheme 3.7.1, step (i)). Similarly, reaction of compound (*R*)-**1** with trityl azide failed in yielding triazole derivative (*S*)-**11**, due to the high steric bulk of the organic azide. Hence, *N*-unsubstituted 1,2,3-triazole (*S*)-**10** was synthesized by using azidotrimethylsilane (which is hydrolyzed to hydrazoic acid in presence of water) and CuBr/NEt_3[15] as catalyst (Scheme 3.7.1, step (e)). Then, reaction of *N*-unsubstituted triazole with trityl chloride in the presence of pyridine afforded the *N*-tritylated triazole (*S*)-**11** (Scheme 3.7.1, step (f)).

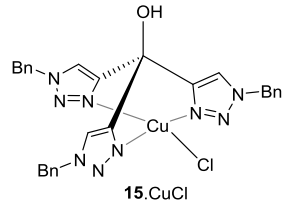
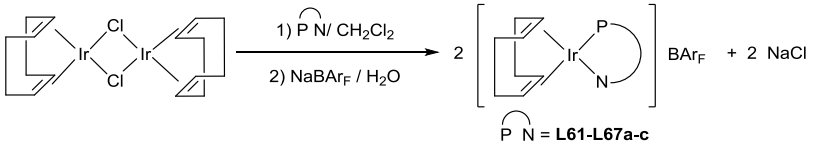


Figure 3.7.2. Catalyst (**15**.CuCl) used for the preparation of triazol-alcohol (*S*)-**14**.

The last step of the ligand synthesis is common for all of them. Hence, treating the corresponding triazole-alcohol with the *in situ* generated phosphochloridite ($ClP(OR)_2$; $(OR)_2$= **a**-**c**) in the presence of pyridine, gave easy access to the desired ligands (Scheme 3.7.1, step (j)).[16] All the ligands were purified on neutral alumina under an argon atmosphere and isolated in moderate-to-good yields as white solids. The HRMS-ESI spectra were in agreement with the assigned structure. The ^{1}H, ^{31}P and ^{13}C NMR spectra were as expected for these ligands. One singlet for each compound was observed in the ^{31}P NMR spectrum. Rapid ring inversions (tropoisomerization) in the biphenyl-phosphorus moiety **a** occurred on the NMR time scale because the expected diastereoisomers were not detected by low temperature ^{31}P NMR.

3.7.2.2. Synthesis of the Ir-catalyst precursors

The catalyst precursors were prepared by refluxing a dichloromethane solution of the appropriate ligand (**L61**-**L67a**-**c**) in the presence of 0.5 equivalent of $[Ir(\mu\text{-}Cl)cod]_2$ for 1 h. The Cl^-/BAr_F^- counterion exchange was then achieved by a reaction with sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate ($NaBAr_F$) (1 equiv) in the presence of water (Scheme). All complexes were isolated as air-stable orange solids, and were used without further purification.



Scheme 3.7.2. Synthesis of Ir- precursors $[Ir(cod)(P\text{-}N)]BAr_F$ (P-N **= L61**-**L67a**-**c**).

The complexes were characterized by HRMS-ESI spectra and ^{1}H, ^{13}C, and ^{31}P NMR spectroscopy. The spectral assignments were based on information from ^{1}H–^{1}H and ^{13}C–^{1}H correlation measurements, and were as expected for these C_1-iridium complexes. The VT-NMR spectra indicated that one isomer is present in solution in the case of ligand **L61a**, **L63b**-**c**, **L65c** and **L67b**,**c**. Thus, only one singlet in the $^{31}P\text{-}\{^{1}H\}$ NMR spectra was obtained in these cases. On the contrary, ligands **L61b**-**c**, **L62b**, **L64b, L65b** and **L66b**-**c** showed the presence of two species in solution. In addition, $^{31}P\text{-}\{^{1}H\}$ and ^{1}H NMR signals showed that the configuration of the phosphite biphenyl moiety dictates in which proportion they are present. In order to establish if these two species are in equilibrium or not, the NMR temperature was increased up to 75 °C for complexes $[Ir(cod)(\mathbf{L61b\text{-}c})]BAr_F$. The two

singlets observed in $^{31}P-\{^{1}H\}$ NMR spectrum remained unchanged, thus indicating that they are not in equilibrium (see supporting information). On the other hand, the 2D DOSY $^{31}P-\{^{1}H\}$ NMR experiments showed that these two species have the same diffusion coefficient (see supporting information), which indicates that they must be isomers. Therefore, we can conclude that complexation of ligands **L61b**-**c** to Ir center leads to two isomers that are not in equilibrium.

A possible explanation of that behaviour could be that 6-membered chelate ring on ligands **L61b**-**c** adopts two different stable conformations. In order to validate this hypothesis, geometries of two possible conformational isomers for each ligand were calculated using the B3LYP functional,[17] the 6-31G*/LANL2DZ basis set,[18] and the PCM solvent model with parameters for CH_2Cl_2,[19] as implemented in Gaussian 09.[20] The energies were further refined by performing single point calculations at the 6-311+G** level,[21] and by dispersion correction with the DFT-D3 model.[22] Figure 3.7.3 showed the two proposed calculated conformers of the Ir-complexes with ligands **L61b**-**c**. Both isomers present a 6-membered chelate ring boat conformation but they differ in the disposition of the C attached to the aryl ring on the ligand backbone (Figure 3.7.3). In structures of **L61b**-**C1** and **L61c**-**C1**, this C is pointing up whereas in the case of **L61b**-**C2** and **L61c**-**C2** it is pointing down.

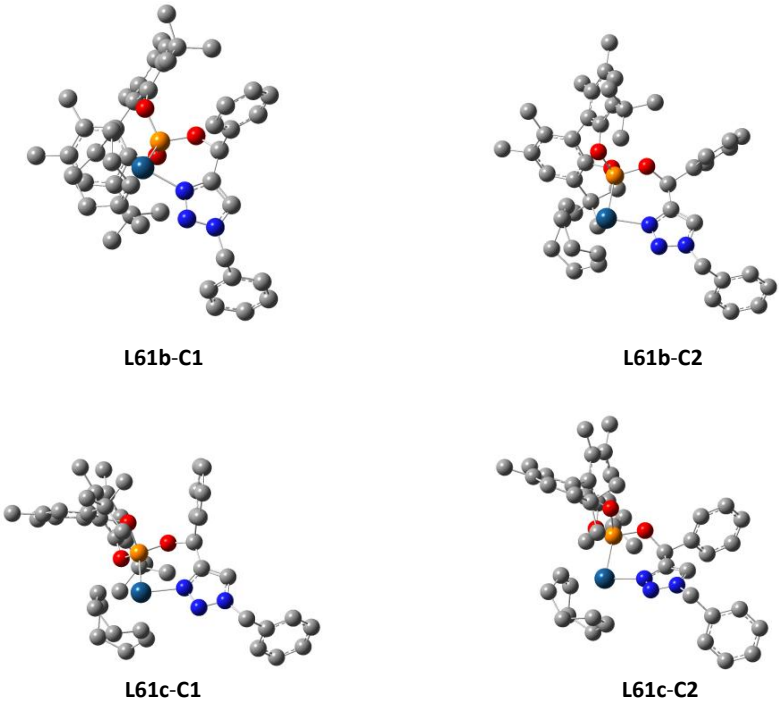


Figure 3.7.3. Calculated geometries of [Ir(cod)(**L61b**-**c**) having two different conformations on chelate ring. Hydrogens of Ir-complexes were omitted for clarity.

Population of each conformer of complexes [Ir(cod)(**L61b**-**c**)]BAr_F obtained from calculated free energies showed that for ligand containing an (*S*)-biaryl phosphite group (**c**) isomer **C2** is the most stable, while isomer **C1** is the most stable one for ligands containing an (*R*)-biaryl phosphite moiety (Table 3.7.1). We can conclude therefore that Ir-complex of ligand **L61b** prefers the conformation where the aryl group is pointing up (**C1**) while in the case of **L61c** is preferred the opposite one (**C2**). In addition there is a matched tendency between the populations observed by NMR experiments and those calculated from the energies of the proposed conformers.

Table 3.7.1. Calculated energies for the two proposed conformational isomers for [Ir(cod)(**L61b**-**c**)]BAr_F.[a]

Starting geometry	**L61b**[a]	Population (%)	$Population_{Exp}$ (%)	**L61c**[a]	Population (%)	$Population_{Exp}$ (%)
C1	0.0	80%	70%	26.9	0.1	10%
C2	3.4	20%	30%	0	99.9	90%

[a] Energies in kJ/mol.

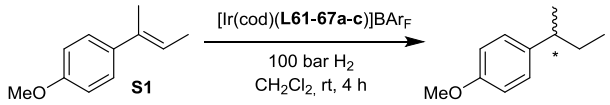
3.7.2.3. Asymmetric hydrogenation

*Asymmetric hydrogenation of minimally functionalized trisubstituted olefins E-2-(4-methoxyphenyl)-2-butene (**S1**)*

We initially evaluated phosphite-triazole ligands **L61**-**L67** in the Ir-catalyzed hydrogenation of the model trisubstituted substrate (*E*)-2-(4-methoxyphenyl)-2-butene (**S1**). Substrate **S1** has been hydrogenated by a large number of ligands and it therefore enables the efficiency of various ligand systems to be compared directly.[3] Results show that configuration of the phosphite biphenyl moiety plays an important role on enantioselectivity. From entries 1-3 (Table 3.7.2) we can conclude that (*S*)-configuration on the phosphite biphenyl moiety is advantageous in terms of enantioselectivity. Therefore, ligands **L61**-**67c** bearing a (*S*)-biphenyl moiety generally provided better enantioselectivities than their corresponding counterparts (**L61**-**67b**) (i.e. entry 3 vs 2). In addition, configuration of biphenyl moiety generally dictates the sense of the enantioselectivity of the hydrogenated product.

The electronic properties of aryl substituents present in the chiral backbone also were found to be important on enantioselectivity. Hence, the introduction of electron donating substituents in *para*-position (**L63b**) led to almost no enantioselectivity (Table 3.7.2, entry 5 vs 5), whereas the presence of electron withdrawing *p*-CF_3 group (**L62b**) increased enantioselectivity up to 72% ee (Table 3.7.2, entry 4 vs 2). Interestingly, despite the poorer enantioselectivity obtained by using **L63b** (2% ee), ligand **L63c** afforded the hydrogenated product in 73% ee (Table 3.7.2, entry 6). Catalytic results together with the fact that the NMR spectra of [Ir(cod)(**L63b**)]BAr_F and [Ir(cod)(**L63c**)]BAr_F showed for each of them the presence of one of the two possible isomers (for Ir/**L63b** is **C1** and for Ir/**L63c** is **C2**) suggests that only isomer **C2** could induce enantioselectivity in the hydrogenation of **S1**.

Table 3.7.2. Selected results for the Ir-catalyzed hydrogenation of **S1** using phosphite-triazole ligands **L61**-**67a**-**c**.[a]



Entry	Ligand	% Conv[b]	ee%[b]
1	**L61a**	100	46 (*S*)
2	**L61b**	100	31 (*R*)
3	**L61c**	100	65 (*S*)
4	**L62b**	100	72 (*R*)
5	**L63b**	100	2 (*S*)
6	**L63c**	100	73 (*S*)
7	**L64b**	100	58 (*R*)
8	**L65b**	100	66 (*R*)
9	**L65c**	100	66 (*S*)
10	**L66b**	100	33 (*R*)
11	**L66c**	100	67 (*S*)
12	**L67b**	100	17 (*S*)
13	**L67c**	100	60 (*S*)

[a] Reactions carried out using 0.5 mmol of **S1** and 2 mol% of Ir-catalyst precursor. [b] Conversion and enantiomeric excesses determined by chiral GC.

In order to see if enantioselectivity could be increased by introducing a bulkier aryl groups in the ligand backbone, ligand **L64b**, which contains a 1-naphtyl group, was tested in the reduction of **S1**. Unfortunately, enantioselectivity was only of 58% ee (entry 7). Having in mind that 1-naphtyl group can easily rotate and therefore, is most probably to be found pointing towards outside the coordination sphere, a decision was made to synthesize ligands **L65b**-**c** bearing a symmetric mesityl group. However, enantioselectivity was only moderate (66% ee; entries 8 and 9).

We finally moved to study the effect of introducing a bulky group in the *N*-1 of the triazole moiety. With this aim, ligands **L66**-**67b**-**c** containing an *N*-phenyl and an *N*-trityl triazole moiety were applied in the hydrogenation of model substrate **S1** (Table 3.7.2, entries 10-13). Again, only moderate enantioselectivities were obtained (ee's up to 67% with **L66c**). It should be pointed out that Ir-complexes with ligands **L66**-**67b** showed the same NMR pattern than **L63b** and similarly, enantioselectivity was very low (ee's up to 33%; Table 3.7.2, entries 10 and 12) (see above). This matches with the idea that only one of the isomeric forms of the Ir-complexes is able of adequately transferring the chiral information to the hydrogenated product.

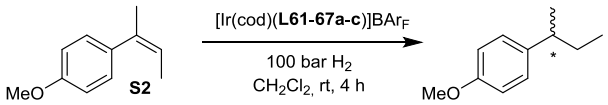
*Asymmetric hydrogenation of minimally functionalized trisubstituted olefins (Z)-2-(4-methoxyphenyl)-2-butene (**S2**)*

We next tested new ligands **L61**-**67a**-**c** in the Ir-catalyzed hydrogenation of the more challenging olefin (*Z*)-2-(4-methoxyphenyl)-2-butene (**S2**) (Table 3.7.3). As expected, ligands **L61**-**67a**-**c** showed in general lower enantiocontrol (ee's up to 56%) than in the reduction of **S1** (ee's up to 73%). Again, enantioselectivities were higher with ligands containing a (*S*)-biphenyl moiety in the phosphite group. However, in this case the difference between

enantioselectivities given by ligands **L61**-**67b** and **L61**-**67c** were lower (31-46% ee *vs* 33-56% ee).

The observed trend when varying the electronic nature of the aryl *para*-susbtituents of the backbone was the same than in the reduction of (*E*)-substrate **S1**. Hence, the *p*-CF_3 containing ligand **L62b**, provided slightly higher enantioselectivity than **L61b** and **L63b** (Table 3.7.3, entry 4 vs 2 and 5). Ligands **L64b** and **L65b**-**c** with bulky aryl groups in the ligand structure didn't showed much improvement on the enantioselectivity (Table 3.7.3, entries 7-9). In contrast, by using ligand **L67b**-**c**, which contain a bulky *N*-trityl group on the triazole ring, a slightly improvement on the enantioselectivity was observed. Unfortunately, enantioselectivity obtained in the hydrogenation of **S2** didn't surpass 56% ee. (entry 13).

Table 3.7.3. Selected results for the Ir-catalyzed hydrogenation of **S2** using phosphite-triazole ligands **L61**-**67a**-**c**.[a]



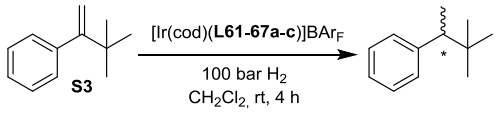
Entry	Ligand	% Conv[b]	ee%[b]
1	**L61a**	100	4 (*R*)
2	**L61b**	100	37(*S*)
3	**L61c**	95	51 (*R*)
4	**L62b**	100	45 (S)
5	**L63b**	100	31 (*S*)
6	**L63c**	100	48 (*R*)
7	**L64b**	100	40 (*S*)
8	**L65b**	100	31 (*S*)
9	**L65c**	100	33 (*R*)
10	**L66b**	100	33 (*S*)
11	**L66c**	100	40 (*R*)
12	**L67b**	100	46 (*S*)
13	**L67c**	100	56 (*R*)

[a] Reactions carried out using 0.5 mmol of **S1** and 2 mol% of Ir-catalyst precursor. [b] Conversion and enantiomeric excesses determined by chiral GC.

*Asymmetric hydrogenation of minimally functionalized disubstituted olefin 3,3-dimethyl-2-phenyl-1-butene (**S3**)*

As already explained in previous chapters, enantioselectivity is more difficult to control in the hydrogenation of disubstitued substrates than in trisubstituted olefins. Few known catalytic systems therefore can provide high enantioselectivities for these substrates, and those that do are usually limited in substrate scope.[3i,5c-d,23] In contrast to the hydrogenation of trisubstituted olefins, the enantioselectivity in the reduction of terminal alkenes is highly pressure dependent.[24] Therefore, hydrogenation at an atmospheric pressure of H_2 gave, in general, significantly higher ee values than at higher pressures. In this context, to further study the potential of the new phosphite-triazole ligand library **L61**-**L67a**-**e**, we also screened it in the Ir-catalyzed hydrogenation of the more demanding terminal olefin 3,3-dimethyl-2-phenyl-1-butene (**S3**). The results are shown in Table 3.7.4.

Table 3.7.4. Selected results for the Ir-catalyzed hydrogenation of **S2** using phosphite-triazole ligands **L61**-**67a**-**c**.[a]



Entry	Ligand	% Conv[b]	ee%[b]
1	**L61a**	100	13 (*R*)
2	**L61b**	100	84 (*S*)
3	**L61c**	100	85 (*R*)
4	**L62b**	100	83 (*S*)
5	**L63b**	100	74 (*S*)
6	**L63c**	100	81 (*R*)
7	**L64b**	100	75 (*S*)
8	**L65b**	100	70 (*S*)
9	**L65c**	100	63 (*R*)
10	**L66b**	100	77 (*S*)
11	**L66c**	100	85 (*R*)
12	**L67b**	100	61 (*S*)
13	**L67c**	100	87 (*R*)

[a] Reactions carried out using 0.5 mmol of **S1** and 2 mol% of Ir-catalyst precursor. [b] Conversion and enantiomeric excesses determined by chiral GC.

Surprisingly, enantioselectivities obtained in the reduction of substrate **S3** with ligands **L61**-**67a**-**c**, were higher (ee's up to 87%) than in the hydrogenation of (*E*)- and (*Z*)-trisubstituted alkenes **S1** and **S2.** In addition, a different trend was observed in this case. Both configurations of the biphenyl moiety of the phosphite group provided similar values of enantioselectivity but in the opposite sense. Therefore, both enantiomers of the hydrogenated product can be obtained in good enantioselectivities (ee's up to 84% (*S*) with ligands **L61**-**67b** and up to 87% (*R*) with ligands **L61**-**67c**).

Regarding the effect of varying the aryl group of the ligand backbone, no significantly changes were observed by varying the electronic properties of *para*-substituents (Table 3.7.4, entries 2, 4 and 5). In contrast, the use of ligands containing bulky aryl groups resulted in lower enantioselectivities (entries 7-9). Finally, although the presence of bulkier *N*-substituents in the triazole moiety led to a decrease on enantioselectivity for ligands **L66**-**67b**, similar values to **L61**-**L63b**-**c** were obtained when **L66**-**67c** were used.

3.7.3. Conclusions

The CuAAC reaction has been proved to be a mild tool for obtaining new highly modular triazole containing ligands. We have been therefore able to successfully develop a new chiral phosphite-triazole ligand library **L61**-**67a**-**c** in a few steps procedure. Ir-complexes made from these ligands were found in some cases as a mixture of two isomers. DFT calculations of [Ir(cod)(**L61b**-**c**)]BAr_F suggests that both isomers could be a result of two different conformations on the chelate ring. All Ir-complexes proved to be active in the Ir-catalyzed hydrogenation of minimally functionalized (*E*)- and (*Z*)-trisubstituted olefins (**S1** and **S2**) and disubstituted olefin **S3**. In general, enantioselectivities were highly affected by

the configuration of the phosphite biphenyl moiety. Although enantioselectivities were only moderate for hydrogenation of trisubstituted substrates (ee's up to 73%), promising results were obtained in the hydrogenation of the more challenging disubstituted substrate 3,3-dimethyl-2-phenyl-1-butene **S3** (ee's up to 87%). Interestingly, by simply changing the configuration of the biaryl phosphite group, both product enantiomers can be obtained in high enantiocontrol.

3.7.4. Experimental Part

3.7.4.1. General considerations

All reactions were carried out using standard Schlenk techniques under an atmosphere of argon. Solvents were purified and dried by standard procedures. Phosphorochloridites are easily prepared in one step from the corresponding biaryls.[25] ^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded using a 400 MHz spectrometer. Chemical shifts are relative to that of $SiMe_4$ (^{1}H and ^{13}C) as internal standard or H_3PO_4 (^{31}P) as external standard. ^{1}H, ^{13}C and ^{31}P assignments were made on the basis of ^{1}H-^{1}H gCOSY, ^{1}H-^{13}C gHSQC and ^{1}H-^{31}P gHMBC experiments.

3.7.4.2. Computational details

Geometries of all transition states were optimized using the Gaussian 09 program,[20] employing the B3LYP[17] density functional and the LANL2DZ[18d] basis set for iridium and the 6-31G*[18a-c] basis set for all other elements. Solvation correction was applied in the course of the optimizations using the PCM model with the default parameters for dichloromethane.[19] The complexes were treated with charge +1 and in the singlet state. No symmetry constraints were applied. The energies were further refined by performing single point calculations using the abovementioned parameters, with the exception that the 6-311+G**[21] basis set was used for all elements except iridium, and by applying dispersion correction using the DFT-D3[22] model. All energies reported are Gibbs free energies at 298.15 K and calculated as $G_{reported} = G_{6\text{-}31G^*} + E_{6\text{-}311+G^{**}} - E_{6\text{-}31G^*} + E_{DFT\text{-}D3}$.

3.7.4.3. General procedure for the preparation of enantiomerically pure propargylic alcohols (*R*)-1-4

The corresponding aldehyde (16 mmol) was solved in THF and was added dropwise to a cold THF solution (0° C) of ethynylmagnesium bromide (20 mmol, 40 mL, 0.5 M). The reaction mixture was allowed to stir overnight at room temperature. The reaction was quenched with saturated aqueous NH_4Cl and extracted with Et_2O (x3). The combined organic extracts were rinsed with brine, dried over $MgSO_4$ and concentrated. The corresponding crude propargylic alcohols were obtained as brown oils in quantitative yield, which were used with further purification.

Kinetic resolution of propargylic alcohols (*rac*)-**1**-**4** was performed using a reported procedure.[10] The enantiomerically pure acetate was separated from the corresponding alcohol by SiO_2-column chromatography (EtOAc/PE = 1:4).

Propargylic acetates (10 mmol) were hydrolyzed in 3 ml of a basic solution of K_2CO_3 (1 mmol, 138.2 mg) in 1:1 MeOH/H_2O. The mixture was stirred overnight and extracted with

ethyl acetate (x3). The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated. The corresponding enantiomerically pure propargylic alcohols were obtained in quantitative yields and were used without further purification. Compounds (*R*)-**1**-**2** and **4** are known compounds in the literature.[26]

(R)-1-(4-(Trifluoromethyl)phenyl)prop-2-yn-1-ol ((*R*)-3). ^{1}H NMR (400 MHz, C_6D_6): δ=2.49 (b, 1H, OH), 2.70 (d, 1H, CH≡, $^4J_{H-H}$ =2.4 Hz), 5.53 (b, 1H, CH-OH), 7.63-7.69 (m, 4H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ=63.7 (CH-OH), 75.5 (C≡), 82.7 (CH≡), 125.5 (CH=), 125.6 (CH=), 125.7 (CH=), 126.9 (CH=), 131.1 (C=), 143.6 (C=).

3.7.4.4. Synthesis of enantiomerically pure propargylic alcohol (*R*)-13

(*R*)-1-mesitylprop-2-yn-1-ol **13** was obtained following a slightly modified procedure.[11] Diethylzinc (1.5 M in toluene, 66 mmol, 43 mL) was added to a solution of (triisopropylsilyl)acetylene (66 mmol, 14.8 mL) in toluene (33 mL) at rt and then heated under reflux for 5 h. The reaction was cooled to room temperature and (*R*)-BINOL (6.1 mmol, 1.74 g) in DCM (40 mL) was added. The reaction mixture was stirred for 1 h before the $Ti(O^i\text{-}Pr)_4$ (15 mmol, 4.28 g) was added and the solution stirred for an additional 1 h. To this vigorously stirred orange solution was added dropwise a solution of mesitaldehyde (15 mmol, 2.1 mL) in dichloromethane (26 mL). The reaction was stirred 12 h and then quenched with sat. aq. NH_4Cl. The aqueous phase was extracted with DCM and the combined organic layers were dried over MgSO4 and concentrated under reduced pressure. The product was purified by flash SiO_2-column chromatography (EtOAc/PE = 1:1) affording a colorless oil which still contained part of unreacted TIPSCl.

The desired alcohol was obtained by treating a solution of (*R*)-**12** (4.2 g, 12.7 mmol) in THF (52 mL) with a THF solution of TBAF (1 M, 38.1 mL, 38.1 mmol). The reaction mixture was stirred for 1 h at room temperature and then H_2O was added to quench the reaction. The aqueous phase was extracted with Et_2O (x3). The combined organic layers were washed with H_2O and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash SiO_2-column chromatography (EtOAc/PE = 1:3) to afford (*R*)-**13** as a white solid (93% ee). The product was solved with the minimum amount of DCM and hexane was added. After leaving the mixture in the freezer (-18 °C), white crystals appeared. The crystals were filtered and washed with cold hexane to afford the enantiomerically pure alcohol (1.8 g, 69% yield for two steps, >99% ee). NMR data for compound **13** was already reported in the literature.[27]

(*R*)-1-mesityl-3-(triisopropylsilyl)prop-2-yn-1-ol (12). ^{1}H NMR (400 MHz, C_6D_6): δ=1.04 (s, 18H, CH_3, TIPS), 1.08 (s, 3H, CH_3, TIPS), 2.25 (s, 3H, CH_3), 2.50 (s, 6H, CH_3), 5.91 (d, 1H, CH-OH, $^3J_{H-H}$ =3.6 Hz), 6.83 (s, 2H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ=11.2 (CH_3, TIPS), 18.6 (CH), 20.3 (CH, TIPS), 60.8 (CH-OH), 86.8 (C≡), 107.0 (C≡), 129.8 (CH=), 133.5 (C=), 136.5 (C=), 137.5 (C).

3.7.4.5. Synthesis of triazole-alcohols (*S*)-5-8

To a solution of the corresponding chiral propargylic alcohol (*R*)-**1**-**4** (1 mmol) and benzyl azide (0.19 mL, 1.5 mmol) in 3 mL of 1:1 $H_2O/^tBuOH$, Na-ascorbate (39.6 mg, 0.2 mmol) and $CuSO_4.5H_2O$ (1.8 mg, 0.02 mmol) were added. The reaction mixture was stirred vigorously at room temperature overnight. Then, the mixture was diluted with ethyl

acetate and washed with water and brine. The organic layer was dried over Mg_2SO_4, filtered and concentrated resulting in a brown solid. Finally, the product was recrystallized from hot toluene, filtered, and washed with cold toluene (x3) to obtain a white powder.

Benzyl azide was prepared according to the literature procedure.[28]

(*S*)-(1-Phenethyl-1*H*-1,2,3-triazol-4-yl)(phenyl)methanol (5). Yield: 2.2 g (76%). ^{1}H NMR (400 MHz, C_6D_6): δ=2.17 (b, 1H, OH), 5.47 (s, 2H, CH_2, Bn), 6.02 (s, 1H, CH-OH), 7.23-7.42 (m, 11H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ=54.2 (CH_2, Bn), 69.1 (CH-OH), 121.2 (CH=, triazole), 126.4 (CH=), 127.9 (CH=), 128.0 (CH=), 128.6 (CH=), 128.8 (CH=), 129.1 (CH=), 134.4 (C=), 141.9 (C=), 151.9 (C=, triazole).

(*S*)-(1-Phenethyl-1*H*-1,2,3-triazol-4-yl)(*p*-tolyl)methanol (6). Yield: 793.9 (71%). ^{1}H NMR (400 MHz, C_6D_6): δ=2.32 (s, 3H, CH_3), 4.04 (b, 1H, OH), 5.39 (s, 2H, CH_2, Bn), 5.94 (s, 1H, CH-OH), 7.11 (d, 2H, CH=, $^3J_{H-H}$ =8.0 Hz), 7.18-7.21 (m, 2H, CH=), 7.22 (s, 1H, CH=), 7.28 (s, 1H, CH=, triazole), 7.30-7.33 (m, 4H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ=21.2 (CH_3), 54.1 (CH_2, Bn), 68.9 (CH-OH), 121.2 (CH=, triazole), 126.4 (CH=), 128.0 (CH=), 128.7 (CH=), 129.1 (CH=), 129.2 (CH=), 134.6 (C=), 137.5 (C=), 139.2 (C=), 152.0 (C=, triazole).

(*S*)-(1-Phenethyl-1*H*-1,2,3-triazol-4-yl)(4-(trifluoromethyl)phenyl)methanol (7). Yield: 986,6 mg (74%). ^{1}H NMR (400 MHz, C_6D_6): δ=1.67 (b, 1H, OH), 5.47 (s, 2H, CH_2, Bn), 6.08 (b, 1H, CH-OH), 7.23-7.25 (m, 3H, CH=), 7.34-7.38 (m, 3H, CH=), 7.56 (d, 2H, CH=, $^3J_{H-H}$ =8.0 Hz), 7.61 (d, 2H, CH=, $^3J_{H-H}$ =8.4 Hz). ^{13}C NMR (100.6 MHz, C_6D_6): δ=55.3 (CH_2, Bn), 68.2 (CH-OH), 121.3 (CH=, triazole), 125.4 (CH=), 125.5 (CH=), 126.7 (CH=), 128.1 (CH=), 128.8 (CH=), 129.1 (CH=), 134.2 (C=), 145.9 (C=), 151.2 (C=, triazole).

(*S*)-Naphthalen-1-yl(1-phenethyl-1*H*-1,2,3-triazol-4-yl)methanol (8). Yield: 974.1 mg (91%). ^{1}H NMR (400 MHz, C_6D_6): δ=4.03 (b, 1H, OH), 5.30 (d, 1H, CH_2, Bn, $^2J_{H-H}$ =14.8 Hz), 5.39 (d, 1H, CH_2, Bn, $^2J_{H-H}$ =14.8 Hz), 6.74 (s, 1H, CH-OH), 7.02 (s, 1H, CH=, triazole), 7.12 (m, 2H, CH=), 7.28 (m, 3H, CH=), 7.39-7.49 (m, 3H, CH=), 7.78-7.86 (m, 3H, CH=), 7.97 (d, 1H, CH=, $^3J_{H-H}$ =8.0 Hz). ^{13}C NMR (100.6 MHz, C_6D_6): δ=54.1 (CH_2, Bn), 66.4 (CH-OH), 121.8 (CH=, triazole), 123.8 (CH=), 123.9 (CH=), 125.5 (CH=), 125.6 (CH=), 126.2 (CH=), 127.9 (CH=), 128.6 (CH=), 128.7 (CH=), 129.0 (CH=), 130.3 (C=), 133.8 (C=), 133.4 (C=), 137.2 (C=), 151.4 (C=, triazole).

3.7.4.6. Synthesis of (*S*)-phenyl(1-phenyl-1*H*-1,2,3-triazol-4-yl)methanol (9)

Triazole-hydroxyl (*S*)-**9** was obtained following a reported procedure.[13] Concentrated aqueous hydrochloric acid solution [37% (v/v), 0.33 mL, 3.9 mmol] was added dropwise to a suspension of aniline (0.12 mL, 1.3 mmol) in water (0.6 mL) at 0 °C. After 15 min, a solution of sodium nitrite (138.0 mg, 2 mmol) in water (0.2 mL) was added via syringe. After 15 min, solid sodium bicarbonate was added until pH~7, followed by addition of a solution of sodium azide (156.0 mg, 2.4 mmol) in water (0.7 mL). The reaction mixture was allowed to warm to room temperature and stirred for 1 h. Then, a solution of propargylic alcohol (*R*)-**1** (132.2 mg, 1.0 mmol) in ^{t}BuOH (1.5 mL) was added to the mixture containing phenyl azide, followed by the addition of Na-ascorbate (39.6 mg, 0.2 mmol) and $CuSO_4.5H_2O$ (1.8 mg, 0.02 mmol). The reaction mixture was stirred overnight at room temperature. Then, the mixture was diluted with ethyl acetate and washed with water and brine. The organic layer was dried over Mg_2SO_4, filtered and concentrated resulting in a brown solid. Finally, the product was recrystallized from hot toluene, filtered, and washed with cold toluene (x3) to

obtain a white powder. Yield: 367.9 mg (49%). ^{1}H NMR (400 MHz, C_6D_6): δ=3.84 (b, 1H, OH), 6.12 (s, 1H, CH-OH), 7.29-7.52 (m, 8H, CH=), 7.64 (d, 2H, $^{3}J_{H-H}$ =8.0 Hz), 7.72 (s, 1H, CH=, triazole). ^{13}C NMR (100.6 MHz, C_6D_6): δ=69.1 (CH-OH), 119.6 (CH=), 120.5 (CH=, triazole), 126.5 (CH=), 128.1 (CH=), 128.7 (CH=), 128.8 (CH=), 129.7 (CH=), 136.9 (C=), 141.8 (C=), 152.2 (C=, triazole).

3.7.4.7. Synthesis of (*S*)-mesityl(1-phenethyl-1*H*-1,2,3-triazol-4-yl)methanol (14)

To a solution of the chiral propargylic alcohol (*R*)-**13** (1 mmol) and benzyl azide (0.19 mL, 1.5 mmol) in 3 mL of 1:1 H_2O/^{t}BuOH and **15**.CuCl[14] (2.8 mg, 0.005 mmol) was added. The reaction mixture was stirred vigorously at room temperature overnight. Then, the mixture was diluted with ethyl acetate and washed with water and brine. The organic layer was dried over Mg_2SO_4, filtered and concentrated resulting in a colorless oil. Yield: 1.0 g (82%). ^{1}H NMR (400 MHz, C_6D_6): δ=2.24 (s, 3H, CH_3), 2.25 (s, 6H, CH_3), 3.31 (b, 1H, OH), 5.46 (s, 2H, CH_2, Bn), 6.36 (s, 1H, CH-OH), 6.81 (s, 2H, CH=), 7.12 (s, 1H, CH=, triazole), 7.18-7.21 (m, 2H, CH=), 7.33-7.35 (m, 3H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ=20.6 (CH_3), 20.9 (CH_3), 54.1 (CH_2, Bn), 65.8 (CH-OH), 120.7 (CH=, triazole), 127.8 (CH=), 128.7 (CH=), 129.0 (CH=), 130.1 (CH=), 134.2 (C=), 134.8 (C=), 136.8 (C=), 137.5 (C=), 150.8 (C=, triazole).

3.7.4.8. Synthesis of (*S*)-Phenyl(1H-1,2,3-triazol-4-yl)methanol (10)

To a solution of the chiral propargylic alcohol (*R*)-**1** (1 mmol) in DMF (2 mL) were added CuBr (20 mg, 0.14 mmol), Et_3N (0.14 mL, 1 mmol), and H_2O (0.04 mL, 2 mmol). The reation mixture was bubbled with argon over 10 min and azidotrimethylsilane (0.15 mL, 1.1 mmol) was added. The reaction mixture was stirred at 100 °C overnight under atmosphere of Ar. Then, the mixture was diluted with ethyl acetate and washed with water and brine. The organic layer was dried over Mg_2SO_4, filtered and concentrated. The crude residue was purified by SiO_2-column chromatography (EtOAc) as a white solid. Yield: 1.1 g (90%). 1H NMR (400 MHz, C6D6): δ=6.04 (s, 1H, CH-OH), 7.31-7.43 (m, 5H, CH=), 7.49 (m, 1H, CH=). ^{13}C NMR (100.6 MHz, C6D6): δ=69.2 (CH-OH), 126.5 (CH=), 128.3 (CH=), 128.8 (CH=).

3.7.4.9. Synthesis of Phenyl(1-trityl-1H-1,2,3-triazol-4-yl)methanol (11)

Tritylchloride (10.8 g, 30.6 mmol) was added to a solution of triazole-alcohol (*S*)-**10** (8.2 g, 26.4 mmol) in pyridine (46 mL, 571.0 mmol). The reaction mixture was allowed to stir at room temperature overnight. The solution was concentrated under vacuum and the resulting residue was purified by SiO_2-column chromatography (EtOAc/PE = 1:1) to yield the product as a white solid. Yield: 1.0 g (40%). 1H NMR (400 MHz, C6D6): δ=6.02 (s, 1H, CH-OH), 7.09-7.11 (m, 6H, CH=), 7.27-7.32 (m, 13H, CH=), 4.41 (d, 2H, CH=, 3JH-H =6.8 Hz). 13C NMR (100.6 MHz, C6D6): δ=69.3 (CH-OH), 79.2 (C, Tr), 124.1 (CH=, triazole), 126.5 (CH=), 127.9 (CH=), 128.0 (CH=), 128.3 (CH=), 128.5 (CH=), 130.0 (CH=), 142.0 (C=), 149.1 (C=, triazole).

3.7.4.10. Typical Procedure for the Preparation of Triazole-Phosphite Ligands L61-L67a-c

The corresponding phosphorochloridite (1.1 mmol) produced in situ was dissolved in toluene (5 mL), and pyridine (0.30 mL, 3.9 mmol) was added. The corresponding triazol-hydroxyl compound (1 mmol) was azeotropically dried with toluene (3 x 2 mL) and then dissolved in toluene (5 mL) to which pyridine (0.30 mL, 3.9 mmol) was added. The alcohol solution was transferred slowly to a solution of phosphorochloridite. The reaction mixture was stirred at 80°C for 90 min, after which the pyridine salts were removed by filtration. Evaporation of the solvent gave a white foam, which was purified by flash chromatography in silica (toluene/hexane/NEt3 = 8:2:0.1) to produce the corresponding ligand as a white solid.

L61a. Yield: 415 mg (59%). ^{31}P NMR (400 MHz, C_6D_6): δ=144.5 (s). ^{1}H NMR (400 MHz, C_6D_6): δ=1.23 (s, 9H, CH_3, ^{t}Bu), 1.24 (s, 9H, CH_3, ^{t}Bu), 1.31 (s, 18H, CH_3, ^{t}Bu), 4.52 (d, 1H, CH_2, Bn, $^2J_{H-H}$ =14.8 Hz), 4.82 (d, 1H, CH_2, Bn, $^2J_{H-H}$ =14.8 Hz), 6.72 (d, 1H, CH-OP, $^3J_{H-P}$ =9.2 Hz), 6.77 (m, 2H, CH=), 6.84 (s, 1H, CH=), 6.92-7.12 (m, 6H, CH=), 7.27 (d, 2H, CH=, $^3J_{H-H}$ =7.2 Hz), 7.30 (d, 1H, CH=, $^4J_{H-H}$ =2.4 Hz), 7.32 (d, 1H, CH=, $^4J_{H-H}$ =2.0 Hz), 7.50 (d, 1H, CH=, $^4J_{H-H}$ =2.0 Hz), 7.53 (d, 1H, CH=, $^4J_{H-H}$ =2.8 Hz). ^{13}C NMR (100.6 MHz, C_6D_6): δ=30.8 (CH_3, ^{t}Bu), 31.2 (CH_3, ^{t}Bu), 34.3 (C, ^{t}Bu), 35.1 (C, ^{t}Bu), 35.2 (C, ^{t}Bu), 53.1 (CH_2, Bn), 73.5 (d, CH-OP, $^2J_{C-P}$ =13.1 Hz), 121.1-150.0 (aromatic carbons). MS HR-ESI [found 726.3795, $C_{44}H_{54}N_3O_3P$ $(M-Na)^+$ requires 726.3795].

L61b. Yield: 401 mg (62%). ^{31}P NMR (400 MHz, C_6D_6): δ=144.1 (s). ^{1}H NMR (400 MHz, C_6D_6): δ=1.33 (s, 9H, CH_3, ^{t}Bu), 1.36 (s, 9H, CH_3, ^{t}Bu), 1.69 (s, 3H, CH_3), 1.75 (s, 3H, CH_3), 2.04 (s, 3H, CH_3), 2.07 (s, 3H, CH_3), 4.51 (d, 1H, CH_2, Bn, $^2J_{H-H}$ =14.8 Hz), 4.88 (d, 1H, CH_2, Bn, $^2J_{H-H}$ =15.2 Hz), 6.64 (d, 1H, CH-OP, $^3J_{H-P}$ =8.4 Hz), 6.80-6.82 (m, 2H, CH=), 6.87 (s, 1H, C=H), 6.98-7.08 (m, 5H, CH=), 7.16 (s, 2H, CH=), 7.18 (s, 1H, CH=), 7.35 (s, 1H, CH=), 7.37 (s, 1H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ=16.3 (CH_3), 16.6 (CH_3), 20.1 (CH_3), 20.2 (CH_3), 31.0 (d, CH_3, ^{t}Bu, J_{C-P} =5.3 Hz), 31.4 (CH_3, ^{t}Bu), 34.4 (C, ^{t}Bu), 34.7 (C, ^{t}Bu), 53.3 (CH_2, Bn), 73.7 (d, CH-OP, $^2J_{C-P}$ =16.9 Hz), 121.2-150.3 (aromatic carbons). MS HR-ESI [found 670.3168, $C_{40}H_{46}N_3O_3P$ $(M-Na)^+$ requires 670.3169].

L61c. Yield: 285 mg (44%). ^{31}P NMR (400 MHz, C_6D_6): δ=137.7 (s). ^{1}H NMR (400 MHz, C_6D_6): δ=1.33 (s, 9H, CH_3, ^{t}Bu), 1.34 (s, 9H, CH_3, ^{t}Bu), 1.68 (s, 3H, CH_3), 1.78 (s, 3H, CH_3), 2.03 (s, 3H, CH_3), 2.11 (s, 3H, CH_3), 4.67 (d, 1H, CH_2, Bn, $^2J_{H-H}$ =13.2 Hz), 4.84 (d, 1H, CH_2, Bn, $^2J_{H-H}$ =14.8 Hz), 6.42 (d, 1H, CH-OP, $^3J_{H-P}$ =9.2 Hz), 6.84-6.85 (m, 2H, CH=), 6.97-7.21 (9H, CH=), 7.32 (s, 1H, CH=), 7.34 (s, 1H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ=16.4 (CH_3), 16.7 (CH_3), 20.3 (CH_3), 20.4 (CH_3), 31.1 (d, CH_3, ^{t}Bu, J_{C-P} =4.5 Hz), 31.5 (CH_3, ^{t}Bu), 34.5 (C, ^{t}Bu), 34.8 (C, ^{t}Bu), 53.4 (CH_2, Bn), 73.9 (d, CH-OP, $^2J_{C-P}$ =9.9 Hz), 127.8-150.0 (aromatic carbons). MS HR-ESI [found 670.3164, $C_{40}H_{46}N_3O_3P$ $(M-Na)^+$ requires 670.3169].

L62b. Yield: 424 mg (64%). ^{31}P NMR (400 MHz, CD_2Cl_2): δ=139.0 (s). ^{1}H NMR (400 MHz, CD_2Cl_2): δ=1.15 (s, 9H, CH_3, ^{t}Bu), 1.18 (s, 9H, CH_3, ^{t}Bu), 1.78 (s, 3H, CH_3), 1.89 (s, 3H, CH_3), 2.26 (s, 3H, CH_3), 2.34 (s, 6H, CH_3), 5.38 (d, 1H, CH_2, Bn, $^2J_{H-H}$ =14.4 Hz), 5.51 (d, 1H, CH_2, Bn, $^2J_{H-H}$ =14.8 Hz), 6.24 (d, 1H, CH-OP, $^3J_{H-P}$ =8.8 Hz), 7.10-7.14 (m, 6H, CH=), 7.26-7.28 (m, 2H, C=H), 7.36-7.41 (m, 4H, CH=). ^{13}C NMR (100.6 MHz, CD_2Cl_2): δ=16.1 (CH_3), 16.4 (CH_3), 20.1 (CH_3), 20.9 (CH_3), 30.6 (d, CH_3, ^{t}Bu, J_{C-P} =4.6 Hz), 30.9 (CH_3, ^{t}Bu), 34.2 (C, ^{t}Bu), 34.4 (C, ^{t}Bu),

53.4 (CH_2, Bn), 72.9 (d, CH-OP, $^2J_{C\text{-}P}$ =14.5 Hz), 121.4-150.0 (aromatic carbons). MS HR-ESI [found 684.3322, $C_{41}H_{48}N_3O_3P$ $(M\text{-}Na)^+$ requires 684.3326].

L63b. Yield: 437 mg (61%). ^{31}P NMR (400 MHz, C_6D_6): δ=140.4 (s). ^{1}H NMR (400 MHz, C_6D_6): δ=1.24 (s, 9H, CH_3, ^{t}Bu), 1.30 (s, 9H, CH_3, ^{t}Bu), 1.63 (s, 3H, CH_3), 1.70 (s, 3H, CH_3), 2.99 (s, 3H, CH_3), 2.02 (s, 3H, CH_3), 4.53 (d, 1H, CH_2, Bn, $^2J_{H\text{-}H}$ =15.6 Hz), 4.83 (d, 1H, CH_2, Bn, $^2J_{H\text{-}H}$ =14.1 Hz), 6.53 (d, 1H, CH-OP, $^3J_{H\text{-}P}$ =8.4 Hz), 6.76-6.80 (m, 3H, CH=), 6.94-7.00 (m, 4H, C=H), 7.19-7.25 (m, 4H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ=16.8 (CH_3), 17.1 (CH_3), 20.6 (CH_3), 20.7 (CH_3), 31.4 (d, CH_3, ^{t}Bu, $J_{C\text{-}P}$ =5.3 Hz), 31.9 (CH_3, ^{t}Bu), 34.9 (C, ^{t}Bu), 35.3 (C, ^{t}Bu), 54.0 (CH_2, Bn), 73.2 (d, CH-OP, $^2J_{C\text{-}P}$ =16.8 Hz), 121.7-150.0 (aromatic carbons). MS HR-ESI [found 738.3040, $C_{41}H_{45}F_3N_3O_3P$ $(M\text{-}Na)^+$ requires 738.3043].

L63c. Yield: 300 mg (42%). ^{31}P NMR (400 MHz, CD_2Cl_2): δ=132.5 (s). ^{1}H NMR (400 MHz, CD_2Cl_2): δ=1.14 (s, 9H, CH_3, ^{t}Bu), 1.19 (s, 9H, CH_3, ^{t}Bu), 1.79 (s, 3H, CH_3), 1.96 (s, 3H, CH_3), 2.26 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 5.43 (d, 1H, CH_2, Bn, $^2J_{H\text{-}H}$ =15.6 Hz), 5.48 (d, 1H, CH_2, Bn, $^2J_{H\text{-}H}$ =14.2 Hz), 5.88 (d, 1H, CH-OP, $^3J_{H\text{-}P}$ =9.8 Hz), 7.25-7.31 (m, 4H, CH=), 7.39-7.45 (m, 5H, C=H), 7.55 (d, 2H, CH=, $^3J_{H\text{-}H}$ =8.8 Hz). ^{13}C NMR (100.6 MHz, CD_2Cl_2): δ=16.0 (CH_3), 16.3 (CH_3), 20.1 (CH_3), 31.4 (d, CH_3, ^{t}Bu, $J_{C\text{-}P}$ =5.3 Hz), 30.8 (CH_3, ^{t}Bu), 34.1 (C, ^{t}Bu), 34.5 (C, ^{t}Bu), 53.4 (CH_2, Bn), 72.7 (CH-OP), 121.7-148.6 (aromatic carbons). MS HR-ESI [found 738.3041, $C_{41}H_{45}F_3N_3O_3P$ $(M\text{-}Na)^+$ requires 738.3043].

L64b. Yield: 467 mg (67%). ^{31}P NMR (400 MHz, CD_2Cl_2): δ=137.7 (s). ^{1}H NMR (400 MHz, CD_2Cl_2): δ=1.16 (s, 9H, CH_3, ^{t}Bu), 1.20 (s, 9H, CH_3, ^{t}Bu), 1.84 (s, 3H, CH_3), 1.96 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 5.31 (d, 1H, CH_2, Bn, $^2J_{H\text{-}H}$ =14.2 Hz), 5.47 (d, 1H, CH_2, Bn, $^2J_{H\text{-}H}$ =14.8 Hz), 7.07 (s, 2H, CH-OP, CH=), 7.19-7.40 (m, 6H, CH=), 7.45-7.52 (m, 3H, CH=), 7.67 (d, 1H, CH=, $^3J_{H\text{-}H}$ =7.2 Hz), 7.86 (d, 1H, CH=, $^3J_{H\text{-}H}$ =8.0 Hz), 7.90 (d, 1H, CH=, $^3J_{H\text{-}H}$ =8.0 Hz), 8.03 (d, 1H, CH=, $^3J_{H\text{-}H}$ =7.6 Hz). ^{13}C NMR (100.6 MHz, CD_2Cl_2): δ=16.2 (CH_3), 16.5 (CH_3), 20.2 (CH_3), 30.6 (d, CH_3, ^{t}Bu, $J_{C\text{-}P}$ =4.6 Hz), 31.0 (CH_3, ^{t}Bu), 34.3 (C, ^{t}Bu), 34.5 (C, ^{t}Bu), 54.0 (CH_2, Bn), 70.8 (d, CH-OP, $^2J_{C\text{-}P}$ =15.4 Hz), 122.0-149.7 (aromatic carbons). MS HR-ESI [found 720.3322, $C_{44}H_{48}N_3O_3P$ $(M\text{-}Na)^+$ requires 720.3326].

L65b. Yield: 407 mg (59%). ^{31}P NMR (400 MHz, C_6D_6): δ=138.7 (s). ^{1}H NMR (400 MHz, C_6D_6): δ=1.31 (s, 9H, CH_3, ^{t}Bu), 1.42 (s, 9H, CH_3, ^{t}Bu), 1.69 (s, 3H, CH_3), 1.76 (s, 3H, CH_3), 2.04 (s, 3H, CH_3), 2.09 (s, 6H, CH_3), 2.32 (s, 6H, CH_3), 4.60 (d, 1H, CH_2, Bn, $^2J_{H\text{-}H}$ =14.8 Hz), 4.88 (d, 1H, CH_2, Bn, $^2J_{H\text{-}H}$ =14.8 Hz), 6.69 (s, 2H, CH=), 6.81 (m, 2H, C=H), 6.98-7.17 (m, 6H, CH=), 7.29 (d, 1H, CH-OP, $^3J_{H\text{-}P}$ =8.0 Hz). ^{13}C NMR (100.6 MHz, C_6D_6): δ=16.9 (CH_3), 17.2 (CH_3), 20.7 (CH_3), 20.8 (CH_3), 21.3 (CH_3), 31.5 (d, CH_3, ^{t}Bu, $J_{C\text{-}P}$ =5.3 Hz), 31.9 (CH_3, ^{t}Bu), 35.0 (C, ^{t}Bu), 35.4 (C, ^{t}Bu), 53.8 (CH_2, Bn), 70.5 (d, CH-OP, $^2J_{C\text{-}P}$ =16.8 Hz), 122.0-138.9 (aromatic carbons). MS HR-ESI [found 712.3637, $C_{43}H_{52}N_3O_3P$ $(M\text{-}Na)^+$ requires 712.3639].

L65c. Yield: 317 mg (46%). ^{31}P NMR (400 MHz, C_6D_6): δ=132.0 (s). ^{1}H NMR (400 MHz, C_6D_6): δ=1.26 (s, 9H, CH_3, ^{t}Bu), 1.29 (s, 9H, CH_3, ^{t}Bu), 1.65 (s, 3H, CH_3), 1.78 (s, 3H, CH_3), 2.00 (s, 3H, CH_3), 2.04 (s, 3H, CH_3), 2.07 (s, 3H, CH_3), 2.33 (b, 6H, CH_3), 4.59 (d, 1H, CH_2, Bn, $^2J_{H\text{-}H}$ =14.8 Hz), 4.81 (d, 1H, CH_2, Bn, $^2J_{H\text{-}H}$ =14.8 Hz), 6.66 (s, 2H, CH=), 6.78 (m, 2H, C=H), 6.84 (d, 1H, CH-OP, $^3J_{H\text{-}P}$ =9.6 Hz), 6.93-7.14 (m, 6H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ=16.9 (CH_3), 17.2 (CH_3), 20.7 (CH_3), 21.2 (CH_3), 31.5 (d, CH_3, ^{t}Bu, $J_{C\text{-}P}$ =5.3 Hz), 31.9 (CH_3, ^{t}Bu), 35.0 (C, ^{t}Bu), 35.3 (C, ^{t}Bu), 53.8 (CH_2, Bn), 71.8 (CH-OP), 122.0-149.8 (aromatic carbons). MS HR-ESI [found 712.3638, $C_{43}H_{52}N_3O_3P$ $(M\text{-}Na)^+$ requires 712.3638].

L66b. Yield: 387 mg (61%). ^{31}P NMR (400 MHz, C_6D_6): δ=138.6 (s). ^{1}H NMR (400 MHz, C_6D_6): δ=1.42 (s, 9H, CH_3, ^{t}Bu), 1.48 (s, 9H, CH_3, ^{t}Bu), 1.76 (s, 3H, CH_3), 1.88 (s, 3H, CH_3), 2.17 (s, 3H, CH_3), 2.18 (s, 3H, CH_3), 6.65 (d, 1H, CH-OP, $^3J_{H-P}$ =8.8 Hz), 6.92-6.98 (m, 3H, CH=), 7.06-7.27 (m, 7H, CH=), 7.47 (s, 1H, CH=), 7.29 (d, 2H, CH=, $^3J_{H-H}$ =7.6 Hz). ^{13}C NMR (100.6 MHz, C_6D_6): δ=16.9 (CH_3), 17.2 (CH_3), 20.7 (CH_3), 20.8 (CH_3), 31.5 (d, CH_3, ^{t}Bu, J_{C-P} =5.3 Hz), 31.9 (CH_3, ^{t}Bu), 35.0 (C, ^{t}Bu), 35.4 (C, ^{t}Bu), 74.2 (d, CH-OP, $^2J_{C-P}$ =13.0 Hz), 119.8-151.6 (aromatic carbons). MS HR-ESI [found 656.3008, $C_{39}H_{44}N_3O_3P$ $(M-Na)^+$ requires 656.3012].

L66c. Yield: 317 mg (50%). ^{31}P NMR (400 MHz, C_6D_6): δ=139.8 (s). ^{1}H NMR (400 MHz, C_6D_6): δ=1.36 (s, 9H, CH_3, ^{t}Bu), 1.42 (s, 9H, CH_3, ^{t}Bu), 1.70 (s, 3H, CH_3), 1.79 (s, 3H, CH_3), 2.04 (s, 3H, CH_3), 2.09 (s, 3H, CH_3), 6.67 (d, 1H, CH-OP, $^3J_{H-P}$ =8.8 Hz), 6.89-6.91 (m, 2H, CH=), 6.99-7.16 (m, 5H, C=H), 7.22-7.26 (m, 3H, CH=), 7.44 (d, 2H, CH=, $^3J_{H-H}$ =7.6 Hz), 7.48 (s, 1H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ=16.9 (CH_3), 17.2 (CH_3), 20.7 (CH_3), 20.8 (CH_3), 31.5 (d, CH_3, ^{t}Bu, J_{C-P} =5.3 Hz), 32.0 (CH_3, ^{t}Bu), 35.0 (C, ^{t}Bu), 35.4 (C, ^{t}Bu), 74.1 (d, CH-OP, $^2J_{C-P}$ =14.6 Hz), 120.5-151.1 (aromatic carbons). MS HR-ESI [found 656.3011, $C_{39}H_{44}N_3O_3P$ $(M-Na)^+$ requires 656.3012].

L67b. Yield: 472 mg (59%). ^{31}P NMR (400 MHz, C_6D_6): δ=140.2 (s). ^{1}H NMR (400 MHz, C_6D_6): δ=1.34 (s, 9H, CH_3, ^{t}Bu), 1.42 (s, 9H, CH_3, ^{t}Bu), 1.69 (s, 3H, CH_3), 1.74 (s, 3H, CH_3), 2.04 (s, 3H, CH_3), 2.09 (s, 3H, CH_3), 6.68 (d, 1H, CH-OP, $^3J_{H-P}$ =8.4 Hz), 6.92-7.18 (m, 20H, CH=), 7.33 (d, 2H, CH=, $^3J_{H-H}$ =6.8 Hz), 7.50 (s, 1H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ=16.9 (CH_3), 17.2 (CH_3), 20.7 (CH_3), 20.8 (CH_3), 31.7 (d, CH_3, ^{t}Bu, J_{C-P} =5.3 Hz), 32.1 (CH_3, ^{t}Bu), 35.0 (C, ^{t}Bu), 35.3 (C, ^{t}Bu), 74.2 (d, CH-OP, $^2J_{C-P}$ =15.3 Hz), 79.8 (C, Tr), 124.2-148.6 (aromatic carbons). MS HR-ESI [found 822.3793, $C_{52}H_{54}N_3O_3P$ $(M-Na)^+$ requires 822.3795].

L67c. Yield: 336 mg (42%). ^{31}P NMR (400 MHz, C_6D_6): δ=135.3 (s). ^{1}H NMR (400 MHz, C_6D_6): δ=1.34 (s, 9H, CH_3, ^{t}Bu), 1.43 (s, 9H, CH_3, ^{t}Bu), 1.70 (s, 3H, CH_3), 1.83 (s, 3H, CH_3), 2.04 (s, 3H, CH_3), 2.14 (s, 3H, CH_3), 6.27 (d, 1H, CH-OP, $^3J_{H-P}$ =9.2 Hz), 6.93-7.19 (m, 20H, CH=), 7.39 (d, 2H, CH=, $^3J_{H-H}$ =6.8 Hz), 7.43 (s, 1H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ=16.8 (CH_3), 17.1 (CH_3), 20.7 (CH_3), 20.8 (CH_3), 31.7 (d, CH_3, ^{t}Bu, J_{C-P} =5.3 Hz), 32.0 (CH_3, ^{t}Bu), 35.0 (C, ^{t}Bu), 35.3 (C, ^{t}Bu), 74.7 (d, CH-OP, $^2J_{C-P}$ =4.5 Hz), 79.7 (C, Tr), 124.9-148.1 (aromatic carbons). MS HR-ESI [found 822.3792, $C_{52}H_{54}N_3O_3P$ $(M-Na)^+$ requires 822.3795].

3.7.4.11. Typical Procedure for the Preparation of [Ir(cod)(L)]BAr$_F$ (L=L61–L67a–c)

The corresponding ligand (0.037 mmol) was dissolved in CH_2Cl_2 (2 mL) and $[Ir(\mu\text{-}Cl)(cod)]_2$ (12.5 mg, 0.0185 mmol) was added. The reaction mixture was refluxed at 50°C for 1 hour. After 5 min at room temperature, $NaBAr_F$ (38.6 mg, 0.041 mmol) and water (2 mL) were added and the reaction mixture was stirred vigorously for 30 min at room temperature. The phases were separated and the aqueous phase was extracted twice with CH_2Cl_2. The combined organic phases were dried with $MgSO_4$, filtered through a plug of celite and the solvent was evaporated to give the product as orange solids.

[Ir(cod)(L61a)]BAr$_F$. Yield: 64 mg (93%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ=99.1 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.31 (s, 9H, CH_3, ^{t}Bu), 1.35 (s, 18H, CH_3, ^{t}Bu), 1.38 (s, 9H, CH_3, ^{t}Bu), 1.92-1.97 (m, 2H, CH_2, cod), 1.98-2.08 (m, 1H, CH_2, cod), 2.15-2.29 (m, 5H, CH_2, cod), 2.93 (b, 1H, CH=, cod), 4.03 (b, 1H, CH=, cod), 5.30-5.45 (m, 3H, CH_2 Bn, CH= cod), 6.09-1.14 (m, 1H, CH=, cod), 6.54 (d, 1H, CH-OP, $^3J_{H-P}$ =7.6 Hz), 7.03-7.71 (m, 27H, CH= aromatic). ^{13}C

NMR (100.6 MHz, $CDCl_3$): δ=27.4 (CH_2, cod), 29.4 (b, CH_2, cod), 31.1 (CH_3, ^tBu), 31.3 (CH_3, ^tBu), 31.4 (CH_3, ^tBu), 31.8 (b, CH_2, cod), 32.2 (CH_3, ^tBu), 33.9 (CH_2, cod), 34.7 (C, ^tBu), 34.9 (C, ^tBu), 35.3 (C, ^tBu), 35.6 (C, ^tBu), 56.5 (CH_2, Bn), 63.2 (CH=, cod), 71.6 (CH=, cod), 73.1 (d, CH-OP, $^2J_{C\text{-}P}$ =7.0 Hz), 106.2 (d, CH=, cod, $J_{C\text{-}P}$ =17.3 Hz), 106.7 (d, CH=, cod, $J_{C\text{-}P}$ =15.8 Hz), 117.4-149.3 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^1J_{C\text{-}B}$ =49.8 Hz). MS HR-ESI [found 1004.4470, $C_{52}H_{54}IrN_3O_3P$ $(M\text{-}BAR_F)^+$ requires 1004.4471].

[Ir(cod)(L61b)]BAr_F. Yield: 64 mg (95%). **Isomer A** (70%): ^{31}P NMR (161.9 MHz, $CDCl_3$): δ=97.0 (s). ^1H NMR (400 MHz, $CDCl_3$): δ=1.32 (s, 9H, CH_3, ^tBu), 1.47 (s, 9H, CH_3, ^tBu), 1.69 (s, 3H, CH_3), 1.82 (s, 3H, CH_3), 1.95-2.36 (m, 8H, CH_2, cod), 2.19 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 2.54 (b, 1H, CH=, cod), 4.15 (b, 1H, CH=, cod), 5.33-5.42 (m, 2H, CH_2, Bn), 5.96 (m, 2H, CH=, cod), 6.17 (d, 1H, CH-OP, $^3J_{H\text{-}P}$ =8.8 Hz), 7.02-7.71 (m, 25H, CH= aromatic). ^{13}C NMR (125.9 MHz, $CDCl_3$): δ=16.4 (CH_3), 16.5 (CH_3), 20.3 (CH_3), 20.4 (CH_3), 27.7 (CH_2, cod), 28.2 (CH_2, cod), 31.3 (CH_3, ^tBu), 32.3 (CH_3, ^tBu), 32.8 (CH_2, cod), 33.3 (d, CH_2, cod, $J_{C\text{-}P}$ =3.9 Hz), 34.7 (C, ^tBu), 35.0 (C, ^tBu), 56.5 (CH_2, Bn), 61.0 (CH=, cod), 69.5 (CH=, cod), 73.5 (CH-OP), 104.9 (d, CH=, cod, $J_{C\text{-}P}$ =16.4 Hz), 107.0 (d, CH=, cod, $J_{C\text{-}P}$ =15.5 Hz), 117.4-148.1 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^1J_{C\text{-}B}$ =51.6 Hz). **Isomer B** (30%): ^{31}P NMR (161.9 MHz, $CDCl_3$): δ=98.6 (s). ^1H NMR (400 MHz, $CDCl_3$): δ=1.28 (s, 9H, CH_3, ^tBu), 1.32 (s, 9H, CH_3, ^tBu), 1.83 (s, 3H, CH_3), 1.84 (s, 3H, CH_3), 1.95-2.36 (m, 8H, CH_2, cod), 2.21 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 2.69 (b, 1H, CH=, cod), 4.15 (b, 1H, CH=, cod), 5.33-5.51 (m, 3H, CH_2 Bn, CH= cod), 6.07 (m, 1H, CH=, cod), 6.48 (d, 1H, CH-OP, $^3J_{H\text{-}P}$ =8.0 Hz), 6.98-7.71 (m, 25H, CH= aromatic). ^{13}C NMR (125.9 MHz, $CDCl_3$): δ=16.4 (CH_3), 20.3 (CH_3), 20.4 (CH_3), 27.5 (b, CH_2, cod), 29.5 (b, CH_2, cod), 29.7 (CH_3, ^tBu), 31.9 (d, CH_2, cod, $J_{C\text{-}P}$ =5.0 Hz), 32.4 (CH_3, ^tBu), 33.9 (CH_2, cod), 34.6 (C, ^tBu), 35.9 (C, ^tBu), 56.4 (CH_2, Bn), 62.6 (CH=, cod), 72.4 (CH=, cod), 73.3 (d, CH-OP, $^2J_{C\text{-}P}$ =7.6 Hz), 105.3 (d, CH=, cod, $J_{C\text{-}P}$ =13.1 Hz), 106.0 (d, CH=, cod, $J_{C\text{-}P}$ =15.5 Hz), 117.4-148.1 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^1J_{C\text{-}B}$ =51.6 Hz). MS HR-ESI [found 948.3841, $C_{48}H_{58}IrN_3O_3P$ $(M\text{-}BAR_F)^+$ requires 948.3845].

[Ir(cod)(L61c)]BAr_F. Yield: 62 mg (93%). **Isomer A** (10%): ^{31}P NMR (161.9 MHz, $CDCl_3$): δ=97.0 (s). ^1H NMR (400 MHz, $CDCl_3$): δ=1.32 (s, 9H, CH_3, ^tBu), 1.47 (s, 9H, CH_3, ^tBu), 1.69 (s, 3H, CH_3), 1.83 (s, 3H, CH_3), 1.95-2.28 (m, 8H, CH_2, cod), 2.19 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 2.55 (b, 1H, CH=, cod), 4.18 (b, 1H, CH=, cod), 5.32-5.38 (m, 2H, CH_2, Bn), 5.95 (m, 2H, CH=, cod), 6.19 (d, 1H, CH-OP, $^3J_{H\text{-}P}$ =8.0 Hz), 7.01-7.71 (m, 25H, CH= aromatic). ^{13}C NMR (125.9 MHz, $CDCl_3$): δ=16.4 (CH_3), 16.5 (CH_3), 20.2 (CH_3), 20.4 (CH_3), 27.6 (CH_2, cod), 28.2 (CH_2, cod), 31.9 (CH_3, ^tBu), 32.3 (CH_3, ^tBu), 32.8 (CH_2, cod), 33.3 (CH_2, cod), 34.7 (C, ^tBu), 35.0 (C, ^tBu), 56.5 (CH_2, Bn), 61.0 (CH=, cod), 69.6 (CH=, cod), 73.5 (CH-OP), 104.9 (d, CH=, cod, $J_{C\text{-}P}$ =16.4 Hz), 107.0 (d, CH=, cod, $J_{C\text{-}P}$ =15.1 Hz), 117.4-148.1 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^1J_{C\text{-}B}$ =50.4 Hz). **Isomer B** (90%): ^{31}P NMR (161.9 MHz, $CDCl_3$): δ=98.6 (s). ^1H NMR (400 MHz, $CDCl_3$): δ=1.28 (s, 9H, CH_3, ^tBu), 1.32 (s, 9H, CH_3, ^tBu), 1.74 (s, 3H, CH_3), 1.84 (s, 3H, CH_3), 1.95-2.31 (m, 8H, CH_2, cod), 2.21 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 2.69 (b, 1H, CH=, cod), 4.18 (b, 1H, CH=, cod), 5.33-5.45 (m, 3H, CH_2 Bn, CH= cod), 6.02-6.09 (m, 1H, CH=, cod), 6.48 (d, 1H, CH-OP, $^3J_{H\text{-}P}$ =8.0 Hz), 6.98-7.71 (m, 25H, CH= aromatic). ^{13}C NMR (125.9 MHz, $CDCl_3$): δ=16.5 (CH_3), 20.2 (CH_3), 20.4 (CH_3), 27.5 (d, CH_2, cod, $J_{C\text{-}P}$ =2.5 Hz), 29.5 (b, CH_2, cod), 31.3 (CH_3, ^tBu), 31.9 (d, CH_2, cod, $J_{C\text{-}P}$ =1.3 Hz), 32.4 (CH_3, ^tBu), 33.9 (d, CH_2, cod, $J_{C\text{-}P}$ =3.8 Hz), 34.7 (C, ^tBu), 35.0 (C, ^tBu), 56.4 (CH_2, Bn), 62.6 (CH=, cod), 72.4 (CH=, cod), 73.3 (d, CH-OP, $^2J_{C\text{-}P}$

=7.6 Hz), 105.3 (d, CH=, cod, $J_{C\text{-}P}$ =16.4 Hz), 106.0 (d, CH=, cod, $J_{C\text{-}P}$ =15.1 Hz), 117.4-148.1 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^1J_{C\text{-}B}$ =50.4 Hz). MS HR-ESI [found 948.3843, $C_{48}H_{58}IrN_3O_3P$ $(M\text{-}BAR_F)^+$ requires 948.3845]

[Ir(cod)(L62b)]BAr_F. Yield: 63 mg (93%). **Isomer A** (25%): ^{31}P NMR (161.9 MHz, $CDCl_3$): δ=97.0 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.31 (s, 9H, CH_3, ^{t}Bu), 1.46 (s, 9H, CH_3, ^{t}Bu), 1.69 (s, 3H, CH_3), 1.83 (s, 3H, CH_3), 1.94-2.25 (m, 8H, CH_2, cod), 2.19 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 2.54 (b, 1H, CH=, cod), 4.17 (b, 1H, CH=, cod), 5.29-5.49 (m, 2H, CH_2, Bn), 5.95 (m, 2H, CH=, cod), 6.13 (d, 1H, CH-OP, $^3J_{H\text{-}P}$ =8.8 Hz), 7.03-7.71 (m, 24H, CH= aromatic). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=16.5 (CH_3), 20.3 (CH_3), 20.4 (CH_3), 21.2 (CH_3), 27.5 (CH_2, cod), 28.2 (CH_2, cod), 31.3 (CH_3, ^{t}Bu), 32.3 (CH_3, ^{t}Bu), 32.9 (CH_2, cod), 33.3 (CH_2, cod), 34.6 (C, ^{t}Bu), 34.8 (C, ^{t}Bu), 56.5 (CH_2, Bn), 60.8 (CH=, cod), 69.4 (CH=, cod), 73.3 (CH-OP), 105.2 (d, CH=, cod, $J_{C\text{-}P}$ =16.8 Hz), 106.9 (d, CH=, cod, $J_{C\text{-}P}$ =15.3 Hz), 116.9-153.5 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^1J_{C\text{-}B}$ =49.7 Hz). **Isomer B** (75%): ^{31}P NMR (161.9 MHz, $CDCl_3$): δ=98.7 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.29 (s, 9H, CH_3, ^{t}Bu), 1.31 (s, 9H, CH_3, ^{t}Bu), 1.74 (s, 3H, CH_3), 1.84 (s, 3H, CH_3), 1.94-2.25 (m, 8H, CH_2, cod), 2.20 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 2.69 (b, 1H, CH=, cod), 4.17 (b, 1H, CH=, cod), 5.29-5.49 (m, 3H, CH_2 Bn, CH= cod), 6.05 (m, 1H, CH=, cod), 6.44 (d, 1H, CH-OP, $^3J_{H\text{-}P}$ =6.0 Hz), 7.00-7.71 (m, 24H, CH= aromatic). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=16.5 (CH_3), 20.3 (CH_3), 20.4 (CH_3), 21.2 (CH_3), 27.1 (CH_2, cod), 29.4 (CH_2, cod), 31.3 (CH_3, ^{t}Bu), 31.9 (CH_2, cod), 32.4 (CH_3, ^{t}Bu), 33.9 (CH_2, cod), 34.7 (C, ^{t}Bu), 34.9 (C, ^{t}Bu), 56.4 (CH_2, Bn), 62.6 (CH=, cod), 72.2 (CH=, cod), 73.3 (CH-OP), 105.2 (d, CH=, cod, $J_{C\text{-}P}$ =16.8 Hz), 105.9 (d, CH=, cod, $J_{C\text{-}P}$ =15.3 Hz), 116.9-153.5 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^1J_{C\text{-}B}$ =50.4 Hz). MS HR-ESI [found 962.3998, $C_{49}H_{60}IrN_3O_3P$ $(M\text{-}BAR_F)^+$ requires 962.4002]

[Ir(cod)(L63b)]BAr_F. Yield: 65 mg (94%). **Isomer A** (100%): ^{31}P NMR (161.9 MHz, $CDCl_3$): δ=96.8 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.33 (s, 9H, CH_3, ^{t}Bu), 1.46 (s, 9H, CH_3, ^{t}Bu), 1.69 (s, 3H, CH_3), 1.83 (s, 3H, CH_3), 2.02-2.36 (m, 8H, CH_2, cod), 2.20 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 2.55 (b, 1H, CH=, cod), 4.15 (b, 1H, CH=, cod), 5.30 (d, 1H, CH_2, Bn, $^2J_{H\text{-}H}$ =14.4 Hz), 5.38 (d, 1H, CH_2, Bn, $^2J_{H\text{-}H}$ =14.4 Hz), 5.98 (m, 2H, CH=, cod), 6.24 (d, 1H, CH-OP, $^3J_{H\text{-}P}$ =8.8 Hz), 6.99-7.71 (m, 24H, CH= aromatic). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=16.5 (CH_3), 16.6 (CH_3), 20.3 (CH_3), 20.4 (CH_3), 27.7 (CH_2, cod), 28.1 (CH_2, cod), 31.3 (CH_3, ^{t}Bu), 32.3 (CH_3, ^{t}Bu), 32.9 (CH_2, cod), 33.3 (CH_2, cod), 34.7 (C, ^{t}Bu), 35.0 (C, ^{t}Bu), 56.6 (CH_2, Bn), 61.2 (CH=, cod), 69.9 (CH=, cod), 72.5 (CH-OP), 105.5 (d, CH=, cod, $J_{C\text{-}P}$ =15.3 Hz), 107.7 (d, CH=, cod, $J_{C\text{-}P}$ =14.6 Hz), 117.4-144.7 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^1J_{C\text{-}B}$ =50.4 Hz). MS HR-ESI [found 1016.3718, $C_{49}H_{57}F_3IrN_3O_3P$ $(M\text{-}BAR_F)^+$ requires 1016.3719].

[Ir(cod)(L63c)]BAr_F. Yield: 58 mg (91%). **Isomer B** (100%): ^{31}P NMR (161.9 MHz, $CDCl_3$): δ=98.6 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.27 (s, 9H, CH_3, ^{t}Bu), 1.31 (s, 9H, CH_3, ^{t}Bu), 1.75 (s, 3H, CH_3), 1.84 (s, 3H, CH_3), 1.97-2.22 (m, 8H, CH_2, cod), 2.23 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 2.74 (b, 1H, CH=, cod), 4.19 (b, 1H, CH=, cod), 5.32 (m, 2H, CH_2 Bn, CH= cod), 5.43 (d, 1H, CH_2, Bn, $^2J_{H\text{-}H}$ =14.8 Hz), 6.08 (b, 1H, CH=, cod), 6.58 (d, 1H, CH-OP, $^3J_{H\text{-}P}$ =6.4 Hz), 6.97-7.70 (m, 24H, CH= aromatic). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=16.5 (CH_3), 20.3 (CH_3), 20.4 (CH_3), 27.4 (CH_2, cod), 29.5 (CH_2, cod), 31.2 (CH_3, ^{t}Bu), 31.8 (CH_2, cod), 32.4 (CH_3, ^{t}Bu), 33.8 (CH_2, cod), 34.6 (C, ^{t}Bu), 34.9 (C, ^{t}Bu), 56.6 (CH_2, Bn), 62.9 (CH=, cod), 72.3 (d, CH-OP, $^2J_{C\text{-}P}$ =8.3 Hz), 72.7 (CH=, cod), 105.9 (d, CH=, cod, $J_{C\text{-}P}$ =16.9 Hz), 106.6 (d, CH=, cod, $J_{C\text{-}P}$ =14.5 Hz),

117.4-147.2 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^1J_{C-B}$ =49.7 Hz). MS HR-ESI [found 1016.3715, $C_{49}H_{57}F_3IrN_3O_3P$ $(M\text{-}BAR_F)^+$ requires 1016.3719].

[Ir(cod)(L64b)]BAr_F. Yield: 92 mg (92%). **Isomer A** (65%): ^{31}P NMR (161.9 MHz, $CDCl_3$): δ=97.3 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.26-1.36 (m, 30H, CH_3, ^{t}Bu), 1.92-2.32 (m, 8H, CH_2, cod), 2.56 (b, 1H, CH=, cod), 4.21 (b, 1H, CH=, cod), 5.30-5.44 (m, 2H, CH_2, Bn), 5.96 (m, 1H, CH=, cod), 6.11 (m, 1H, CH=, cod), 6.72 (b, 1H, CH-OP), 6.78-7.93 (m, 27H, CH= aromatic). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=16.3-34.8 (CH_3, ^{t}Bu, CH_2, cod), 56.3 (CH_2, Bn), 60.7 (CH=, cod), 72.5 (CH-OP), 69.6 (CH=, cod), 105.0-107.2 (CH=, cod), 117.2-134.6 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^1J_{C-B}$ =42.6 Hz). **Isomer B** (45%): ^{31}P NMR (161.9 MHz, $CDCl_3$): δ=98.7 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.26-1.36 (m, 30H, CH_3, ^{t}Bu), 1.92-2.32 (m, 8H, CH_2, cod), 2.74 (b, 1H, CH=, cod), 4.21 (b, 1H, CH=, cod), 5.19-5.44 (m, 3H, CH_2 Bn, CH= cod), 6.11 (m, 1H, CH=, cod), 7.30 (b, 1H, CH-OP), 6.78-7.93 (m, 27H, CH= aromatic). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=16.3-34.8 (CH_3, ^{t}Bu, CH_2, cod), 56.3 (CH_2, Bn), 63.1 (CH=, cod), 69.4 (CH-OP), 72.0 (CH=, cod), 105.0-107.2 (CH=, cod), 117.2-134.6 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^1J_{C-B}$ =42.6 Hz). MS HR-ESI [found 998.3997, $C_{52}H_{60}IrN_3O_3P$ $(M\text{-}BAR_F)^+$ requires 998.4002].

[Ir(cod)(L65b)]BAr_F. Yield: 66 mg (97%). **Isomer A** (91%): ^{31}P NMR (161.9 MHz, $CDCl_3$): δ=97.2 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.39 (s, 9H, CH_3, ^{t}Bu), 1.56 (s, 9H, CH_3, ^{t}Bu), 1.71 (s, 3H, CH_3), 1.85 (s, 3H, CH_3), 1.99-2.39 (m, 8H, CH_2, cod), 2.21 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 2.58 (b, 1H, CH=, cod), 4.24 (b, 1H, CH=, cod), 6.04 (b, 1H, CH=, cod), 6.15 (b, 1H, CH=, cod), 6.29 (d, 1H, CH-OP, $^3J_{H-P}$ =8.0 Hz), 7.14-7.71 (m, 25H, CH= aromatic). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=16.5 (CH_3), 16.6 (CH_3), 20.3 (CH_3), 20.4 (CH_3), 27.9 (CH_2, cod), 31.3 (CH_3, ^{t}Bu), 32.4 (CH_3, ^{t}Bu), 33.1 (d, CH_2, cod, J_{C-P} =17.5 Hz), 34.8 (C, ^{t}Bu), 35.1 (C, ^{t}Bu), 61.1 (CH=, cod), 70.2 (CH=, cod), 73.1 (CH-OP), 105.1 (d, CH=, cod, J_{C-P} =16.0 Hz), 107.5 (d, CH=, cod, J_{C-P} =15.2 Hz), 117.4-146.3 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^1J_{C-B}$ =49.7 Hz). **Isomer B** (9%): ^{31}P NMR (161.9 MHz, $CDCl_3$): δ=98.4 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.27 (s, 9H, CH_3, ^{t}Bu), 1.32 (s, 9H, CH_3, ^{t}Bu), 1.76 (s, 3H, CH_3), 1.85 (s, 3H, CH_3), 1.99-2.39 (m, 8H, CH_2, cod), 2.26 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 2.73 (b, 1H, CH=, cod), 4.25 (b, 1H, CH=, cod), 5.41 (m, 1H, CH= cod), 6.04 (m, 1H, CH=, cod), 6.59 (d, 1H, CH-OP, $^3J_{H-P}$ =6.0 Hz), 7.12-7.91 (m, 25H, CH= aromatic). ^{31}C NMR signals could not detected due to the low presence of this isomer. MS HR-ESI [found 990.4313, $C_{51}H_{64}IrN_3O_3P$ $(M\text{-}BAR_F)^+$ requires 990.4315].

[Ir(cod)(L65c)]BAr_F. Yield: 64 mg (93%). **Isomer A** (14%): ^{31}P NMR (161.9 MHz, $CDCl_3$): δ=97.3 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.27 (s, 9H, CH_3, ^{t}Bu), 1.40 (s, 9H, CH_3, ^{t}Bu), 1.72 (s, 3H, CH_3), 1.86 (s, 3H, CH_3), 1.98-2.38 (m, 8H, CH_2, cod), 2.21 (s, 3H, CH_3), 2.24 (s, 3H, CH_3), 2.58 (b, 1H, CH=, cod), 4.26 (b, 1H, CH=, cod), 6.04 (b, 1H, CH=, cod), 6.13 (b, 1H, CH=, cod), 6.29 (d, 1H, CH-OP, $^3J_{H-P}$ =8.4 Hz), 7.15-7.90 (m, 25H, CH= aromatic). ^{31}C NMR signals could not detected due to the low presence of this isomer. **Isomer B** (86%): ^{31}P NMR (161.9 MHz, $CDCl_3$): δ=98.5 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.32 (s, 9H, CH_3, ^{t}Bu), 1.40 (s, 9H, CH_3, ^{t}Bu), 1.76 (s, 3H, CH_3), 1.87 (s, 3H, CH_3), 1.98-2.38 (m, 8H, CH_2, cod), 2.23 (s, 3H, CH_3), 2.33 (s, 3H, CH_3), 2.73 (b, 1H, CH=, cod), 4.26 (b, 1H, CH=, cod), 5.41 (m, 1H, CH=, cod), 6.15 (m, 1H, CH=, cod), 6.59 (d, 1H, CH-OP, $^3J_{H-P}$ =6.4 Hz), 7.12-7.72 (m, 25H, CH= aromatic). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=16.5 (CH_3), 20.3 (CH_3), 20.4 (CH_3), 27.5 (CH_2, cod), 29.5 (CH_2, cod), 31.3 (CH_3, ^{t}Bu), 31.9 (CH_2, cod), 32.4 (CH_3, ^{t}Bu), 34.0 (CH_2, cod), 34.7 (C, ^{t}Bu), 35.0 (C, ^{t}Bu),

63.0 (CH=, cod), 72.8 (CH=, cod), 73.3 (d, CH-OP, $^{2}J_{C\text{-}P}$ =7.6 Hz), 105.4 (d, CH=, cod, $J_{C\text{-}P}$ =16.8 Hz), 106.2 (d, CH=, cod, $J_{C\text{-}P}$ =15.3 Hz), 117.4-148.3 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^{1}J_{C\text{-}B}$ =49.7 Hz). MS HR-ESI [found 990.4311, $C_{51}H_{64}IrN_3O_3P$ $(M\text{-}BAR_F)^+$ requires 990.4315].

[Ir(cod)(L66b)]BAr$_F$. Yield: 62 mg (94%). **Isomer A** (23%): ^{31}P NMR (161.9 MHz, $CDCl_3$): δ=97.2 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.31 (s, 9H, CH_3, ^{t}Bu), 1.35 (s, 9H, CH_3, ^{t}Bu), 1.71 (s, 3H, CH_3), 1.83 (s, 3H, CH_3), 1.91-2.30 (m, 8H, CH_2, cod), 1.98 (s, 3H, CH_3), 2.21 (s, 3H, CH_3), 2.24 (s, 6H, CH_3), 2.31 (s, 3H, CH_3), 2.31 (b, 1H, CH=, cod), 4.14 (b, 1H, CH=, cod), 5.38-5.51 (m, 2H, CH_2, Bn), 5.93 (b, 1H, CH=, cod), 6.02 (b, 1H, CH=, cod), 6.70 (d, 1H, CH-OP, $^{3}J_{H\text{-}P}$ =6.4 Hz), 76.82-7.71 (m, 22H, CH= aromatic). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=16.4 (CH_3), 16.5 (CH_3), 19.8 (CH_3), 20.3 (CH_3), 20.5 (CH_3), 20.8 (CH_3), 21.0 (CH_3), 27.5 (CH_2, cod), 28.2 (CH_2, cod), 31.4 (CH_3, ^{t}Bu), 31.7 (CH_3, ^{t}Bu), 32.7 (CH_2, cod), 33.4 (CH_2, cod), 34.6 (C, ^{t}Bu), 35.1 (C, ^{t}Bu), 56.3 (CH_2, Bn), 60.2 (CH=, cod), 68.6 (CH=, cod), 69.2 (b, CH-OP), 105.2 (d, CH=, cod, $J_{C\text{-}P}$ =15.2 Hz), 107.0 (d, CH=, cod, $J_{C\text{-}P}$ =15.6 Hz), 117.4-146.3 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^{1}J_{C\text{-}B}$ =49.7 Hz). **Isomer B** (77%): ^{31}P NMR (161.9 MHz, $CDCl_3$): δ=97.9 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.31 (s, 9H, CH_3, ^{t}Bu), 1.35 (s, 9H, CH_3, ^{t}Bu), 1.73 (s, 3H, CH_3), 1.84 (s, 3H, CH_3), 1.91-2.30 (m, 8H, CH_2, cod), 1.98 (s, 3H, CH_3), 2.21 (s, 3H, CH_3), 2.24 (s, 6H, CH_3), 2.31 (s, 3H, CH_3), 2.69 (b, 1H, CH=, cod), 4.16 (b, 1H, CH=, cod), 5.32-5.51 (m, 3H, CH_2 Bn, CH= cod), 6.08 (m, 1H, CH=, cod), 6.77 (d, 1H, CH-OP, $^{3}J_{H\text{-}P}$ =3.6 Hz), 6.82-7.71 (m, 22H, CH= aromatic). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=16.4 (CH_3), 16.5 (CH_3), 19.8 (CH_3), 20.3 (CH_3), 20.4 (CH_3), 20.8 (CH_3), 21.0 (CH_3), 27.3 (CH_2, cod), 29.5 (CH_2, cod), 31.4 (CH_3, ^{t}Bu), 31.7 (CH_2, cod), 32.3 (CH_3, ^{t}Bu), 34.0 (CH_2, cod), 34.6 (C, ^{t}Bu), 34.8 (C, ^{t}Bu), 56.3 (CH_2, Bn), 62.8 (CH=, cod), 70.0 (d, CH-OP, $^{2}J_{C\text{-}P}$ =6.5 Hz), 71.8 (CH=, cod), 105.7 (d, CH=, cod, $J_{C\text{-}P}$ =17.1 Hz), 106.0 (d, CH=, cod, $J_{C\text{-}P}$ =14.2 Hz), 117.4-147.1 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^{1}J_{C\text{-}B}$ =60.5 Hz). MS HR-ESI [found 934.3687, $C_{47}H_{56}IrN_3O_3P$ $(M\text{-}BAR_F)^+$ requires 934.3689].

[Ir(cod)(L66c)]BAr$_F$. Yield: 61 mg (93%). **Isomer B** (100%): ^{31}P NMR (161.9 MHz, $CDCl_3$): δ=97.9 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.30 (s, 9H, CH_3, ^{t}Bu), 1.34 (s, 9H, CH_3, ^{t}Bu), 1.73 (s, 3H, CH_3), 1.84 (s, 3H, CH_3), 1.93-2.29 (m, 8H, CH_2, cod), 1.98 (s, 3H, CH_3), 2.21 (s, 3H, CH_3), 2.24 (s, 6H, CH_3), 2.31 (s, 3H, CH_3), 2.69 (b, 1H, CH=, cod), 4.16 (b, 1H, CH=, cod), 5.33 (m, 2H, CH_2 Bn, CH= cod), 5.48 (d, CH_2, Bn, $^{2}J_{H\text{-}H}$ = 14.8 Hz), 6.06-6.10 (m, 1H, CH=, cod), 6.77 (d, 1H, CH-OP, $^{3}J_{H\text{-}P}$ =4.0 Hz), 6.82-7.71 (m, 22H, CH= aromatic). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=16.4 (CH_3), 16.5 (CH_3), 19.8 (CH_3), 20.3 (CH_3), 20.4 (CH_3), 20.8 (CH_3), 21.0 (CH_3), 27.3 (CH_2, cod), 29.5 (CH_2, cod), 31.4 (CH_3, ^{t}Bu), 31.7 (CH_2, cod), 32.3 (CH_3, ^{t}Bu), 34.0 (CH_2, cod), 34.6 (C, ^{t}Bu), 34.8 (C, ^{t}Bu), 56.3 (CH_2, Bn), 62.8 (CH=, cod), 70.0 (d, CH-OP, $^{2}J_{C\text{-}P}$ =6.1 Hz), 71.9 (CH=, cod), 105.7 (d, CH=, cod, $J_{C\text{-}P}$ =16.1 Hz), 106.0 (d, CH=, cod, $J_{C\text{-}P}$ =14.5 Hz), 117.4-147.1 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^{1}J_{C\text{-}B}$ =60.5 Hz). MS HR-ESI [found 934.3688, $C_{47}H_{56}IrN_3O_3P$ $(M\text{-}BAR_F)^+$ requires 934.3689].

[Ir(cod)(L67b)]BAr$_F$. Yield: 67 mg (94%). **Isomer A** (100%): ^{31}P NMR (161.9 MHz, $CDCl_3$): δ=96.2 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.29 (s, 9H, CH_3, ^{t}Bu), 1.47 (s, 9H, CH_3, ^{t}Bu), 1.72 (s, 3H, CH_3), 1.84 (s, 3H, CH_3), 1.87-2.26 (m, 8H, CH_2, cod), 2.20 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 2.51 (b, 1H, CH=, cod), 4.10 (b, 1H, CH=, cod), 5.56 (b, 2H, CH=, cod), 6.26 (d, 1H, CH-OP, $^{3}J_{H\text{-}P}$ =8.8 Hz), 6.92-7.72 (m, 35H, CH= aromatic). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=16.5 (CH_3), 16.6 (CH_3), 20.3 (CH_3), 20.4 (CH_3), 27.4 (CH_2, cod), 28.5 (CH_2, cod), 31.3 (CH_3, ^{t}Bu), 32.5 (CH_3, ^{t}Bu), 33.7 (CH_2, cod), 34.7 (C, ^{t}Bu), 35.0 (C, ^{t}Bu), 61.3 (CH=, cod), 69.4 (CH=, cod), 74.1 (CH-

OP), 83.4 (C, Tr), 105.1 (d, CH=, cod, $J_{C\text{-}P}$ =16.1 Hz), 106.8 (d, CH=, cod, $J_{C\text{-}P}$ =16.1 Hz), 117.4-146.8 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^1J_{C\text{-}B}$ =50.5 Hz). MS HR-ESI [found 1100.4468, $C_{60}H_{66}IrN_3O_3P$ $(M\text{-}BAR_F)^+$ requires 1100.4471].

[Ir(cod)(L67c)]BAr_F. Yield: 66 mg (92%). **Isomer B** (100%): ^{31}P NMR (161.9 MHz, $CDCl_3$): δ=98.3 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.29 (s, 9H, CH_3, ^{t}Bu), 1.38 (s, 9H, CH_3, ^{t}Bu), 1.75 (s, 3H, CH_3), 1.84 (s, 3H, CH_3), 1.90-2.25 (m, 8H, CH_2, cod), 2.21 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 2.67 (b, 1H, CH=, cod), 4.21 (b, 1H, CH=, cod), 5.07 (b, 1H, CH=, cod), 5.71 (m, 1H, CH=, cod), 6.52 (d, 1H, CH-OP, $^3J_{H\text{-}P}$ =6.0 Hz), 6.94-7.72 (m, 35H, CH= aromatic). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=16.5 (CH_3), 20.3 (CH_3), 20.4 (CH_3), 27.6 (CH_2, cod), 29.3 (CH_2, cod), 31.3 (CH_3, ^{t}Bu), 32.1 (CH_2, cod), 32.6 (CH_3, ^{t}Bu), 33.7 (CH_2, cod), 34.7 (C, ^{t}Bu), 35.0 (C, ^{t}Bu), 62.6 (CH=, cod), 72.6 (CH=, cod), 73.5 (d, CH-OP, $^2J_{C\text{-}P}$ =7.6 Hz), 83.2 (C, Tr), 105.6 (d, CH=, cod, $J_{C\text{-}P}$ =16.8 Hz), 106.0 (d, CH=, cod, $J_{C\text{-}P}$ =15.3 Hz), 117.4-146.8 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^1J_{C\text{-}B}$ =49.7 Hz). MS HR-ESI [found 1100.4467, $C_{60}H_{66}IrN_3O_3P$ $(M\text{-}BAR_F)^+$ requires 1100.4471].

3.7.4.12. Typical procedure for the hydrogenation of olefins

The alkene (0.5 mmol) and Ir complex (2 mol%) were dissolved in CH_2Cl_2 (2 mL) in a high-pressure autoclave, which was purged four times with hydrogen. Then, it was pressurized at the desired pressure. After the desired reaction time, the autoclave was depressurized and the solvent evaporated off. The residue was dissolved in Et_2O (1.5 ml) and filtered through a short celite plug. The enantiomeric excess was determined by chiral GC or chiral HPLC and conversions were determined by ^{1}H NMR. The enantiomeric excesses of hydrogenated products from **S1**,[29] **S2**,[30] and **S3**[29] were determined using the conditions previously described.

3.7.5. Acknowledgements

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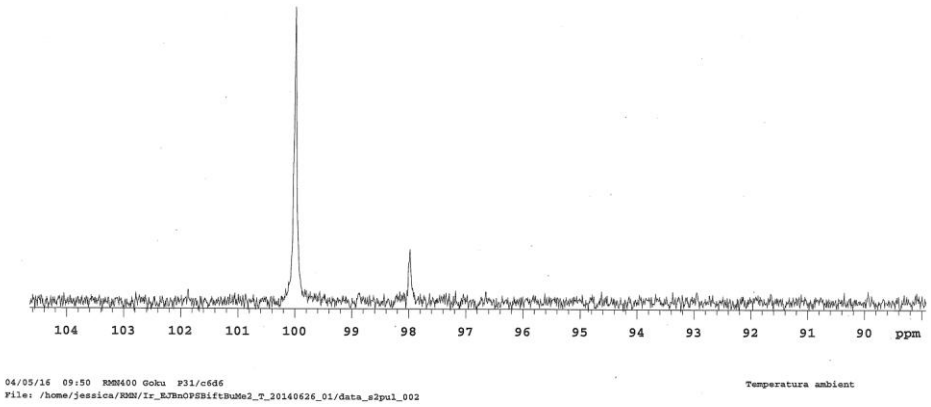
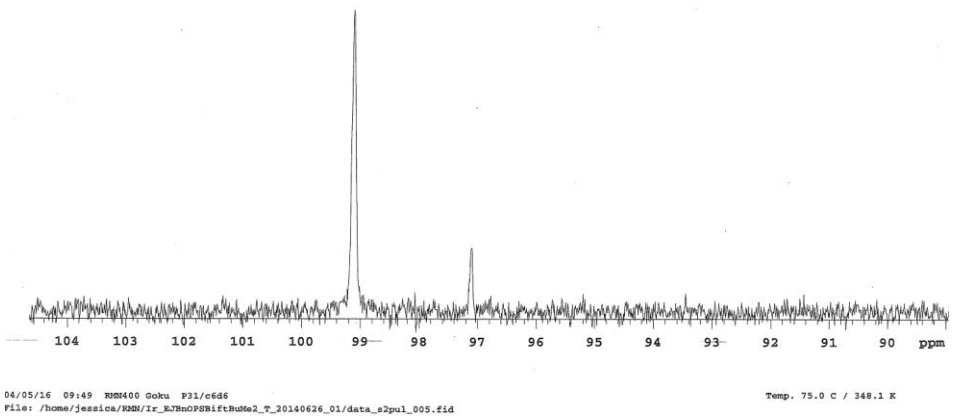
3.7.6. Supporting information

3.7.6.1. NMR ^{31}P $\{^{1}H\}$ spectra of complex [Ir(cod)(**L61c**)]BAr_F at (a) room temperature and (b) at 75 °C.

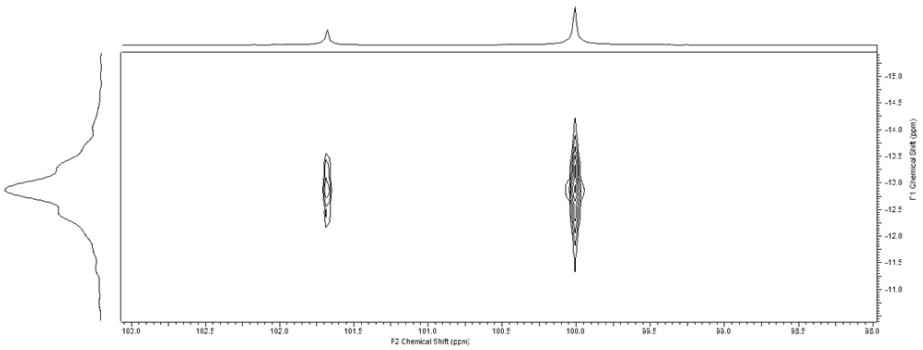
(a) Room temperature



(b) 75 °C



3.7.6.2. 2D DOSY ^{31}P $\{^{1}H\}$ spectrum of complex [Ir(cod)(**L61b**)]BAr_F



UNIVERSITAT ROVIRA I VIRGILI
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Jèssica Margalef Pallarès

Chapter 4

Asymmetric transfer hydrogenation of ketones

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4. Asymmetric transfer hydrogenation (ATH) of ketones

4.1. Background. Designing new readily available sugar-based ligands for asymmetric transfer hydrogenation of ketones. In the guest to expand the substrate scope

Jèssica Margalef, Oscar Pàmies and Montserrat Diéguez in *Tetrahedron Lett.* **2016**, *57*, 1301.

***Abstratct**: Asymmetric transfer hydrogenation (ATH) has emerged as one of the most effective and sustainable synthetic tool for synthesizing enantiopure alcohols. Since Noyori's group successfully applied Ru-catalysts modified with chiral β-amino alcohols or diamines as ligands, a large number of catalytic systems has been successfully developed. However, further improvement in terms of substrate scope, selectivity and turnover frequency are required to make the process competitive with conventional hydrogenations. Overcoming these limitations requires research toward the design of new ligands. Such a task becomes easier if readily modulable chiral ligands are at hand. Sugar-based ligands are particularly useful for addressing this need. They are readily available, highly functionalized and their modular constructions are easy. Series of chiral ligands can be screened in the search for high activities and selectivities for each type of substrate. This digest paper will discuss the progress on the use of sugar-based ligands in ATH reactions.*

4.1.1. Introduction

Enantiopure alcohols are valuable and versatile synthetic building blocks for the synthesis of many natural, pharmaceutical and agricultural products.[1] The enantioselective reduction of prochiral ketones has emerged as an efficient and direct synthetic tool for preparing these compounds. Transition metal-catalyzed asymmetric transfer hydrogenation (ATH) provides a powerful alternative to asymmetric hydrogenation due to its operational simplicity, the easy availability of hydrogen sources, low cost and safety.[2] Most transfer hydrogenations are performed using Ru[3], Rh[4] or Ir-catalysts[4a-c,5]. Recently, the use of iron[6] and osmium[7]-based catalysts has also provided interesting results, but their scope is still low compared to that of the Ru, Rh and Ir-catalysts. Since Noyori and coworkers successfully applied Ru-arene catalysts modified with chiral β-amino alchohol or diamines as ligands in 1990,[2f,i,3a-b] (Figure 4.1.1) the scope of this ligand class has been expanded with the development of a large number of new ligands.[8]

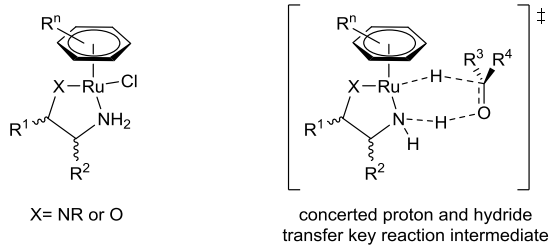


Figure 4.1.1. General structure of Noyori-type catalyst precursors and structure of the proposed key reaction intermediate for ATH reactions.

Adolfsson's group reported a new type of ligands -amino acid-derived hydroxy amides and thioamides- that in combination with Ru and Rh half-sandwich complexes are also excellent catalysts for the ATH of aryl-alkyl ketones (Figure 4.1.2).[8f-g,9] These ligands are based on the combination of several N-Boc-protected α-amino acids and β-amino alcohols[8f,9a-f,h] (for type **1**) or on thioamides[8g,9g] (for type **2**), respectively. The main difference between previously successful catalysts is the lack of a basic NH group in the latter's ligand structures. The authors also found that the presence of a chiral α-amino acid is crucial to obtain high enantioselectivity and that enantioselectivity is affected by the configuration of the stereogenic center of amino acid part. In addition, changing the amide group in hydroxy amides **1** to the thioamide as in **2**, results in most cases in a switch of the product's absolute configuration. Highly enantiomerically enriched secondary alcohols of either configuration can be therefore achieved using catalysts ligated with **1** or **2**, where the ligands are constructed from the same amino acid with the same sense of chirality.

Despite all these important contributions, further improvement in terms of substrate scope, selectivity and turnover frequency are required to make the process competitive with conventional hydrogenations. Overcoming these limitations requires research toward the development of new ligands. Such a task becomes significantly more facile if readily modulable chiral ligands are at hand. Carbohydrate-based ligands are particularly useful for addressing this need.[10,11] They are readily available, highly functionalised with several stereogenic centres and they have a highly modular construction. Series of chiral ligands can be synthesised and screened in the search for high activities and selectivities for each type of substrate.

Taking advantage of these features, we and others have designed carbohydrate-based ligands for asymmetric transfer hydrogenation reactions. This digest paper will therefore discuss the progress on the use of sugar-based ligands in asymmetric metal-catalyzed transfer hydrogenation reactions.

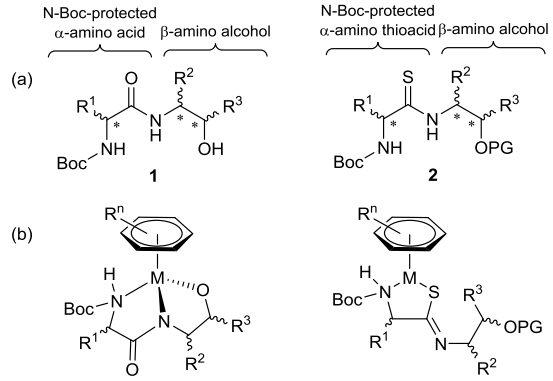
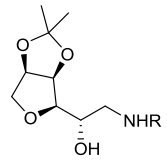


Figure 4.1.2. (a) General structure of hydroxy amide and thioamide ligands and (b) structure of the proposed key reaction intermediate for ATH reactions.

4.1.2. ATH using sugar-based Noyori-type catalysts

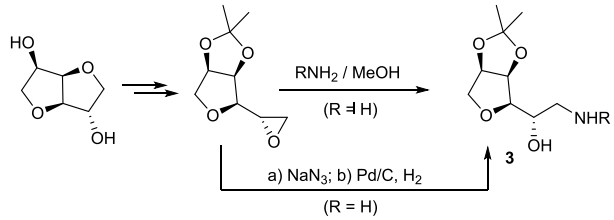
Since Noyori and coworkers successfully applied Ru-arene catalysts modified with chiral β-amino alcohols and diamines, many research groups further developed β-amino alcohol or diamine-based catalysts. However, the first carbohydrate-derived β-amino alcohols were not reported until 2008 (Figure 4.1.3).[12] These ligands were synthesized in only 3 steps from isosorbide, a byproduct from starch industry (Scheme 4.1.1). They were applied in the reduction of the standard substrate acetophenone using $[Ru(benzene)Cl_2]_2$ as source of metal. The conversion into the 1-phenylethanol was low to high (10-95%), while enantioselectivity (0-78%) was highly dependent on the β-amino alcohol ligand structure (Table 4.1.1). The chiral amino alcohol **3g** proved to be the most efficient, albeit the enantioselectivity achieved is low compared to the state of art.



	R
a	H
b	Me
c	^{i}Pr
d	Cy
e	^{t}Bu
f	Ph

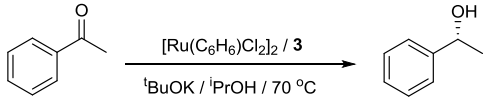
	R
g	Bn
h	(*R*)-CH(Me)Ph
i	(*S*)-CH(Me)Ph
j	(*R*)-CH(Et)CH_2OH
k	(*S*)-CH(Et)CH_2OH

Figure 4.1.3. General structure of β-amino alcohol **3** derived from isosorbide.



Scheme 4.1.1. Synthesis of chiral β-aminoalcohols **3**.

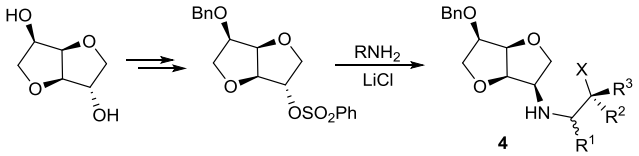
Table 4.1.1. Asymmetric transfer hydrogenation of acetophenone using β-amino alcohols **3**.[a]



Entry	Ligand	% Conv (h)	% ee	Entry	Ligand	% Conv (h)	% ee
1	3a	72 (21)	64 (*R*)	7	3g	96 (21)	60 (*R*)
2	3b	48 (21)	< 5	8	3h	83 (21)	21 (*R*)
3	3c	83 (21)	30 (*R*)	9	3i	90 (21)	18 (*R*)
4	3d	86 (21)	6	10	3j	28 (21)	24 (*R*)
5	3e	67 (21)	<5	11	3k	10 (21)	<5
6	3f	66 (21)	20 (*R*)	12[b]	3g	58 (3)	78 (*R*)

[a] Reaction carried out in a 0.2M solution in 2-propanol with substrate/^{t}BuOK/**3**/Ru = 100/1.5/1.5/1. [b] Substrate/^{t}BuOK/**3**/Ru = 100/4/4/1.

Then a new contribution on the use of isosorbide as chiral renewable resource was developed, however no significant improvements on enantioselectivities were obtained.[13] The authors developed new β-amino alcohol or diamine-based catalysts where the skeleton of the bicycle of the isosorbide was retained (Scheme 4.1.2).

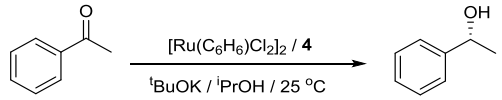


	X	R^1	R^2	R^3		X	R^1	R^2	R^3
a	OH	H	H	H	**f**	OH	H	Ph	H
b	OH	(*S*)-^{i}Pr	H	H	**g**	OH	H	H	Ph
c	OH	(*R*)-^{i}Pr	H	H	**h**	OH	H	Ph	Ph
d	OH	(*S*)-Ph	H	H	**i**	NH_2	H	H	H
e	OH	(*R*)-Ph	H	H	**j**	NHTs	H	H	H

Scheme 4.1.2. Synthesis of chiral β-aminoalcohols **4a**-**h** and diamines **4i**-**j**.

Another difference with previous isosorbide derived ligands **3** is that the sugar unit acts as a chiral substituent of the amine moiety. Although the highest enantioselectivities in the reduction of acetophenone was achieved using ligand **4f** containing an *R*-phenyl group adjacent to the hydroxyl group (Table 4.1.2; ee's up to 91%, entry 6), ligand **4a** showed the highest ability for transfer hydrogenation of various ketones with good conversion (Figure 4.1.4). They found that steric and electronic properties of the substrates also affected the chemical yields and enantioselectivities. Thus, the presence of electron-withdrawing or electron-donating groups on the phenyl group and the increase of the steric demands of the substrate has a negative effect on both yields and enantioselectivities.

Table 4.1.2. Asymmetric transfer hydrogenation of acetophenone using isosorbide-based ligands **4**.[a]



Entry	Ligand	% Conv (h)	% ee	Entry	Ligand	% Conv (h)	% ee
1	4a	99 (2)	70 (*R*)	6	4f	94 (24)	91 (*R*)
2	4b	63 (24)	3 (*R*)	7	4g	95 (24)	60 (*R*)
3	4c	32 (24)	36 (*R*)	8	4h	10 (2)	65 (*R*)
4	4d	28 (24)	47 (*R*)	9[b,c]	4i	97 (21)	5[d]
5	4e	55 (24)	35 (*R*)	10[b]	4j	65 (24)	73[d]

[a] Reaction carried out in a 0.2M solution in 2-propanol with substrate/^{t}BuOK/L/Ru = 40/2/2/1. [b] Substrate/^{t}BuOK/L/Ru = 40/1/1/2. [c] T= 50 °C. [d] Absolute configuration not reported.

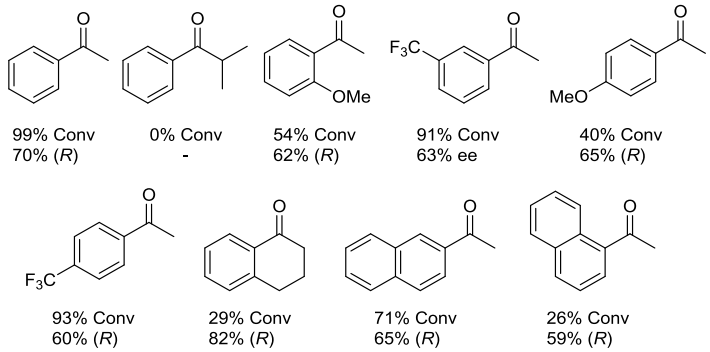


Figure 4.1.4. Selected results for the ATH of aromatic ketones using ligand

4.1.3. ATH using sugar-based hydroxy amide and thioamide ligands

A breakthrough in the development of sugar based ligands for this process appeared in 2011 when our group in collaboration with the Adolfsson's group developed a new sugar based ligand library (Figure 4.1.5).[14] These ligands are based on previous hydroxy amide ligands **1** in which the β-amino alcohol part was replaced by a readily available sugar β-amino alcohol moiety. The new ligands **5**-**7a**-**g** were efficiently prepared by coupling a series of *N*-Boc protected amino acids with the corresponding sugar amino alcohols by using isobutyl chloroformate in the presence of *N*-methylmorpholine (Scheme 4.1.3). The corresponding sugar amino alcohols were readily prepared on a large scale from inexpensive D-glucose.

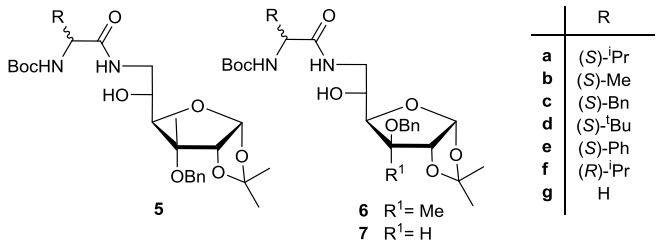
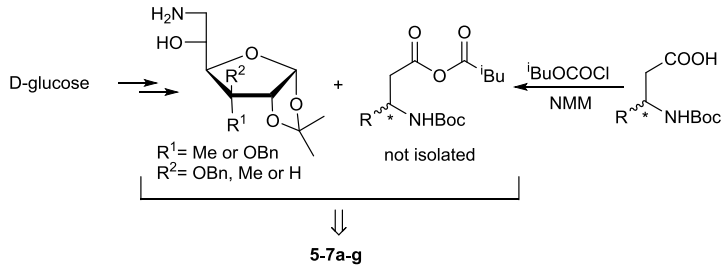


Figure 4.1.5. Furanoside hydroxy amide ligands **5**-**7a**-**g**.

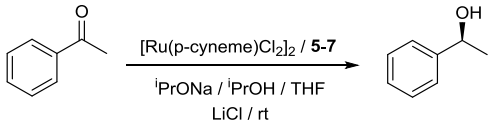


Scheme 4.1.3. Synthesis of furanoside hydroxy amide ligands **5**-**7a**-**g**.

With these ligands it was studied the catalytic performance by systematically varying the substituents/configuration of the α-amino acid moiety and the substituent/configuration of C-3 of the sugar backbone (Table 4.1.3). The results indicated that varying the substituents of the α-amino acid has not effect on enantioselectivity (>99% ee in all cases) although the highest activities were obtained with catalysts based on ligands **5a-c** (Table 4.1.3, entries 1-3). The use of ligand **5g**, with an achiral or racemic α-amino acid moiety into the ligand design also provided excellent enantioselectivity (entry 7). In contrast to previous successful hydroxy amides **1**, the enantioselectivity is therefore exclusively controlled by the sugar moiety which enables the use of inexpensive achiral or racemic α-amino acid derivatives. The use of ligand **6a**, with opposite configuration at C-3 of the furanoside backbone in comparison to **5a**, has no effect on activity and enantioselectivity (Table 4.1.3, entry 1 vs 8). Interestingly, the use of ligands **7**, which are synthesized in fewer steps than corresponding ligands **5** and **6**, also provided excellent enatioselectivities (Table 4.1.3, entries 9 and 10). Finally, these ligands were also successfully applied in a broad range of other ketones (Figure 4.1.6). $[RuCl_2(\pi\text{-cymene})]_2$/**5a** and **7a**, efficiently catalyze the ATH of several other aryl-alkyl ketones. The results show that the catalytic performance is not affected by the steric and electronic properties of the aryl group. This behavior contrasts with the electronic and steric effect on enantioselectivity observed for previous hydroxy amide ligands **1**. As previously observed, the use of LiCl as additive had a positive effect on both activity and selectivity. This has been explained by an intimate involvement of the lithium ion in the process.[0f] Thus, Adolfsson and coworkers have demonstrated that a bifuntional catalyst is formed. In the key transition state the lithium coordinates to both the alkali metal alcoxide and the

oxygen of ketone which forms a tighter transition state than without the presence of the smaller cation.

Table 4.1.3. Asymmetric transfer hydrogenation of acetophenone using hydroxy amide ligands **5**-**7a**-**g**.[a]



Entry	Ligand	% Conv (h)	% ee	Entry	Ligand	% Conv (h)	% ee
1	5a	80 (3)	>99 (*S*)	6	5f	1 (3)	n.d.
2	5b	80 (3)	>99 (*S*)	7	5g	56 (3)	99 (*S*)
3	5c	81 (3)	>99 (*S*)	8	6a	78 (3)	>99 (*S*)
4	5d	49 (3)	>99 (*S*)	9	7a	79 (3)	>99 (*S*)
5	5e	42 (3)	>99 (*S*)	10	7g	51 (3)	99 (*S*)

[a] Reaction conditions: substrate (1 equiv, 0.2M in 2-propanol/THF (1:1), $[RuCl_2(p\text{-cymene})]_2$ (0.25 mol% in Ru), ligand (0.55 mol%), NaO^iPr (5 mol%), LiCl (10 mol%)

In summary, it was found that the introduction of a furanoside aminosugar moiety into the ligand design was advantageous; surpassing the enantioselectivities obtained with previous successful hydroxy amide ligands **1**. Ru-catalysts modified with carbohydrate hydroxy amide ligands **5**-**7a**-**g** (Figure 4.1.5) therefore proved to efficiently catalyze the reduction of a wide range of aryl alkyl ketones (ee's ranging from 99% to >99%).

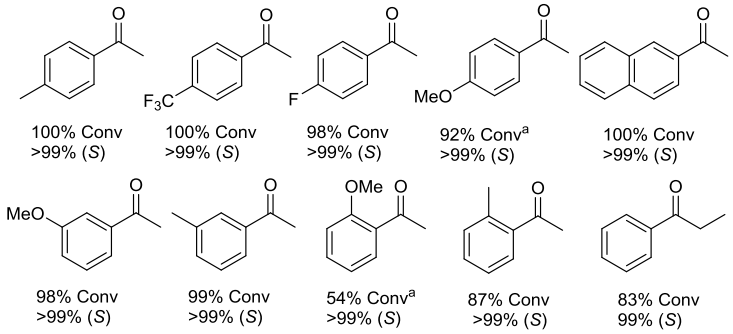


Figure 4.1.6. Selected results for the ATH of aromatic ketones using **5a**. Reaction conditions: 0.25 mol% $[RuCl_2(p\text{-cymene})]_2$, 0.55 mol% **5a**, 1 mmol substrate, 3 h at room temperature. [a] 1 mol% of $[RuCl_2(p\text{-cymene})]_2$, 2.2 mol% **5a** 24 h.

Following this contribution came the developments of new hydroxy amide and also the synthesis of thioamides ligand libraries based on carbohydrates.

The first of these described the application of a new carbohydrate-based library of 36 potential hydroxyl amide ligands (**8**-**11a**-**i**; Figure 4.1.7).[15] These ligands are based on the previous sugar-based hydroxyl amide ligands **5**-**7**, in which a 1,3-aminoalcohol sugar core was used instead of a classical 1,2-amino alcohol motif. These ligands were prepared from the corresponding easily accessible 1,3 amino alcohol sugar derivatives, which were

prepared from the D-xylose (ligands **8**-**9**) or D-glucose (ligands **10**-**11**). Ligands **8**-**11a**-**i** were synthesized following the general methodology depicted in Scheme 4.1.3.

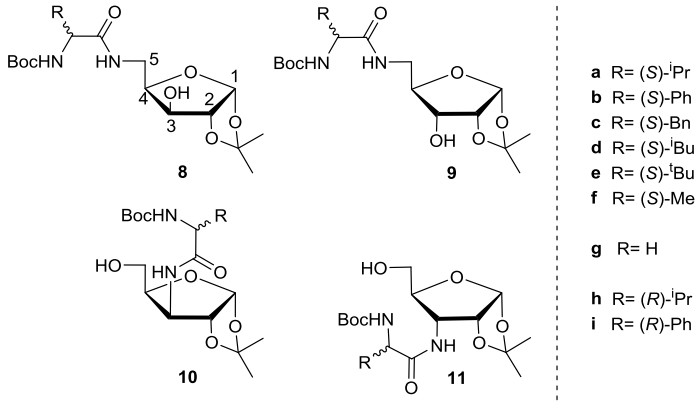


Figure 4.1.7. Furanoside hydroxyl amide ligands **8**-**11a**-**i**.

The use of either Ru/**8**-**11a**-**i** or Rh/**8**-**11a**-**i** catalytic systems provided low activities and enantioselectivities (typically conversions were below 10%, even at 50 °C, and ee's were up to 18%). This behavior can be explained by the previous mechanistic studies using hydroxy amides **1** (0).[9d,f] The species responsible for the catalytic activity is an intermediate where the ligand coordinates to the metal through both nitrogens and the oxygen atom forming two five-membered chelate rings (0). Our hydroxyl amide ligand library **8**-**11a**-**i** differs from previous successful hydroxyl amide ligands **1** in the fact that 1,3-aminoalcohols are used instead of previously described 1,2-aminoalcohols. This change should result in the formation of a reaction intermediate in which the coordination of the alcohol as an alkoxide forms a six-membered chelate, which is less favored than when 1,2-amino alcohols are used, thus favoring catalyst decomposition after only a few turnovers.

With the aim to improve catalytic performance the same authors developed the corresponding thioamide ligand library **12**-**15a**-**i**, where the peptide bond in the previous ligands **8**-**11a**-**i** was converted to a thioamide group (Figure 4.1.8).[15] Its design was based in previous mechanistic studies with successful thioamide ligands **2** that showed that this type of ligand coordinates to the metal in a bidentate fashion, through the carbamate nitrogen and the thioamide sulfur atoms, to form a five-membered ring (Figure 4.1.2).[9g] In order to obtain the same coordination pattern the thioamide ligands **12**-**15a**-**i** in which the hydroxyl group is protected to prevent its coordination to the metal in the form of alkoxide was developed. These ligands were synthesized, from the previously obtained hydroxyl amide ligands **8**-**11a**-**i** in a two step procedure (Scheme 4.1.4). The first step was the benzoylation of the hydroxyl group attached at either C-3 (**16** and **17**) or C-5 (**18** and **19**) of the furanoside backbone. The second step is the formation of the desired thioamide ligands **12**-**15a**-**i** by treating the corresponding benzoyl protected hydrozyamide compounds with Lawesson's reagent.

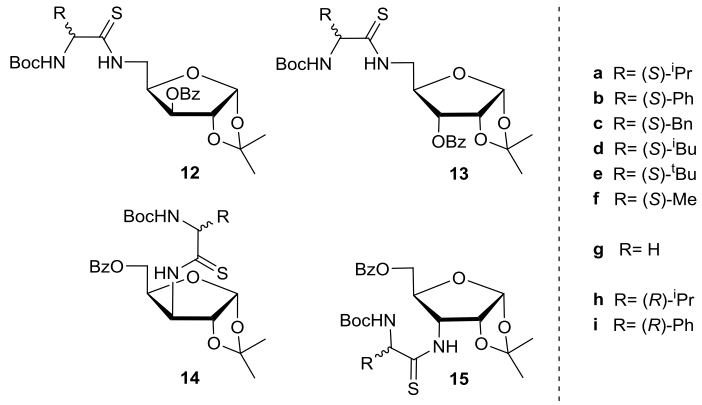
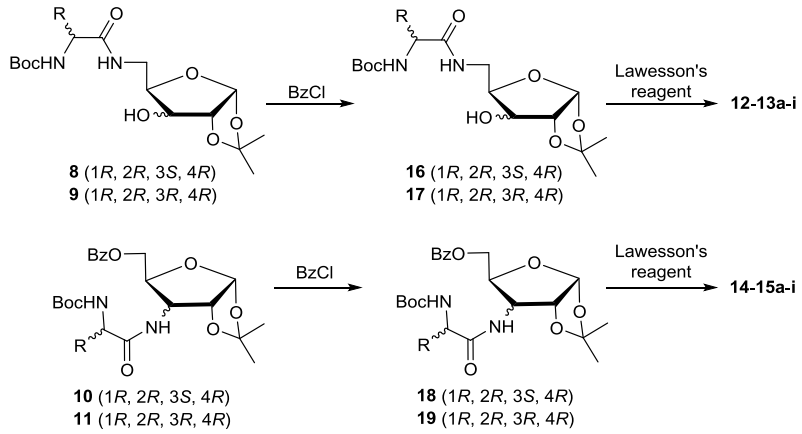


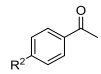
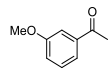
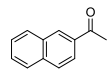
Figure 4.1.8. Furanoside thioamide ligands **12**-**15a**-**i**.

The authors found that both activity and enantioselectivity are better using $[RhCl_2Cp^*]_2$ as the catalyst precursor than $[RuCl_2(\pi\text{-cymene})]_2$. These results are in line with those previously observed using related thioamide-based ligands **2**.[8g,9g] Both enantiomers of the reduction products were obtained for a range of substrates in high enantioselectivity simply by changing the absolute configuration of the thioamide substituent (Table 4.1.4). This represents an advantage compared with the hydroxyl amide analogues **5**-**7** which only give access to the (*S*)-alcohols. The results indicate that enantioselectivity is highly affected by the position of the thioamide group at either C-5 or C-3 of the furanoside backbone, the configuration of C-3 and the substituents/configurations in the thioamide moiety. The best results were obtained with ligands **14a** and **14h**, containing bulky thioamide substituents at C-3 of the xylofuranoside backbone (ee's up to 99%). Interestingly, they provided higher enantioselectivities than those obtained using previously described Rh-**2** catalysts (ee's up to 96%).



Scheme 4.1.4. Synthesis of furanoside thioamide ligands **12**-**15a**-**i**.

Table 4.1.4. Selected results for the Rh-catalyzed asymmetric transfer hydrogenation of aryl ketones using thioamide ligands **12**-**15**-**i**.[a]

Entry	Substrate	R	L14a		L14h	
			% Conv	% ee	% Conv	% ee
1		R^1= Me	85	98 (*R*)	64	93 (*S*)
2		R^1= Et	76	96 (*R*)	57	92 (*S*)
3		R^1= ^{i}Pr	68	98 (*R*)	51	93 (*S*)
4		R^2=Me	68	98 (*R*)	56	94 (*S*)
5		R^2=Br	94	97 (*R*)	84	94 (*S*)
6		R^2=F	95	97 (*R*)	81	94 (*S*)
7		R^2=CF_3	90	96 (*R*)	88	95 (*S*)
8		-	87	95 (*R*)	54	93 (*S*)
9		-	87	99 (*R*)	59	97 (*S*)
10		-	18	37 (*S*)	-	-

[a] Reaction conditions: Reaction conditions: ketone (1 equiv, 0.2M in 2-propanol/THF: 1/1), $[RhCl_2Cp^*]_2$ (0.25 mol%), ligand (0.55 mol%), NaO^iPr (5 mol%), LiCl (10 mol%) and at room temperature for 3 h. [b] Reaction carried out for 24 h.

Despite the good results obtained with this family of furanoside-based ligands further improvements in terms of substrate scope are required. Then, the decision was made to replace in the previous privileged ligand **5**-**7a**-**g** the carbonyl oxygen by a thioamide group (Figure 4.1.9, ligands **20**-**23a**-**f**).[16] Ligands **20**-**23a**-**f** were efficiently prepared from the corresponding hydroxyl amide compounds in a two step process following the methodology described for previous ligands **12**-**15a**-**i** (Scheme 4.1.4).[16] Interesting, these new furanoside-based ligand library containing the thioamide functionality (Figure 4.1.9) gave access to both enantiomers of the desired alcohols, while maintaining the excellent enantiocontrol exhibited by hydroxyl amide **5**-**7a**-**g**, and allowed to expand the scope of the substrates to include more challenging heteroaromatic ketones.

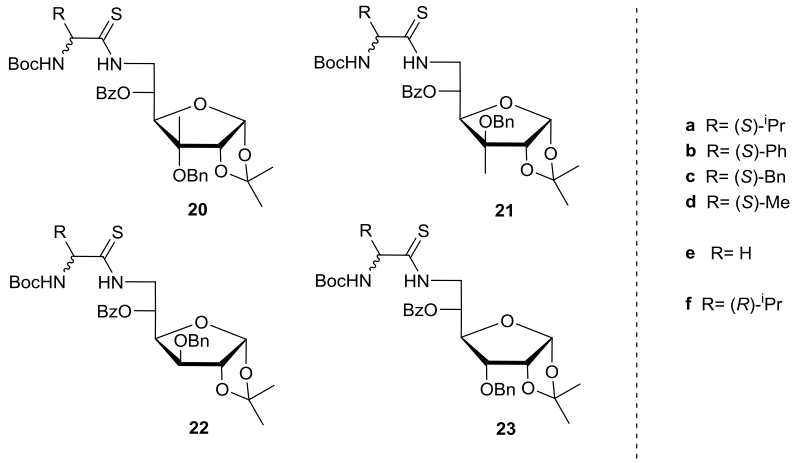
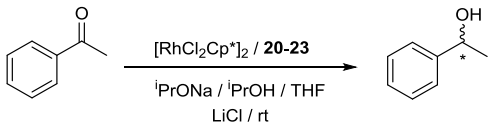


Figure 4.1.9. Furanoside-based thioamide ligands **20**-**23a**-**f**.

The authors found that enantioselectivities were mainly controlled by the steric properties of thioamide substituents and were higher when more sterically demanding substituents were present (i.e. ^{i}Pr>Bn>Ph>Me; Table 4.1.5, entries 1, 3-6). In addition, the presence of a chiral thioamide substituent is crucial if levels of enantioselectivity are to be high (entry 6 vs 1, 3-5). This behavior contrasts with the results achieved using related hydroxy amide analogues **5**-**7** (Figure 5). Rh-**20e** also led to the lowest activity of the series, which suggest that the presence of an alkyl or aryl thioamide substituent stabilizes the catalytic intermediates.

Table 4.1.5. Asymmetric transfer hydrogenation of acetophenone using thioamide ligands **20**-**23a**-**f**.[a]



Entry	Ligand	% Conv (h)	% ee	Entry	Ligand	% Conv (h)	% ee
1	20a	25 (3)	91 (*R*)	7	21a	30 (3)	82 (*R*)
2	20f	32 (3)	89 (*S*)	8	22a	75 (3)	94 (*R*)
3	20b	29 (3)	88 (*R*)	9	22f	70 (3)	93 (*S*)
4	20c	32 (3)	84 (*R*)	10	23a	41 (3)	93 (*R*)
5	20d	31 (3)	78 (*R*)	11	23f	39 (3)	92 (*S*)
6	20e	12 (3)	23 (*R*)	12[b]	22a	100 (3)	92 (*R*)

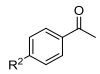
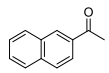
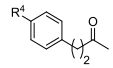
[a] Reaction conditions: substrate (1 equiv, 0.2 M in 2-propanol/THF: 1/1), $[RhCl_2Cp^*]_2$ (0.25 mol%), ligand (0.55 mol%), NaO^{i}Pr (5 mol%) and LiCl (10 mol%). [b] Reaction carried out at 40 °C.

It was also found that the sense of enantioselectivity is governed by the absolute configuration of the substituent in the thioamide moiety (Table 4.1.5, entries 1 vs 2). Both enantiomers of the reduction products can therefore be accessed in high enantioselectivity. Concerning the effect of the substituents/configuration at C-3 of the

furanoside backbone, the presence of a methyl substituent at C-3 has a negative effect on enantioselectivity. Ligands **20**-**21** afforded therefore lower enantioselectivities than ligands **22**-**23**. Interestingly, glucofuranoside ligands **22** afforded higher activities than the rest of ligands. In summary the highest activities and enantioselectivities in both enantiomers of the reduction product were achieved using glucofuranoside ligands **22a** and **22f** containing bulky isopropyl groups at the thioamide ligands. Note that from an application point of view this is advantageous because glucofuranoside ligands **22** are prepared in fewer steps than ligands **20**, **21** and **23**.

Finally, this family of ligands (**20**-**23a**-**f**) we evaluated in the asymmetric Rh-catalyzed transfer hydrogenation of other aryl/alkyl, alkyl/alkyl and heteroaryl/alkyl ketones (Table 4.1.6). Both enantiomers of the secondary alcohol products were obtained in high enantioselectivities (ee's up to 99%). The results show that the electronic properties of the substrate have little effect at activity and enantioselectivity although the highest enantioselectivity of the series was achieved in the reduction of *p*-tolyl methyl ketone (Table 4.1.6, entry 3). In contrast to previous **5**-**7**, the catalytic performance, however, was influenced by steric factors on the aryl substituent. Activity and enantioselectivity decreased considerably when *ortho*-substituted aryl ketones were used (i.e. entry 10). Nevertheless, the use of several meta-substituted ketones led to activities and enantioselectivities as high as those achieved using *para*-substituted ones (ee's up to 98%; entries 7-9). On the other hand, enantioselectivities are not affected by the steric bulk of the alkyl substituent (entries 1 and 2). Unfortunately, the reduction of alkyl-alkyl ketones proceeded with low enantiocontrol (entry 11).

Table 4.1.6. Selected results for the Rh-catalyzed asymmetric transfer hydrogenation of aryl ketones using thioamide ligands **20**-**23a**-**f**.[a]

Entry	Substrate	R	L14a		L14h	
			% Conv	% ee	% Conv	% ee
1		R^1=Me	75	94 (*R*)	70	93 (*S*)
2		R^1=Et	79	93 (*R*)	78	92 (*S*)
3		R^2=Me	100	99 (*R*)	100	99 (*S*)
4		R^2=Br	81	94 (*R*)	79	93 (*S*)
5		R^2=F	83	94 (*R*)	84	92 (*S*)
6		R^2=CF_3	81	93 (*R*)	80	92 (*S*)
7		R^3=OMe	96	97 (*R*)	87	96 (*S*)
8		R^3=CF_3	86	97 (*R*)	87	98 (*R*)
9		-	88	94 (*R*)	91	93 (*S*)
10		-	49	38 (*R*)	45	34 (*S*)
11		R^4=OMe	18	34 (*R*)	17	31 (*S*)

[a] Reaction conditions: ketone (1 equiv, 0.2M in 2-propanol/THF: 1/1), $[RhCl_2Cp^*]_2$ (0.25 mol%), ligand (0.55 mol%), NaO^iPr (5 mol%), LiCl (10 mol%) and at room temperature for 3 h.

Enantiopure alcohols with heteroaromatic substituents are crucial intermediates in the synthesis of biologically active compounds, and developing new methods for their synthesis is therefore of high relevance for the pharma- and agrochemical industries. For this substrate class, coordination of the heteroaromatic moiety to the metal-catalysts has to be avoided to achieve high enantioselectivities. There are therefore very few catalytic systems able to reduce heteroaromatic ketones under transfer hydrogenation conditions in high enantioselectivities.[17] Figure 4.1.10 shows the most notable results uisng ligands **20**-**23a**-**f**. Advantageously, by suitable tuning the ligand parameters, both enantiomers of the resulting heteroaromatic alcohols were obtained in high enantioselectivities (ee's up to 99%). Although as expected the activities were lower than in the reduction of acetophenone, they were similar to those obtained using other successful ligands under similar reaction conditions.[17]

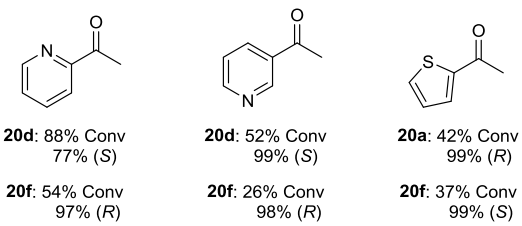


Figure 4.1.10. Selected results for the ATH of heteroaromatic ketones using thioamide ligands **20**-**23a**-**f**. Reaction conditions: ketone (1 equiv, 0.2M in 2-propanol/THF: 1/1), $[RhCl_2Cp^*]_2$ (1 mol%), ligand (2.2 mol%), NaO^iPr (10 mol%), LiCl (10 mol%) and at room temperature for 3h.

With the aim to increase even further the number and type of substrates that can be successfully reduced our group developed a new carbohydrate-based library of 24 potential hydroxy amide **24**-**26a**-**h** and 24 potential thioamide **27**-**29a**-**h** ligands, with a pyranoside backbone (Figure 4.1.11).[18] Pyranoside ligands **24**-**26a**-**h** were synthesized from the corresponding sugar amino alcohols, easily made from D-glucose (ligands **24** and **26**) and D-glucosamine (ligands **25**), by coupling them with a series of N-Boc-protected amino acids as depicted in Scheme 3. The thioamide ligands **27**-**29a**-**h** were prepared from hydroxy amide compounds **24**-**26a**-**h** by benzoylation of the alcohol followed by the thiation of the amide as depicted in Scheme 4.

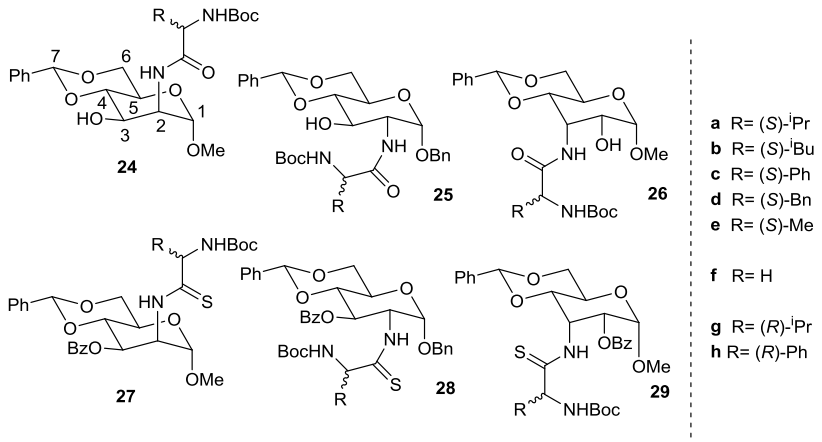


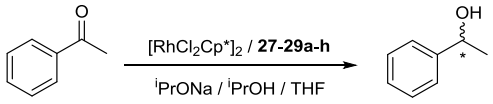
Figure 4.1.11. Pyranoside-based α-amino acid hydroxy amide/thioamide ligands **24**-**29a**-**h**.

In this study it was investigated the effect of systematically varying the substituents/configurations at the amide/thioamide moiety (**a**-**h**), the replacement of the hydroxy amide group (ligands **24**-**26**) with thioamide (ligands **27**-**29**), the position of the amide/thioamide moiety at either C-2 (ligands **24**-**25** and **27**-**28**) or C-3 (ligands **26** and **29**) of the pyranoside backbone and the configuration at C-2 (**24**-**25** and **27**-**28**). By thoroughly selecting the ligand components we obtained both enantiomers of the desired alcohols in high-to-excellent enantioselectivities and yields for a wide range of substrates, including the more challenging aryl/fluoroalkyl and heteroaromatic ketones.

In contrast to previously reported furanoside-based hydroxy amide ligands **5**-**7** (Figure 4.1.5),[14] the use of hydroxy amide ligands **24**-**26** led to poor catalytic activity (typically conversion below 5%). This can be attributed to the higher rigidity of the pyranoside backbone which hinders its coordination to the metal center in contrast to the less steric environment generated by the furanoside backbone. Note that for furanoside ligands **5**-**7**, the amido group was attached to the flexible primary carbon (C-6), which facilitates the coordination in a tridentate fashion. In contrast, thioamide ligands **27**-**29** provided high conversion and activities. Even more interesting, is that these pyranoside thioamide ligands displayed higher activities and enantioselectivities than previously reported furanoside-based thioamide ligands **20**-**23**.

Concerning the effect of the ligand parameters it was found that enantioselectivities were higher when more sterically demanding amide substituents were present (i.e. ^{i}Pr>^{i}Bu>Bn>Ph>Me>>H; Table 4.1.7, entries 1-6). As observed for other thioamide ligands, the sense of the enantioselectivity is governed by the absolute configuration of the substituent in the thioamide moiety (entries 1 vs 7). Varying the configuration of the pyranoside carbon in which the thioamide is coupled has little impact on the activity and stereochemical outcome of the reaction. Finally, ligands **27** and **28**, which contain the thioamide group at the C-2 position, produced better activities and enantioselectivities than ligands **29**, with the thioamide group at C-3 (i.e. entries 1 and 9 vs 14). The lower catalytic activity can be due to the higher steric congestion around the metal center exerted using this latter pyranoside backbone.

Table 4.1.7. Asymmetric transfer hydrogenation of acetophenone using thioamide ligands **27**-**29a**-**h**.[a]



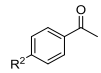
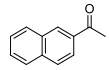
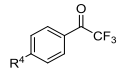
Entry	Ligand	% Conv (h)	% ee	Entry	Ligand	% Conv (h)	% ee
1	27a	88 (3)	99 (*R*)	9	28a	82 (3)	98 (*R*)
2	27b	91 (3)	97 (*R*)	10	28e	84 (3)	86 (*R*)
3	27c	76 (3)	90 (*R*)	11	28f	79 (3)	8 (*R*)
4	27d	92 (3)	96 (*R*)	12	28g	72 (3)	95 (*S*)
5	27e	88 (3)	86 (*R*)	13	28h	69 (3)	89 (*S*)
6	27f	86 (3)	33 (*S*)	14	29a	19 (3)	84 (*R*)
7	27g	76 (3)	98 (*S*)	15	29e	38 (3)	93 (*R*)
8	27h	72 (3)	89 (*S*)	16	29g	18 (3)	83 (*S*)

[a] Reaction conditions: substrate (1 equiv, 0.2 M in 2-propanol/THF: 1/1), $[RhCl_2Cp^*]_2$ (0.25 mol%), ligand (0.55 mol%), NaO^{i}Pr (5 mol%) and LiCl (10 mol%).

Thioamide ligands **27**-**29a**-**h** were also evaluated in the asymmetric Rh-catalyzed transfer hydrogenation of other aryl alkyl/trifluoroalkyl ketones (Table 4.1.8). Both enantiomers of the secondary alcohol products were obtained in high-to-excellent enantioselectivities (ee's up to 99%), regardless the *para* and *meta*-substituents on the aryl ketone group (entries 5-12). Excellent enantioselectivities were obtained in the ATH of

several aryl/alkyl ketones bearing increasingly sterically demanding alkyl substituents (entries 1 and 4). For the reduction of the more hindered cyclohexyl-containing ketone the enantioselectivity was highest with ligand **27e**, which contained the smallest methyl thioamide substituent (footnote b in Table 4.1.8). Finally, it should be noted the high enantioselectivity obtained with catalyst precursors Rh/**27a** and Rh/**27g** in ATH of aryl trifluoroalkyl ketones (ee's up to 89%, entries 14 and 15). These results compete favourably with the results obtained using the Ru/TSDPEN catalyst (38% ee), which is considered the state of art in ATH reactions.[19]

Table 4.1.8. Selected results for the Rh-catalyzed asymmetric transfer hydrogenation of aryl ketones using thioamide ligands **27**-**29a**-**h**.[a]

Entry	Substrate	R	L14a		L14h	
			% Conv	% ee	% Conv	% ee
1		R^1=Me	88	99 (*R*)	76	97 (*S*)
2		R^1=Et	82	97 (*R*)	77	96 (*S*)
3		R^1=^{i}Bu	64	91 (*R*)	68	90 (*S*)
4[b]		R^1=Cy	16	72 (*R*)	15	70 (*S*)
5		R^2=Me	64	98 (*R*)	61	97 (*S*)
6		R^2=Br	87	98 (*R*)	72	98 (*S*)
7		R^2=F	92	99 (*R*)	84	99 (*S*)
8		R^2=CF_3	99	96 (*R*)	92	98 (*S*)
9		R^2=OMe	74	99 (*R*)	68	98 (*S*)
10		R^3=OMe	98	99 (*R*)	92	98 (*S*)
11		R^3=CF_3	99	99 (*R*)	96	99 (*S*)
12		-	92	98 (*R*)	87	98 (*S*)
13		-	40	56 (*S*)	34	55 (*R*)
14		R^4=H	92	87 (*S*)	93	87 (*R*)
15		R^4=OMe	81	89 (*S*)	79	88 (*R*)

[a] Reaction conditions: ketone (1 equiv, 0.2M in 2-propanol/THF: 1/1), $[RhCl_2Cp^*]_2$ (0.25 mol%), ligand (0.55 mol%), NaO^iPr (5 mol%), LiCl (10 mol%) and at room temperature for 3 h. [b] The use of ligand **27e** affords 18% conversion and 79% (*R*) ee.

Finally, these ligands were also successfully applied to a range ketones containing pyridine, furan and thiophene groups (Figure 4.1.12).

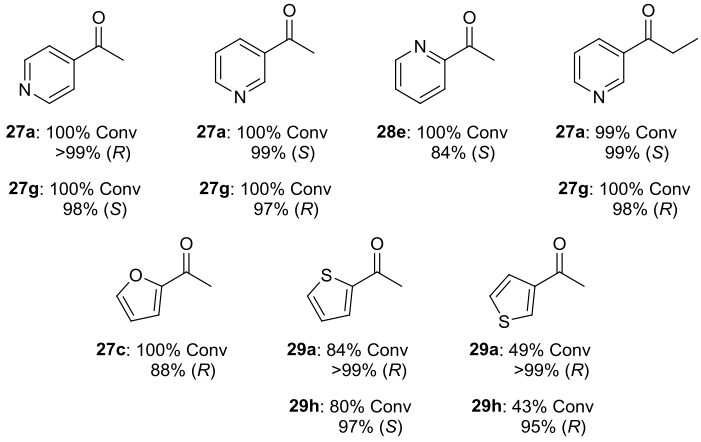
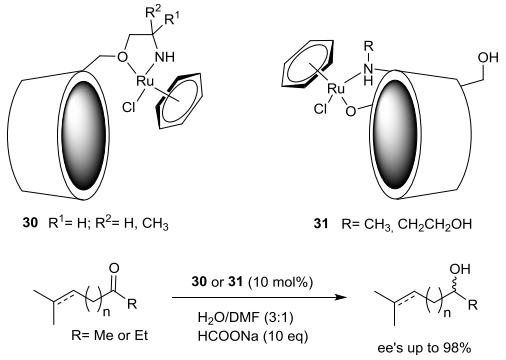


Figure 4.1.12. Selected results for the ATH of heteroaromatic ketones using thioamide ligands **27**-**29a**-**h**. Reaction conditions: ketone (1 equiv, 0.2M in 2-propanol/THF: 1/1), $[RhCl_2Cp^*]_2$ (1 mol%), ligand (2.2 mol%), NaO^iPr (10 mol%), LiCl (10 mol%) and at room temperature for 3h.

4.1.4. ATH using β-cyclodextrin-based catalysts

In the last decade, Woggon et al. have made use of a supramolecular approach where the β-cyclodextrin provides the ligand sphere for Ru-catalysts for ATH reactions (Scheme 4.1.5).[20] The hydrophobic cavity of the water soluble cyclodextrins facilitates the binding orientation and activation of lipophilic substrates. Therefore, ruthenium-η-arene complexes attached to the primary (**30**) or to the secondary (**31**) face of β-cyclodextrin catalyzed the enantioselective reduction of aliphatic and aromatic ketones (ee's up to 98%) in aqueous medium in the presence of sodium formate, albeit with low activity (typically reactions were carried out using 10 mol% catalyst during 12-24 h; Scheme 4.1.5).



Scheme 4.1.5. ATH of ketones using β-cyclodextrin Ru-catalysts **30** and **31**.

4.1.5. Conclusions and outlook

Carbohydrate-based ligands provide a promising approach in the search for effective catalysts in asymmetric transfer hydrogenation reactions. As we have seen during this digest paper, the structural diversity of carbohydrates offer a wide variety of opportunities for derivatization and tailoring of synthetic tools in the search of the right ligand for each substrate type. Another important feature of carbohydrate-based cores compared with other sources of chiral ligands is they are readily available from cheap feedstocks. In this respect, the sugar ligands collected in this digest are synthesized from isosorbide, D-xylose, D-glucose, D-glucosamine and β-cyclodextrin all cheap natural sources. In addition, thanks to their high modularity both enantiomers of the reaction product can be obtained without the use of expensive unnatural, prohibitively expensive L-carbohydrate. Although important progress has been made, especially in the successful ATH of a variety of substrates including the more demanding heteroaromatic ketones and the aliphatic ketones using cyclodextrin-based catalysts in water there still remain challenges such as to further increase the substrate scope and to develop a system that provides high activities in water media.

4.1.6. Acknowledgments

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4.1.7. References

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4.2. Highly versatile Ru- and Rh-catalysts for the asymmetric transfer hydrogenation of ketones. Application to tandem reactions

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***Abstract**. A library of furanoside-based hydroxyamide and thioamide ligands **L68**-**L73a-j** has been successfully applied in the ATH of several substrates, including more challenging ones such as trifluoromethyl-containing ketones, propargylic and alkyl/alkyl ketones among others. These ligands have the advantage that they are prepared from commercial D-mannose and α-amino acids, inexpensive natural chiral feedstocks. The modular ligand design has been shown to be highly successful in identifying two general catalytic systems (Ru-**L68a** and Rh-**L72a**) that allows to achieve both enantiomers of the reduced products in high ee's over the entire range of substrates (ee's typically ranging between 95% and >99%). We have also shown the potential application of the new catalyst in the simple tandem isomerization/ATH of readily available allylic alcohols and the tandem α-alkylation/ATH to produce chiral alcohols with an elongation of the alkyl chain.*

4.2.1. Introduction

Optically pure secondary alcohols are useful intermediates in the synthesis of biologically active compounds and therapeutic drugs.[1] For their preparation, asymmetric transfer hydrogenation (ATH) of polarized double bounds (i.e. ketones) has been established as an important alternative, from industrial and academic point of view, to the use of other methodologies because of the beneficial feature of the hydrogen donors used compared to the hazardous use of hydrogen gas and moisture sensitive hydride reagents.[2] Among all the catalyst developed, the use of transition metals, such as Ru,[3] Rh,[4] Ir[4a-c,5] has played a dominant role. More recently Os[6] and Fe[7]-based catalysts have also shown interesting results, but their scope is still low compared to that of Ru and Rh-catalysts. The first important breakthrough in the field of ATH appeared in the mid 1990's when Noyori and coworkers introduced a new class of ATH catalysts, Ru-arene complexes modified with chiral monosulfonated diamines or β-amino alcohols, which were able to efficiently reduce ketones and ketimines.[2f,l,3a,b] This discovery paved the way to the development of a large plethora of Noyori-type ligands with the aim not to only considerably expand the substrate scope but also to increase the stability of catalyst and hence the TON.[8] All these catalytic systems rely on the presence of a basic N-H moiety to control the efficient hydride transfer from the M-H to the prochiral carbonyl carbon of the substrate. After that several alternative ligands have been developed that do not require the presence of N-H moiety. So, for instance the groups of Reetz[9] and Yu[10] have developed Ru-diphosphonite and Ru-pyrazolyl-pyridyl-oxazolinyl catalysts, respectively. These ligands have been successfully applied in the ATH of a limited range of aryl-alkyl and alkyl-alkyl ketones. Aldolfsson's group has reported another type of ligands lacking the basic NH group. These ligand are based on

a combination of N-Boc-protected α-amino acids and β-amino alcohols (for hydroxyamide ligands **1**) or on thioamides (for thioamide ligands **2**). These acid-derived hydroxyamides and thioamides ligands (Figure 4.2.1) in combination with Ru or Rh half-sandwich complexes have shown a high enantioselectivity in ATH of a broad range of aryl alkyl ketones.[11] Despite all these important contributions, there is still a lack of a catalyst able to provide the desired secondary alcohols in enantiopure form (>99% ee) for a broad range of substrates as the enzymes do. Most successful catalysts developed afforded the desired products in a range 95-99% ee. Overcoming this limitation requires research toward the development of new ligands. In this context, in 2011 we developed new hydroxyamide ligands **3** (Figure 4.2.1) in which the β-amino alcohol part was replaced by a readily available sugar β-amino alcohol moiety.[12] The introduction of a furanoside aminosugar moiety into the ligand design represented an important breakthrough. Ru-catalysts modified with carbohydrate hydroxyamide ligands **3** (Figure 1) efficiently catalyze the reduction of a wide range of aryl alkyl ketones (typically 99% ee), surpassing the enantioselectivities obtained with previous successful hydroxyamide ligands **1**. However the latter catalytic systems cannot reduce industrially relevant heteroaromatic ketones and only one of the enantiomers of the product can be accessed. To overcome these limitations, we recently prepared a second generation of the furanoside-based ligand library containing the thioamide functionality (**4**, Figure 4.2.1), based on previous sugar hydroxyamide ligands **3**.[13]

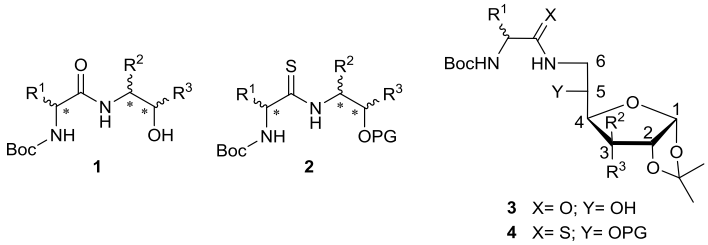


Figure 4.2.1. General structure of hydroxyamide ligands **1**, thioamide ligands **2** and sugar-based hydroxyamide **3** and thioamide ligands **4**.

Despite all these important advances, further improvement in terms of substrate scope, selectivity and turnover frequency was required to make the process competitive towards the conventional hydrogenations. Thus, for instance, the ATH of important substrates classes (i.e. trifluorometil-containing ketones, aryl/alkyl ketones containing bulky substituents, propargylic ketones, alkyl/alkyl ketones, …) needs to be further studied. For this purpose, the design of new modular ligands based on simple starting materials needed to be developed for this transformation. To this aim, in this chapter we introduced several systematic variations in the previous successful furanoside-based ligands **3** and **4**. With the new ligands (**L68**-**L73a**-**j**, Figure 4.2.2), which are derived from readily available D-(+)-mannose, we have varied the configuration of C-2 of the furanoside backbone and the position of the acetal protecting group respect to ligands **3** and **4**. These ligands also allowed to study the effect of the carbon at which the amide/thioamide is coupled either at

C-6 (ligands **L68** and **L71**) or at C-5 (ligands **L69** and **L72**) as well as the effect of the configuration of C-5 (ligands **L69** and **L72** vs **L70** and **L73**, respectively).

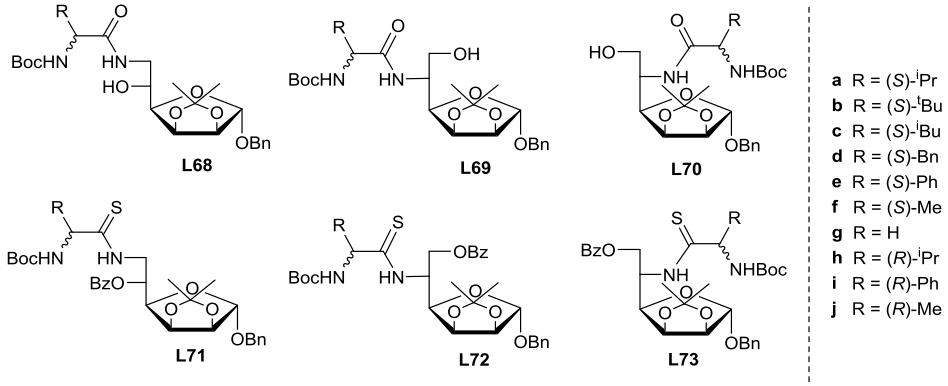
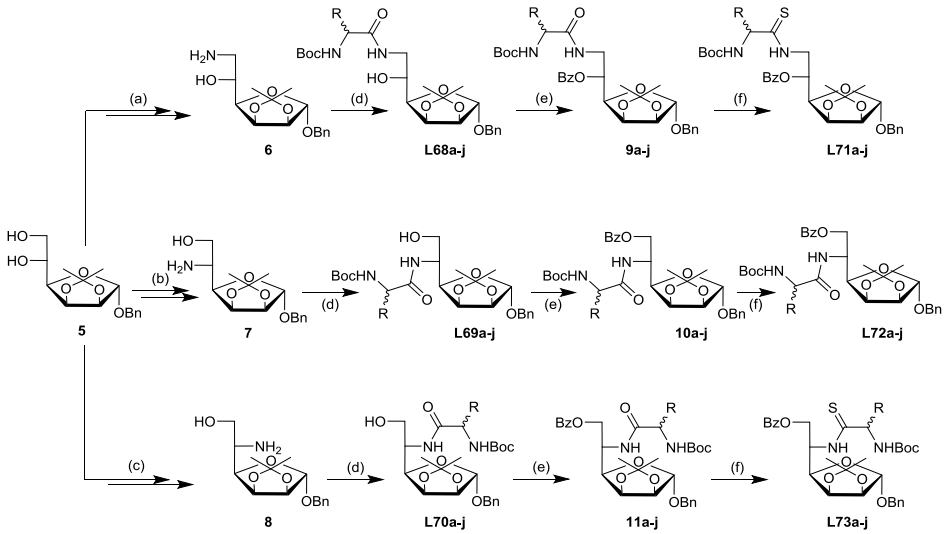


Figure 4.2.2. Hydroxyamide and thioamide ligands **L68**-**L73a**-**j**.

4.2.2. Results and discussion

4.2.2.1. Synthesis of ligands

A library of modular 30 hydroxyamide **L68**-**L70a-j** and 30 thioamide **L71**-**L73a-j** ligands was prepared as outlined in Scheme 4.2.1 using a combination of ten amino acids (i.e. L-Val, L-^{t}Leu, L-Leu, L-Phe, L-phenyl-Gly, L-Ala, Gly, D-Val, D-phenyl-Gly and D-Ala) and 3 amino alcohols (**6**-**8**). The diversity in the sugar backbone was achieved from benzyl 2,3-O-isopropylidene-α-D-mannofuranoside **5**, which is easily prepared in a multigram scale from readily available D-mannose.[14] Taking advantage of the different reactivity of the hydroxyl groups attached to C-5 and C-6 in **5**, we prepared key amino-alcohol intermediates **6**-**8** that made possible to study the effect of the carbon at which the amide/thioamide is coupled (either C-6 in compound **6** or C-5 in compound **7**) as well as the effect of the configuration of C-5 (compound **7** vs **8**).



Scheme 4.2.1. Synthesis of hydroxyamide and thioamide ligands **L68**-**L73a**-**j**.

Hydroxyamide ligands **L68**-**L70a**-**j** were prepared straightforward in one-step by coupling the corresponding commercially available N-Boc-protected amino acid derivative with the desired amino alcohol **6**-**8**, using isobutyl chloroformate as coupling reagent. These ligands were isolated after purification on neutral silica gel as white solids. In this step the desired diversity in the substituents and configuration of the amino acid part (**a**-**j**) was also achieved. Thioamide ligands **L71**-**L73a**-**j** were prepared from hydoxyamides **L68**-**L70** following a two-step procedure. The first step was the benzoylation of the free hydroxyl group in compounds **L68**-**L70** (step (e)). Subsequently, treatment of intermediates **9**-**11** with Lawesson's reagent gave access to thioamide ligands (step (f)). It should be pointed out that we could not obtain the desired thioamides when *tert*-butyl groups were present in the α-amino acid moiety. Thioamide ligands **L71**-**L73a**-**j** were also isolated as white solids.

4.2.2.2. Asymmetric transfer hydrogenation of acetophenone

In a first set of experiments, acetophenone **S1** was used as a model to study the effectiveness of the new ligands. For comparison purposes, we tested them using the optimal reaction conditions found in previous studies with hydroxyamide/thioamide ligands. Reactions were therefore performed at room temperature, using 0.5 mol% of in-situ generated catalyst ($[RuCl_2(p\text{-cymene})]_2$ for ligands **L69**-**L70** and $[RhCl_2Cp^*]_2$ for ligands **L71**-**L73**) in presence of KO^tBu as base. The results are collected in Table 4.2.1. The catalytic performance was found to be highly dependent on the position of the α-amino acid/thioamide moieties in either C-5 or C-6 of the sugar backbone and also dependent on the configuration of C-5. This dependence was different for hydroxyamide ligands than for thioamide ligands. On the other hand, while changing the amino acid substituents in hydroxyamide ligands does not affect enantioselectivity, these substituents do have an important effect with thioamide ligands. By the appropriate choice of the ligands (**L68a**,

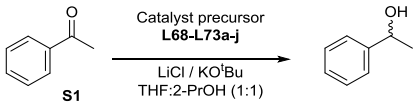
L72a and **L73h**) we achieved both enantiomers of the reduced product with excellent enantioselectivity (ee' up to >99%) and yield, comparable to the best one reported.

Hydroxyamide ligands **L68a**-**f** provided excellent enantioselectivities, ranging from 95% to >99%, independently on the electronic and steric properties of the (*S*)-amino acid moieties (Table 4.2.1, entries 1-6). The best trade-off between activity and enantioselectivity was achieved with ligand **L68a** (entry 1). Note also that the use of ligand **L68g**, with an achiral Gly α-amino acid moiety, also provided high enantioselectivities (up to 95%; Table 4.2.1, entry 7). This indicates that, contrary to other Ru-hydroxyamide catalysts described in the literature, enantioselectivity is mainly determined by the sugar backbone rather than by the α-amino acid moiety. Hence, inexpensive achiral α-amino acid derivatives can be used as long as the sugar backbone is selected properly. Finally, hydroxyamide ligands **L68h**-**j** with (*R*)-amino acid moieties were a mismatched combination providing low activities and enantioselectivities (entries 8-10).

The use of hydroxyamide ligands **L69**, with the α-amino acid moiety in C-5 instead of in C-6 (ligands **L68**) also provided high enantiomeric excesses, albeit with very low conversions (Table 4.2.1, entries 11 and 12 vs 1 and 6). Previous mechanistic studies with successful Ru/hydroxyamide catalysts showed that hydroxyamide ligands coordinates to the metal in a tridentate manner, though both nitrogens and the oxygen atom. The lower activity with ligands **L69** can be attributed to the higher rigidity of ligand **L69** which hinders its coordination to the metal center in contrast to the less steric environment generated by ligand **L68**. Note that for ligands **L68**, the amido group is attached to the flexible primary C-6. The use of ligands **L70**, with an opposite configuration at C-5 than in **L69**, provided somewhat higher activities than **L69**, but lower enantioselectivities (entries 13-16).

As already mentioned, Rh-thioamide catalytic systems followed a different trend than the Ru-hydroxyamide catalysts. With ligands **L71a**-**j** enantioselectivity was affected by the type of thioamide (Table 4.2.1, entries 17-25). Enantioselectivities increased with more sterically hindered substituents (i.e. ^{i}Pr>^{i}Bu>Bn>Ph≈Me). Moreover, in contrast to hydroxyamide ligands, the configuration of the thioamide controlled the sense of enantioselectivity, with a cooperative effect between the configuration of the thioamide and the sugar backbone that resulted in a matched combination for the Rh-**L71a** catalytic system. Advantageously, we also found that moving the thioamide group from C-6 to C-5 (ligands **L72**) increased enantioselectivities from 87% to 98% (Table 4.2.1, entry 26 vs 17). Finally, comparing the results of using ligands **L72** and **L73** it can be seen a cooperative effect between the configuration of C-5 of the furanoside backbone and the configuration of the thioamide substituent, which results in a matched combination with ligands **L72a** and **L73h**, containing (*S*)- and (*R*)-thioamide isopropyl groups, respectively (entries 26 and 29). This behavior is highly advantageous because it allows obtaining both enantiomers in high enantioselectivities which was not possible using Ru-**L68** catalysts.

Table 4.2.1 Asymmetric transfer hydrogenation reaction of **S1** using ligands **L68**-**L73a**-**j**.[a]



Entry	Ligand	% Conv (h)[b]	% ee[b]	Entry	Ligand	% Conv (h)[b]	% ee[b]
1	**L68a**	86 (3)	>99 (*S*)	16	**L70j**	11 (1)	40 (*R*)
2	**L68b**	56 (3)	95 (*S*)	17	**L71a**	87 (3)	87 (*R*)
3	**L68c**	86 (3)	99 (*S*)	18	**L71c**	68 (3)	82 (*R*)
4	**L68d**	54 (3)	98 (*S*)	19	**L71d**	90 (3)	80 (*R*)
5	**L68e**	84 (3)	98 (*S*)	20	**L71e**	83 (3)	62 (*R*)
6	**L68f**	87 (3)	99 (*S*)	21	**L71f**	91 (3)	62 (*R*)
7	**L68g**	95 (3)	95 (*S*)	22	**L71g**	74 (3)	2 (*R*)
8	**L68h**	4 (1)	4 (*S*)	23	**L71h**	79 (3)	79 (*S*)
9	**L68i**	11 (3)	8 (S)	24	**L71i**	62 (3)	52 (*S*)
10	**L68j**	5 (1)	4 (*S*)	25	**L71j**	65 (3)	77 (*S*)
11	**L69a**	4 (3)	99 (*S*)	26	**L72a**	93 (3)	98 (*R*)
12	**L69f**	6 (3)	99 (*S*)	27	**L72f**	96 (3)	50 (*R*)
13	**L70a**	12 (1)	80 (*S*)	28	**L73a**	80 (3)	88 (*R*)
14	**L70f**	41 (1)	85 (*S*)	29	**L73h**	90 (3)	98 (*S*)
15	**L70h**	11 (1)	72 (*R*)				

[a] Reaction conditions: **S1** (1 equiv, 0.2 M in 2-propanol/THF: 1/1), $[RuCl_2(p\text{-cymene})]_2$ (0.25 mol%) or $[RhCl_2Cp^*]_2$ (0.25 mol%), ligand (0.55 mol%), KO^{t}Bu (5 mol%), LiCl (10 mol%) and at room temperature. [b] Conversion and enantiomeric excess were determined by GC (CP Chirasil DEX CB).

4.2.2.3. Asymmetric transfer hydrogenation of several ketones

To establish the versatility of the reaction with the new ligand families, we evaluated a series of substrates with the optimized catalytic systems. We initially considered the ATH of a broad range of aryl ketones. Table 4.2.2 shows the results using catalysts Ru-**L68a** and Rh-**L72a** that had provided, together with Rh-**L73h**, the best results in the asymmetric transfer hydrogenation of **S1**. Again, both enantiomers of the reduced products were accessible in high enantioselectivities.

We noted that Ru-**L68a** and Rh-**L72a** catalytic systems easily tolerate variations of the electronic properties of the substituents in the aryl moiety of the substrate. A broad range of aryl ketones (17 of them, Table 4.2.2, entries 1-17) with electron-withdrawing or electron-donating substituents was reduced in high yields and excellent enantioselectivities, comparable to those achieved with substrate **S1**. Among them, it should be denoted the excellent results with electron rich ketones (**S7** and **S18**) and for *ortho*-substituted aryl ketones (**S12**-**S16**) that usually proceed with much lower activities and yields.

We next considered the asymmetric transfer hydrogenation of aryl ketones bearing increasingly sterically demanding alkyl substituents (Table 4.2.2, entries 18-23). Despite its relevance, few successful examples can be found in the literature and they are limited in substrate scope. One of this examples reported by Feringa *et al.* showed that **S22** and **S23** could be efficiently reduced using mild reaction conditions.[15] They needed, however, to synthesize and isolate the precatalyst prior to use. More recently Adolfsson *et al.* have

disclosed that the combination of earlier *in-situ* formed Ru/amino acid hydroxyamide catalysts together with the appropriate choice of the reaction conditions could efficiently reduce these challenging substrates, although only a limited range of them and using more drastic reaction conditions.[16] Our results with Ru-**L68a** and Rh-**L72a** indicate that enantioselectivities are again quite unaffected by the nature of the alkyl substituent, with ee's typically above 97%. We could therefore reach high yields and ee's up to >99% in the reduction of a broad range of these challenging substrates. Even more remarkable is the high catalytic performance of the reduction of substrates **S19**-**S21** and **S24** using standard (milder) reaction conditions. This represents the first successful application of readily available Rh/thioamide catalysts in the reduction of such substrates, which allows to obtain both enantiomers of the reduction products by simple change the catalyst precursor.

Ru-**L68a** and Rh-**L72a** catalytic systems also proved to be highly efficient in the reduction of benzo-fused cyclic ketones such as α-tetralones (**S25**-**S27**), indanone **S28** and chromanone **S29** (Table 4.2.2, entries 24-28). In all cases excellent enantiocontrol was achieved, in contrast with the moderate ee's achieved using other Ru/hydroxyamide and Rh/thioamide catalytic systems found in the literature.[16] The effective reduction of these substrates is important because the resulting products are often intermediates in the synthesis of biologically active products.

We also investigated the asymmetric transfer hydrogenation of aryl/fluoroalkyl ketones **S30** and **S31** (Table 4.2.2, entries 29 and 30).[17] The formation of optically active α-trifluoromethyl alcohols has attracted the attention of many researchers because they are intermediates in the improvement of medicines, agrochemicals and other materials owing to the unique properties of the fluorine atom.[18] The preparation of chiral α-trifluoromethyl alcohols relies mainly on the use of asymmetric hydrogenation and hydroboration with biocatalysts.[19] The asymmetric transfer hydrogenation of these challenging substrates will open up a new straightforward and sustainable route for preparing α-trifluoromethyl alcohols. So far, only a few reports have been published and with little success.[20] We are pleased to see that Ru-**L68a** and Rh-**L72a** could also reduce demanding fluoroalkyl ketones **S30** and **S31** with high yields and high enantioselectivities in both enantiomers of the resulting chiral products. These results compare favorably with those using the Ru/**TSDPEN** catalyst (38% ee), which is considered the state of art in ATH reactions.[17]

Table 4.2.2. Asymmetric transfer hydrogenation of aryl ketones **S2**-**S32**.[a]

			Ru-**L68a**		Rh-**L72a**	
Entry	Substrate		%Conv (%Yield)[b]	% ee[c]	%Conv (%Yield)[b]	% ee[c]
1	**S2**	R^1= NO_2	100 (94)	99 (*S*)	100 (92)	98 (*R*)
2	**S3**	R^1= CF_3	99 (92)	98 (*S*)	100 (93)	98 (*R*)
3	**S4**	R^1= Br	97 (90)	99 (*S*)	100 (90)	97 (*R*)
4	**S5**	R^1= F	100 (93)	98 (*S*)	100 (93)	97 (*R*)
5	**S6**	R^1= Me	100 (95)	96 (*S*)	100 (93)	98 (*R*)
6	**S7**	R^1= OMe	62 (55)	98 (*S*)	57 (49)	97 (*R*)
7	**S8**	R^2= CF_3	82 (76)	98 (*S*)	92 (84)	99 (*R*)
8	**S9**	R^2= Br	98 (91)	>99 (*S*)	100 (94)	99 (*R*)
9	**S10**	R^2= Me	80 (75)	99 (*S*)	100 (89)	98 (*R*)
10	**S11**	R^2= OMe	90 (82)	99 (*S*)	95 (84)	99 (*R*)
11	**S12**	R^3= CF_3	54 (46)	98 (*S*)	62 (55)	99 (*R*)
12	**S13**	R^3= Br	84 (80)	98 (*S*)	100 (92)	98 (*R*)
13	**S14**	R^3= F	99 (87)	97 (*S*)	100 (91)	98 (*R*)
14	**S15**	R^3= Me	71 (64)	98 (*S*)	84 (79)	98 (*R*)
15	**S16**	R^3= OMe	75 (69)	98 (*S*)	83 (71)	98 (*R*)
16	**S17**		75 (70)	98 (*S*)	94 (91)	98 (*R*)
17	**S18**		51 (49)	>99 (*S*)	47 (43)	97 (*R*)
18	**S19**	R^4= Et	90 (84)	>99 (*S*)	98 (91)	98 (*R*)
19	**S20**	R^4= CH_2CH_2Ph	100 (86)	99 (*S*)	100 (83)	99 (*R*)
20	**S21**	R^4= ^{i}Bu	44 (39)	97 (*S*)	76 (72)	97 (*R*)
21	**S22**	R^4= ^{i}Pr	100 (92)[d]	90 (*S*)[d]	51 (43)	93 (*R*)
22	**S23**	R^4= Cy	52 (47)[d]	99 (*S*)[d]	40 (32)	>99 (*R*)
23	**S24**	R^4= C_4H_7	100 (93)	99 (*S*)	97 (92)	97 (*R*)
24	**S25**	R^5= R^6= H	84 (78)	>99 (*S*)	52 (48)	>99 (*R*)
25	**S26**	R^5= H; R^6= OMe	100 (84)	99 (*S*)	69 (53)	>99 (*R*)
26	**S27**	R^5= OMe; R^6= H	92 (86)	>99 (*S*)	53 (45)	>99 (*R*)
27	**S28**		94 (81)	95 (*S*)	59 (50)	96 (*R*)
28	**S29**		79 (70)	>99 (*S*)	61 (58)	>99 (*R*)
29	**S30**	R^1= OMe	100 (91)	76 (*R*)	100 (90)	82 (*S*)
30	**S31**	R^1= H	100 (87)	74 (*R*)	100 (92)	81 (*S*)
31[e]	**S32**		100 (-)	>99 (*S*)	81 (-)	97 (*R*)

[a] Reaction conditions: ketone (1 equiv, 0.2 M in 2-propanol/THF: 1/1), $[RuCl_2(p\text{-cymene})]_2$ (0.25 mol%) or $[RhCl_2Cp^*]_2$ (0.25 mol%), ligand (0.55 mol%), KO^tBu (5 mol%), LiCl (10 mol%) and at room temperature. [b] Conversion measured by ^{1}H NMR. Isolated yield in parenthesis. [c] Enantiomeric excess were determined by GC (CP Chirasil DEX CB) or HPLC. [d] Reaction carried out at 40 °C for 18 h using THF/EtOH (1/3). [e] The ATH of **S32** led to the corresponding epoxide.

We finally turned our attention to the asymmetric transfer hydrogenation of α-halo ketone **S32**, which reduction provides an epoxide (Table 4.2.2, entry 31). Among the existing methods for providing chiral epoxides, this is one of the most sustainable and most straightforward. The synthesis of chiral epoxides has received considerable attention; they

are valuable intermediates because they can be stereoselectively opened by azides,[21] cyanide derivatives,[22] and amines,[23] giving easy access to aziridines and β-and γ-amino alcohols. Ru-**L68a** and Rh-**L72a** were also successfully applied in the reduction of the α-halo ketone **S32** to form the corresponding epoxide in excellent enantioselectivity (Table 4.2.2, entry 31).

Heteroaromatic ketones are another relevant set of substrates that are receiving much consideration. The reduction of these substrates is an elegant route for producing chiral heteroaromatic alcohols that are found in biologically active compounds. The reduction of heteroaromatic ketones has been less investigated and since the coordination of the heteroaromatic group of the substrate to the metal has to be avoided, very few catalytic systems have provided high enantioselectivities under transfer hydrogenation conditions.[24] Table 4.2.3 shows that several type of heteroaromatic ketones (acetylpyridines, acetylfurans and acetylthiophenes) can be efficiently reduced with Ru-**L68a** and Rh-**L71a** to provide both enantiomers of the corresponding compounds with high yields and enantioselectivities up to >99% (Table 4.2.3, entries 1-5). In contrast to the previous substrates where Ru-**L68a** and Rh-**L72a** provided the best catalytic performance, here Ru/hydroxyamide **L68a** still provided the best catalytic performance but the best results with thioamide compounds were achieved with ligand **L71a**.

Table 4.2.3. Asymmetric transfer hydrogenation of heteroaromatic ketones **S33**-**S37**.[a]

		Ru-**L68a**		Rh-**L71a**	
Entry	Substrate	% Conv (%yield)[b]	% ee[c]	% Conv (%yield)[b]	% ee[c]
1	 **S33**	100 (91)	99 (*R*)	100 (89)	>99 (*S*)
2	 **S34**	100 (89)	98 (*S*)	100 (90)	99 (*R*)
3	 **S35**	100 (92)	>99 (*R*)	100 (91)	97 (*S*)
4	 **S36**	100 (88)	99 (*S*)	100 (90)	95 (*R*)
5	 **S37**	100 (90)	95 (*S*)	100 (87)	88 (*R*)

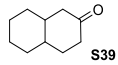
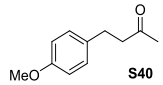
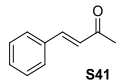
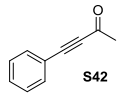
[a] Reaction conditions: ketone (1 equiv, 0.2 M in 2-propanol/THF: 1/1), $[RuCl_2(p\text{-cymene})]_2$ (0.25 mol%) or $[RhCl_2Cp^*]_2$ (0.25 mol%), ligand (0.55 mol%), KO^tBu (5 mol%), LiCl (10 mol%) and at room temperature for 3 h. [b] Conversion measured by ^1H NMR. Isolated yield in parenthesis. [c] Enantiomeric excess were determined by HPLC.

The excellent results achieved up to this point encouraged us to test the reduction of alkyl/alkyl, α,β-unsaturated and propargylic ketones (Table 4.2.4). For these only a few catalytic systems had provided high yields and enantioselectivities.[2] The results for alkyl/alkyl ketones **S38**-**S40** indicated that to achieve high enantioselectivities the steric demands between the two alkyl substituents must be very different (Table 4.2.4, entries 1-3). For instance, while enantioselectivities were only moderate for β-tetralone **S39**, the reduction of cyclohexylmethyl ketone **S38** proceeded with excellent ee's (up to 98%).

Ru-**L68a** and Rh-**L72a** were also able to reduce the α,β-unsaturated ketone **S41** in high ee's (up to 95%). However, large amounts of 4-phenylbutan-2-one and 4-phenylbutan-2-ol were also isolated. This indicates that isomerization of the ATH product (4-phenylbut-3-en-2-ol) takes also place under reaction conditions. This unexpected result led us think that the new catalysts could be effective in the tandem isomerization/asymmetric transfer hydrogenation reaction of allylic alcohols (see Section 4.2.2.4).

Finally, the scope of our catalysts was expanded to the ATH of propargylic ketones. The stereoselective construction of propargylic alcohols is important because these alcohols are versatile building blocks widely used to synthesize biologically active compounds and structurally interesting molecules. As such, the enantioselective transfer hydrogenation is currently being studied as a more direct and atom-efficient method than the existing methods. However, few successful examples have been reported so far. [25] Adolfsson *et al.* have recently reported the successful use of Ru/hydroxyamide type catalysts in this transformation under milder reactions conditions than the existing ATH protocols reported.[25d] Using the optimal reaction conditions found by Adolfsson *et al.*, we found that Ru-**L68a** and Rh-**L72a** provided high yields and enantioselectivities comparable to the best one reported in the literature (Table 4.2.4, entry 5). For the first time Rh/thioamide catalysts have been able to reduce this type of substrate allowing us to obtain both enantiomers of the reduction product in high enantioselectivity.

Table 4.2.4. Asymmetric transfer hydrogenation of alkyl/alkyl, α,β-unsaturated and propargylic ketones **S37**-**S41**.[a]

		Ru-**L68a**		Rh-**L72a**	
Entry	Substrate	% Conv (%yield)[b]	% ee[c]	% Conv (%yield)[b]	% ee[c]
1	 **S38**	100 (85)	98 (*S*)	100 (85)	96 (*R*)
2	 **S39**	100 (91)	59 (*S*)	100 (88)	61 (*R*)
3	 **S40**	100 (93)	50 (*S*)	99 (90)	48 (*R*)
4[d]	 **S41**	100 (34)	95 (S)	100 (32)	82 (*R*)
5[d]	 **S42**	100 (89)	96 (*S*)	100 (90)	87 (*R*)

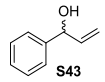
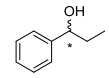
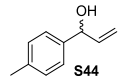
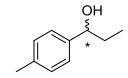
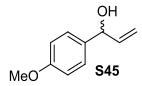
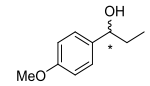
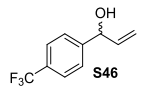
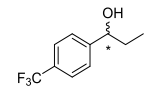
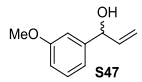
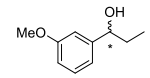
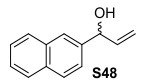
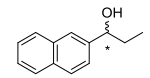
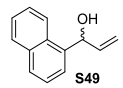
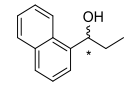
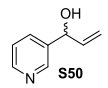
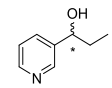
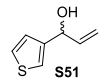
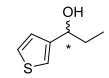
[a] Reaction conditions: ketone (1 equiv, 0.2 M in 2-propanol/THF: 1/1), $[RuCl_2(p\text{-cymene})]_2$ (0.25 mol%) or $[RhCl_2Cp^*]_2$ (0.25 mol%), ligand (0.55 mol%), KO^tBu (5 mol%), LiCl (10 mol%) and at room temperature for 3 h. [b] Conversion measured by ^1H NMR. Isolated yield in parenthesis. [c] Enantiomeric excess were determined by HPLC. [d] ketone (1 equiv, 0.2 M in 2-propanol/THF: 1/1), $[RuCl_2(p\text{-cymene})]_2$ (1 mol%), ligand (2.2 mol%), KO^tBu (10 mol%), LiCl (10 mol%) and at room temperature for 10 min.

4.2.2.4. Tandem isomerization/ATH and α-alkylation/ATH reactions

Tandem reactions offer cost-effective synthetic pathways with a reduced overall reaction time, reduced chemical waste and little energy consumption. Therefore, the search of a single catalyst able to promote two or more successive transformations in the same reaction medium has attracted the interest of many researchers. In this section we show that our Ru-**L68a** catalyst can be successfully used in two types of tandem reactions that involve ATH reactions.

The first reaction is the simple tandem isomerization/asymmetric transfer hydrogenation of allylic alcohols. Allylic alcohols are readily available natural feedstocks. This justifies their use as starting materials for transformation into more valuable compounds.[26] The isomerization of allylic alcohols followed by enantioselective ketone reduction would allow obtaining chiral saturated alcohols in a straightforward manner. Another sustainable path to obtain these compounds is direct hydrogenation although this has poor selectivity due to the both allylic and benzylic nature of this type of substrate. To date only three recent publications have reported the asymmetric isomerization/transfer hydrogenation of allylic alcohols with enantioselectivities between 11-98% ee.[27] Moreover, their results largely depend on the substrate and important differences in enantioselectivity were obtained by simple modifications in the electronic properties of α-vinylbenzyl alcohols. To be of practical interest, isomerization/ATH still requires substantial improvements in terms of enantioselectivity, chemical yield and substrate versatility. Table 4.2.5 shows the results of using Ru/**L68a** in the tandem isomerization/ATH of nine allylic alcohols (**S43**-**S51**). In all cases only the desired alcohol was obtained. Neither the intermediates aryl/alkyl ketone nor the undesired alkylated ketones were detected. Improving previous published results, we found that Ru-**L68a** is quite tolerant to varying electronic and steric properties of the substrate phenyl ring (Table 4.2.5, entries 1-7). A broad range of allylic alcohols were therefore converted into the saturated product with excellent yields and high enantioselectivities (ee's ranging from 94% to 96%). Interestingly, we could also reach ee's (up to 97%) and high yields in the isomerization/reduction of secondary allylic alcohols containing heteroaromatic groups (entries 8 and 9). These results surpass the best ones reported.[27c]

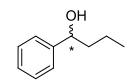
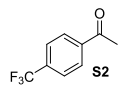
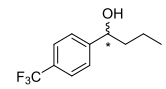
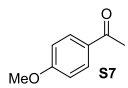
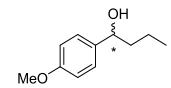
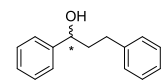
Table 4.2.5. Tandem isomerization/ATH reactions of allylic alcohols using Ru-**L68a**.[a]

Entry	Substrate	Product	% Conv (%yield)[b]	% ee[c]
1	 **S43**		100 (91)	96 (*S*)
2	 **S44**		100 (92)	95 (*S*)
3	 **S45**		100 (89)	94 (*S*)
4	 **S46**		98 (90)	95 (*S*)
5	 **S47**		100 (93)	95 (*S*)
6	 **S48**		100 (88)	95 (*S*)
7	 **S49**		100 (90)	96 (*S*)
8	 **S50**		100 (88)	97 (*S*)
9	 **S51**		96 (87)	86 (*S*)

[a] Reaction conditions: ketone (1 equiv, 0.5 M in etanol/THF: 3/1), $[RuCl_2(p\text{-cymene})]_2$ (0.5 mol%), ligand (1.1 mol%), KO^tBu (30 mol%), LiCl (10 mol%) and at 40 °C for 24 h. [b] Conversion measured by ^1H NMR. Isolated yield in parenthesis. [c] Enantiomeric excess were determined by GC or HPLC.

The second tandem reaction studied is the α-alkylation/asymmetric transfer hydrogenation of acetophenones with primary alcohols to produce chiral alcohols with an elongation of the alkyl chain. This is an environmentally friendly catalytic reaction that forms water as the only byproduct. Despite its importance, only two communications have been reported with limited substrate scope.[28] One of them, reported by Uemura et al, showed the α-alkylation/asymmetric transfer hydrogenation of eleven substituted acetophenones with good to excellent enantioselectivities (88-98%) and high to good yields (50-80%).[28a] However, two different catalysts were required together with drastic reaction conditions. Adolfsson et al. has recently showed that one single catalyst can mediate α-alkylation/ATH process with low to moderate yields (15-40%) and moderate to good enantioslectivities (57-89%).[28b] Although fewer substrates were alkylated/reduced than with the Uemura's systems, it allowed this transformation to take place with a single catalyst, which would be advantageous for sustainable industrial process. Owing to the limited substrate scope of the two advances mentioned, new developments in this field are still needed. Table 4.2.6 shows the results of using Ru/**L68a** in the tandem α-alkylation/ATH of acetophenones.

Table 4.2.6. Tandem α-alkylation/asymmetric reactions of arylketones using Ru-**L68a**.[a]

Entry	Substrate	Alcohol	Product	% Conv (%yield)	% ee
1	 **S1**	EtOH		100 (41)	84 (*S*)
2	 **S2**	EtOH		100 (28)	70 (*S*)
3	 **S7**	EtOH		100 (38)	90 (*S*)
4	 **S1**	$PhCH_2OH$		100 (31)	77 (*S*)

[a] Reaction conditions: ketone (5 mmol), $[RuCl_2(p\text{-cymene})]_2$ (0.025 mol), ligand (0.055 mol), KO^tBu (2.5 mmol), LiCl (0.5 mmol), DMSO (1.6 mL), alcohol (15 mmol) and at 30 °C for 0.5h then 40 °C for 4.5 h. [b] Conversion measured by ^1H NMR. Isolated yield in parenthesis. [c] Enantiomeric excess were determined by GC or HPLC.

In all cases full conversions were achieved. However, as observed by Adolfsson, moderate yields of the desired products were obtained. This is mainly because parts of the acetophenones are directly reduced under reaction conditions and also because of the presence of the intermediate alkylated ketones. The results indicated that enantioselectivities are highly affected by the electronic nature of the acetophenone. Enantioselectivities were therefore best with electron-rich aryl substituents (entry 2 vs 1 and 3). These results are in line with what is expected for enolate condensation reactions. If we compare these results with the previously published by the Adolfsson group, our catalytic system provided higher enantioselectivities (i.e. the alkylation/ATH of **S2** provided 70% ee which is higher than the 57% ee achieved with the Adolfsson's system). We were pleased to see that we could also use benzyl alcohol as alkylating reagent, with enantioselectivity up to 77% in the desired product.

4.2.3. Conclusions

A large library of furanoside-based hydroxyamide and thioamide ligands **L68**-**L73a**-**j** has been synthesized for ATH in order to expand the scope of the substrates to cover a broader range of ketones, including more challenging ones such as trifluoromethyl-containing ketones, propargylic and alkyl/alkyl ketones among others. These ligands have the advantage that they are prepared from commercial D-mannose and α-amino acids, inexpensive natural chiral feedstocks. Moreover, the modular nature of the ligand library allows several ligand parameters to be easily and systematically varied, so activities and enantioselectivities can be maximized for each substrate as required. By carefully selecting the ligand components, we found excellent enantioselectivities (ee's typically ranging between 95% and >99%) in a broad range of ketones. Note that both enantiomers of the reduction products can be obtained with excellent enantioselectivities by simply changing either the Ru-hydroxyamide catalyst precursor to Rh-thioamide (i.e. Ru-**L68a** vs Rh-**72a**) or the absolute configuration of the thioamide substituent. The results of our mannose-based catalyst library compare very well with the best ones reported in the literature. In addition,

we have also shown the potential application of the new catalyst in the simple tandem isomerization/ATH of readily available allylic alcohols and the tandem a-alkylation/ATH to produce chiral alcohols with an elongation of the alkyl chain. These findings represent an improvement on the previously reported furanoside-derived hydroxyamide and thioamide ligands and open up a new type of ligand for the highly enantioselective reduction of industrially relevant substrates as well as their use in tandem reactions.

4.2.4. Experimental section

4.2.4.1. General considerations

All reactions were carried out using standard Schlenk techniques under an atmosphere of argon. Solvents were purified and dried by standard procedures. 1-*O*-Benzyl-2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranose **3** was prepared as previously described.[29] ^{1}H and ^{13}C{^{1}H} NMR spectra were recorded using a 400 MHz spectrometer. Chemical shifts are relative to that of $SiMe_4$ (^{1}H and ^{13}C) as internal standard. ^{1}H and ^{13}C assignments were made on the basis of ^{1}H-^{1}H gCOSY and ^{1}H-^{13}C gHSQC experiments.

4.2.4.2. Typical procedure for the preparation hydroxyamide ligands L68-L70a-j

To a cooled solution (-15 ^{o}C) of the desired N-Boc-protected amino acid (2 mmol) in THF (4 mL), N-methylmorpholine (2.3 mmol, 252 µL) and isobutyl chloroformate (2.3 mmol, 300 µL) were slowly added. After 45 min, a solution of the desired amino alcohol (2 mmol), in THF (4 mL) was added and the resulting mixture was stirred at room temperature for 2 h. The crude mixture was purified by SiO_2-flash chromatography (ethyl acetate/petroleum ether: 2/3 for ligands **L68a**-**e** and **L68h**-**i** or ethyl acetate/petroleum ether: 3/2 for ligands **L68f**-**g**,**j**, **L69a**,**f** and **L70a**-**j**) to produce the corresponding ligands as white solids.

***N*-(*tert*-Butoxycarbonyl)-L-valine-(6-amido-1-*O*-benzyl-6-deoxy-2,3-*O*-isopropylidene-α-D-mannofuranose) (L68a)**. Yield: 692 mg (68%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.90 (d, 3H, CH_3, ^{i}Pr, $^{3}J_{H-H}$ =6.8 Hz), 0.94 (d, 3H, CH_3, ^{i}Pr, $^{3}J_{H-H}$ =6.4 Hz), 1.31 (s, 3H, CH_3), 1.43 (s, 9H, CH_3, ^{t}Bu), 1.44 (s, 3H, CH_3), 2.10 (bs, 1H, CH, ^{i}Pr), 3.34-3.41 (m, 1H, H-6), 3.61-3.67 (m, 1H, H-6), 3.85 (dd, 1H, H-4, $^{3}J_{H-H}$ =8.4 Hz, $^{3}J_{H-H}$ =3.6 Hz), 3.90 (dd, 1H, CH, $^{3}J_{H-H}$ =8.4 Hz, $^{3}J_{H-H}$ =6.0 Hz), 3.97-4.02 (m, 1H, H-5), 4.48 (d, 1H, OCH_2, $^{2}J_{H-H}$ =12.0 Hz), 4.61-4.65 (m, 2H, OCH_2, H-2), 4.82 (dd, 1H, H-3, $^{3}J_{H-H}$ =5.6 Hz, $^{3}J_{H-H}$ =3.2 Hz), 5.09 (s, 1H, H-1), 5.15 (bs, 1H, NH-Boc), 6.49 (bs, 1H, NH), 7.27-7.37 (m, 5H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=17.5 (CH_3, ^{i}Pr), 17.8 (CH_3, ^{i}Pr), 24.6 (CH_3), 25.9 (CH_3), 28.3 (CH_3, ^{t}Bu), 30.1 (CH, ^{i}Pr), 43.4 (C-6), 60.1 (CH), 69.2 (OCH_2), 69.5 (C-5), 79.9 (C-3), 80.0 (C, ^{t}Bu), 80.2 (C-4), 84.9 (C-2), 105.5 (C-1), 112.7 ($\underline{C}Me_2$), 127.9 (CH=), 128.1 (CH=), 128.5 (CH=), 137.3 (C), 155.9 (C=O, NHBoc), 172.9 (C=O). MS HR-ESI [found 531.2680, $C_{26}H_{40}N_2O_8$ $(M\text{-}Na)^+$ requires 531.2677].

***N*-(*tert*-Butoxycarbonyl)-L-*tert*-leucine-(6-amido-1-*O*-benzyl-6-deoxy-2,3-*O*-isopropylidene-α-D-mannofuranose) (L68b)**. Yield: 292 mg (28%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.99 (s, 9H, CH_3, ^{t}Bu), 1.31 (s, 3H, CH_3), 1.43 (s, 9H, CH_3, ^{t}Bu), 1.44 (s, 3H, CH_3), 3.36-3.48 (m, 1H, H-6), 3.56-3.65 (m, 1H, H-6), 3.83-3.88 (m, 2H, H-4, CH), 3.97-4.02 (m, 1H, H-5), 4.46 (d, 1H, OCH_2, $^{2}J_{H-H}$ =12.0 Hz), 4.60-4.65 (m, 2H, OCH_2, H-2), 4.84 (dd, 1H, H-3, $^{3}J_{H-H}$ =5.6 Hz, $^{3}J_{H-H}$ =3.2 Hz), 5.08 (s, 1H, H-1), 5.36 (bs, 1H, NH-Boc), 6.41 (bs, 1H, NH), 7.27-7.36

(m, 5H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=24.6 (CH_3), 25.9 (CH_3), 26.6 (CH_3, ^{t}Bu), 28.3 (CH_3, ^{t}Bu), 34.5 (C, ^{t}Bu), 43.5 (C-6), 62.4 (CH), 69.2 (OCH_2), 69.5 (C-5), 79.9 (C-3), 80.0 (C, ^{t}Bu), 80.4 (C-4), 84.9 (C-2), 105.5 (C-1), 112.7 ($\underline{C}Me_2$), 127.9 (CH=), 128.1 (CH=), 128.5 (CH=), 137.3 (C), 155.9 (C=O, NHBoc), 172.2 (C=O). MS HR-ESI [found 545.2839, $C_{27}H_{42}N_2O_8$ (M-Na)$^+$ requires 545.2833].

N-(*tert*-Butoxycarbonyl)-L-leucine-(6-amido-1-*O*-benzyl-6-deoxy-2,3-*O*-isopropylidene-α-D-mannofuranose) (L68c). Yield: 418 mg (40%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.89 (s, 3H, CH_3, ^{i}Bu), 0.90 (s, 3H, CH_3, ^{i}Bu), 1.28 (s, 3H, CH_3), 1.40 (s, 12H, CH_3, ^{t}Bu), 1.43 (bs, 1H, CH_2, ^{i}Bu), 1.61 (bs, 2H, CH, CH_2, ^{i}Bu), 3.32-3.39 (m, 1H, H-6), 3.57-3.61 (m, 1H, H-6), 3.83 (dd, 1H, H-4, $^3J_{H\text{-}H}$ =7.6 Hz, $^3J_{H\text{-}H}$ =2.4 Hz), 3.96-4.01 (m, 1H, H-5), 4.07-4.11 (m, 1H, CH), 4.45 (d, 1H, OCH_2, $^2J_{H\text{-}H}$ =12.0 Hz), 4.59-4.62 (m, 2H, OCH_2, H-2), 4.82 (pt, 1H, H-3, $^3J_{H\text{-}H}$ =5.2 Hz), 5.05 (s, 1H, H-1), 5.20 (bs, 1H, NH-Boc), 6.85 (bs, 1H, NH), 7.25-7.31 (m, 5H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=22.0 (CH_3, ^{i}Bu), 22.9 (CH_3, ^{i}Bu), 24.6 (CH_3), 24.7 (CH, ^{i}Bu), 26.0 (CH_3), 28.3 (CH_3, ^{t}Bu), 41.5 (CH_2, ^{i}Bu), 43.5 (C-6), 53.2 (CH), 69.0 (OCH_2), 69.1 (C-5), 79.9 (C-3), 80.0 (C, ^{t}Bu), 80.3 (C-4), 84.9 (C-2), 105.5 (C-1), 112.6 ($\underline{C}Me_2$), 127.8 (CH=), 128.0 (CH=), 128.4 (CH=), 137.3 (C), 155.8 (C=O, NHBoc), 174.0 (C=O). MS HR-ESI [found 545.2847, $C_{27}H_{42}N_2O_8$ (M-Na)$^+$ requires 545.2833].

***N*-(*tert*-Butoxycarbonyl)-L-phenylalanine-(6-amido-1-*O*-benzyl-6-deoxy-2,3-*O*-isopropylidene-α-D-mannofuranose) (L68d)**. Yield: 502 mg (45%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.31 (s, 3H, CH_3), 1.40 (s, 9H, CH_3, ^{t}Bu), 1.45 (s, 3H, CH_3), 3.05 (d, 2H, CH_2, $^3J_{H\text{-}H}$ =5.6 Hz), 3.22-3.29 (m, 1H, H-6), 3.57-3.64 (m, 1H, H-6), 3.76 (dd, 1H, H-4, $^3J_{H\text{-}H}$ =8.0 Hz, $^3J_{H\text{-}H}$ =3.6 Hz), 3.88-3.93 (m, 1H, H-5), 4.33-4.35 (m, 1H, CH), 4.47 (d, 1H, OCH_2, $^2J_{H\text{-}H}$ =12.0 Hz), 4.59-4.64 (m, 2H, OCH_2, H-2), 4.80 (pt, 1H, H-3, $^3J_{H\text{-}H}$ =5.6 Hz), 5.07 (s, 1H, H-1), 5.14 (bs, 1H, NH-Boc), 6.32 (bs, 1H, NH), 7.19-7.25 (m, 4H, CH=), 7.27-7.36 (m, 6H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=24.6 (CH_3), 25.9 (CH_3), 28.3 (CH_3, ^{t}Bu), 38.7 (CH_2), 43.4 (C-6), 56.0 (CH), 69.1 (OCH_2), 69.5 (C-5), 79.9 (C-3), 80.0 (C-4), 80.1 (C, ^{t}Bu), 84.9 (C-2), 105.4 (C-1), 112.6 ($\underline{C}Me_2$), 127.0 (CH=), 127.9 (CH=), 128.1 (CH=), 128.5 (CH=), 128.7 (CH=), 129.3 (CH=), 136.6 (C), 137.3 (C), 155.4 (C=O, NHBoc), 172.5 (C=O). MS HR-ESI [found 579.2690, $C_{30}H_{40}N_2O_8$ (M-Na)$^+$ requires 579.2677].

***N*-(*tert*-Butoxycarbonyl)-L-phenylglycine-(6-amido-1-*O*-benzyl-6-deoxy-2,3-*O*-isopropylidene-α-D-mannofuranose) (L68e)**. Yield: 814 mg (75%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.29 (s, 3H, CH_3), 1.41 (s, 12H, CH_3, ^{t}Bu), 3.33-3.39 (m, 1H, H-6), 3.58-3.64 (m, 1H, H-6), 3.72 (dd, 1H, H-4, $^3J_{H\text{-}H}$ =8.4 Hz, $^3J_{H\text{-}H}$ =4.0 Hz), 3.91-3.96 (m, 1H, H-5), 4.46 (d, 1H, OCH_2, $^2J_{H\text{-}H}$ =12.0 Hz), 4.57-4.62 (m, 2H, OCH_2, H-2), 4.74 (dd, 1H, H-3, $^3J_{H\text{-}H}$ =6.4 Hz, $^3J_{H\text{-}H}$ =4.0 Hz), 5.04 (s, 1H, H-1), 5.13 (bs, 1H, CH), 5.79 (bs, 1H, NH-Boc), 6.16 (pt, 1H, NH, $^3J_{H\text{-}H}$ =5.6 Hz), 7.27-7.37 (m, 10H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=24.7 (CH_3), 25.9 (CH_3), 28.3 (CH_3, ^{t}Bu), 43.6 (C-6), 58.3 (CH), 68.4 (C-5), 68.8 (OCH_2), 79.8 (C-3, C-4), 80.3 (C, ^{t}Bu), 84.8 (C-2), 105.3 (C-1), 112.4 ($\underline{C}Me_2$), 127.2 (CH=), 127.8 (CH=), 128.0 (CH=), 128.1 (CH=), 128.4 (CH=), 128.8 (CH=), 137.4 (C), 138.4 (C), 155.3 (C=O, NHBoc), 171.3 (C=O). MS HR-ESI [found 565.2516, $C_{29}H_{38}N_2O_8$ (M-Na)$^+$ requires 565.2520].

***N*-(*tert*-Butoxycarbonyl)-L-alanine-(6-amido-1-*O*-benzyl-6-deoxy-2,3-*O*-isopropylidene-α-D-mannofuranose) (L68f)**. Yield: 658 mg (68%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.27 (s, 3H, CH_3), 1.30 (d, 3H, CH_3, $^3J_{H\text{-}H}$ =7.6 Hz), 1.40 (s, 9H, CH_3, ^{t}Bu), 1.41 (s, 3H,

CH_3), 3.32-3.39 (m, 1H, H-6), 3.57-3.63 (m, 1H, H-6), 3.83 (dd, 1H, H-4, $^3J_{H-H}$ =8.0 Hz, $^3J_{H-H}$ =3.6 Hz), 3.96-4.01 (m, 1H, H-5), 4.16 (bs, 1H, CH), 4.44 (d, 1H, OCH_2, $^2J_{H-H}$ =11.6 Hz), 4.59-4.62 (m, 2H, OCH_2, H-2), 4.82 (dd, 1H, H-3, $^3J_{H-H}$ =6.0 Hz, $^3J_{H-H}$ =3.6 Hz), 5.05 (s, 1H, H-1), 5.40 (bs, 1H, NH-Boc), 6.87 (bs, 1H, NH), 7.23-7.33 (m, 5H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=18.7 (CH_3), 24.6 (CH_3), 25.9 (CH_3), 28.3 (CH_3, ^{t}Bu), 43.4 (C-6), 50.2 (CH), 69.0 (OCH_2, C-5), 79.9 (C-3), 80.0 (C, ^{t}Bu), 80.1 (C-4), 84.8 (C-2), 105.4 (C-1), 112.5 ($\underline{C}Me_2$), 127.8 (CH=), 128.0 (CH=), 128.4 (CH=), 137.3 (C), 155.5 (C=O, NHBoc), 174.0 (C=O). MS HR-ESI [found 503.2352, $C_{24}H_{36}N_2O_8$ $(M\text{-}Na)^+$ requires 503.2364].

***N*-(*tert*-Butoxycarbonyl)-glycine-(6-amido-1-*O*-benzyl-6-deoxy-2,3-*O*-isopropylidene-α-D-mannofuranose) (L68g)**. Yield: 656 mg (70%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.29 (s, 3H, CH_3), 1.42 (s, 12H, CH_3, ^{t}Bu), 3.32-3.39 (m, 1H, H-6), 3.61-3.66 (m, 1H, H-6), 3.78 (bs, 2H, CH_2), 3.83 (dd, 1H, H-4, $^3J_{H-H}$ =8.4 Hz, $^3J_{H-H}$ =4.0 Hz), 3.97-4.01 (m, 1H, H-5), 4.46 (d, 1H, OCH_2, $^2J_{H-H}$ =12.0 Hz), 4.60-4.63 (m, 2H, OCH_2, H-2), 4.82 (dd, 1H, H-3, $^3J_{H-H}$ =6.0 Hz, $^3J_{H-H}$ =4.0 Hz), 5.08 (s, 1H, H-1), 5.43 (bs, 1H, NH-Boc), 6.78 (bs, 1H, NH), 7.25-7.35 (m, 5H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=24.6 (CH_3), 25.9 (CH_3), 28.3 (CH_3, ^{t}Bu), 43.4 (C-6), 44.2 (CH_2), 69.1 (OCH_2), 69.3 (C-5), 79.9 (C-3), 80.1 (C-4), 80.2 (C, ^{t}Bu), 84.9 (C-2), 105.5 (C-1), 112.6 ($\underline{C}Me_2$), 127.8 (CH=), 128.0 (CH=), 128.5 (CH=), 137.4 (C), 156.1 (C=O, NHBoc), 170.7 (C=O). MS HR-ESI [found 489.2208, $C_{23}H_{34}N_2O_8$ $(M\text{-}Na)^+$ requires 489.2207].

***N*-(*tert*-Butoxycarbonyl)-D-valine-(6-amido-1-*O*-benzyl-6-deoxy-2,3-*O*-isopropylidene-α-D-mannofuranose) (L68h)**. Yield: 640 mg (63%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.91 (d, 3H, CH_3, ^{i}Pr, $^3J_{H-H}$ =6.8 Hz), 0.95 (d, 3H, CH_3, ^{i}Pr, $^3J_{H-H}$ =6.4 Hz), 1.31 (s, 3H, CH_3), 1.43 (s, 9H, CH_3, ^{t}Bu), 1.45 (s, 3H, CH_3), 2.11 (bs, 1H, CH, ^{i}Pr), 3.36-3.40 (m, 1H, H-6), 3.63-3.68 (m, 1H, H-6), 3.83 (dd, 1H, H-4, $^3J_{H-H}$ =8.0 Hz, $^3J_{H-H}$ =3.6 Hz), 3.92 (pt, 1H, CH, $^3J_{H-H}$ =7.2 Hz), 3.98-4.01 (m, 1H, H-5), 4.48 (d, 1H, OCH_2, $^2J_{H-H}$ =12.0 Hz), 4.60-4.65 (m, 2H, OCH_2, H-2), 4.84 (dd, 1H, H-3, $^3J_{H-H}$ =6.0 Hz, $^3J_{H-H}$ =4.0 Hz), 5.09 (s, 1H, H-1), 5.10 (bs, 1H, NH-Boc), 6.48 (bs, 1H, NH), 7.29-7.36 (m, 5H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=17.8 (CH_3, ^{i}Pr), 19.3 (CH_3, ^{i}Pr), 24.6 (CH_3), 25.9 (CH_3), 28.3 (CH_3, ^{t}Bu), 30.9 (CH, ^{i}Pr), 43.4 (C-6), 60.0 (CH), 69.2 (OCH_2), 69.8 (C-5), 77.2 (C, ^{t}Bu), 80.0 (C-3, C-4), 84.9 (C-2), 105.6 (C-1), 112.7 ($\underline{C}Me_2$), 127.9 (CH=), 128.1 (CH=), 128.5 (CH=), 137.4 (C), 155.9 (C=O, NHBoc), 173.0 (C=O). MS HR-ESI [found 531.2676, $C_{26}H_{40}N_2O_8$ $(M\text{-}Na)^+$ requires 531.2677].

***N*-(*tert*-Butoxycarbonyl)-D-phenylglycine-(6-amido-1-*O*-benzyl-6-deoxy-2,3-*O*-isopropylidene-α-D-mannofuranose) (L68i)**. Yield: 466 mg (43%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.29 (s, 3H, CH_3), 1.40 (s, 9H, CH_3, ^{t}Bu), 1.43 (s, 3H, CH_3), 2.87 (bs, 1H, OH), 3.40-3.47 (m, 1H, H-6), 3.52-3.58 (m, 1H, H-6), 3.76 (dd, 1H, H-4, $^3J_{H-H}$ =8.4 Hz, $^3J_{H-H}$ =4.0 Hz), 3.91-3.96 (m, 1H, H-5), 4.40 (d, 1H, OCH_2, $^2J_{H-H}$ =12.0 Hz), 4.53 (d, 1H, OCH_2, $^2J_{H-H}$ =12.0 Hz), 4.60 (d, 1H, H-2, $^3J_{H-H}$ =4.8 Hz), 4.80 (dd, 1H, H-3, $^3J_{H-H}$ =5.6 Hz, $^3J_{H-H}$ =3.6 Hz), 5.05 (s, 1H, H-1), 5.19 (bs, 1H, CH), 5.84 (bs, 1H, NH-Boc), 6.43 (bs, 1H, NH), 7.28-7.37 (m, 10H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=24.5 (CH_3), 25.9 (CH_3), 28.3 (CH_3, ^{t}Bu), 43.6 (C-6), 58.6 (CH), 69.1 (OCH_2), 69.4 (C-5), 79.9 (C-3), 80.0 (C-4), 80.1 (C, ^{t}Bu), 84.8 (C-2), 105.3 (C-1), 112.7 ($\underline{C}Me_2$), 127.2 (CH=), 127.9 (CH=), 128.1 (CH=), 128.4 (CH=), 128.5 (CH=), 129.0 (CH=), 137.2 (C), 138.3 (C), 155.2 (C=O, NHBoc), 171.3 (C=O). MS HR-ESI [found 565.2507, $C_{29}H_{38}N_2O_8$ $(M\text{-}Na)^+$ requires 565.2520].

***N*-(*tert*-Butoxycarbonyl)-D-alanine-(6-amido-1-*O*-benzyl-6-deoxy-2,3-*O*-isopropylidene-α-D-mannofuranose) (L68j)**. Yield: 626 mg (65%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.30 (s, 3H, CH_3), 1.34 (d, 3H, CH_3, $^3J_{H-H}$ =7.2 Hz), 1.42 (s, 9H, CH_3, ^{t}Bu), 1.44 (s, 3H, CH_3), 3.36-3.42 (m, 1H, H-6), 3.60-3.64 (m, 1H, H-6), 3.83 (dd, 1H, H-4, $^3J_{H-H}$ =8.0 Hz, $^3J_{H-H}$ =3.6 Hz), 3.98-4.02 (m, 1H, H-5), 4.18 (bs, 1H, CH), 4.47 (d, 1H, OCH_2, $^2J_{H-H}$ =11.6 Hz), 4.61-4.64 (m, 2H, OCH_2, H-2), 4.84 (dd, 1H, H-3, $^3J_{H-H}$ =5.6 Hz, $^3J_{H-H}$ =3.6 Hz), 5.08 (s, 1H, H-1), 5.20 (bs, 1H, NH-Boc), 6.77 (bs, 1H, NH), 7.28-7.35 (m, 5H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=18.5 (CH_3), 24.6 (CH_3), 26.0 (CH_3), 28.3 (CH_3, ^{t}Bu), 43.4 (C-6), 50.2 (CH), 69.1 (OCH_2), 69.6 (C-5), 80.0 (C-3, C-4), 80.2 (C, ^{t}Bu), 84.9 (C-2), 106.5 (C-1), 112.7 ($\underline{C}Me_2$), 127.8 (CH=), 128.1 (CH=), 128.5 (CH=), 137.3 (C), 155.6 (C=O, NHBoc), 174.1 (C=O). MS HR-ESI [found 503.2365, $C_{24}H_{36}N_2O_8$ $(M\text{-}Na)^+$ requires 503.2364].

***N*-(*tert*-Butoxycarbonyl)-L-valine-(5-amido-1-*O*-benzyl-5-deoxy-2,3-*O*-isopropylidene-α-D-mannofuranose) (L69a)**. Yield: 580 mg (57%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.91 (d, 3H, CH_3 ^{i}Pr, $^3J_{H-H}$ =6.4 Hz), 0.97 (d, 3H, CH_3 ^{i}Pr, $^3J_{H-H}$ =7.2 Hz), 1.29 (s, 3H, CH_3), 1.43 (s, 9H, CH_3, ^{t}Bu), 1.50 (s, 3H, CH_3), 2.14-2.19 (m, 1H, CH, ^{i}Pr), 3.76-3.79 (m, 1H, H-6), 3.84-3.88 (m, 1H, H-6), 3.90 (bs, 1H, CH), 4.23-4.25 (m, 1H, H-4), 4.36 (bs, 1H, H-5), 4.46 (d, 1H, OCH_2, $^2J_{H-H}$ =12.0 Hz), 4.62-4.66 (m, 2H, OCH_2, H-2), 4.79 (dd, 1H, H-3, $^3J_{H-H}$ =6.0 Hz, $^3J_{H-H}$ =3.2 Hz), 5.04 (bs, 1H, NH-Boc), 5.06 (s, 1H, H-1), 7.09 (bs, 1H, NH), 7.27-7.35 (m, 5H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=17.6 (CH_3, ^{i}Pr), 19.3 (CH_3, ^{i}Pr), 24.3 (CH_3), 26.0 (CH_3), 28.3 (CH_3, ^{t}Bu), 30.7 (CH, ^{i}Pr), 51.6 (C-5), 60.4 (CH), 62.7 (C-6), 69.1 (OCH_2), 77.4 (C-4), 80.1 (C, ^{t}Bu), 80.4 (C-3), 85.1 (C-2), 105.0 (C-1), 112.5 ($\underline{C}Me_2$), 127.9 (CH=), 128.1 (CH=), 128.5 (CH=), 137.2 (C), 156.0 (C=O, NHBoc), 171.8 (C=O). MS HR-ESI [found 531.2680, $C_{26}H_{40}N_2O_8$ $(M\text{-}Na)^+$ requires 531.2677].

***N*-(*tert*-Butoxycarbonyl)-L-alanine-(5-amido-1-*O*-benzyl-5-deoxy-2,3-*O*-isopropylidene-α-D-mannofuranose) (L69f)**. Yield: 560 mg (59%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.29 (s, 3H, CH_3), 1.36 (d, 3H, CH_3, $^3J_{H-H}$ =7.6 Hz), 1.43 (s, 9H, CH_3, ^{t}Bu), 1.50 (s, 3H, CH_3), 3.27 (bs, 1H, OH), 3.82 (bs, 2H, H-6), 4.08-4.11 (m, 1H, CH), 4.23 (bs, 1H, H-4), 4.32 (bs, 1H, H-5), 4.47 (d, 1H, OCH_2, $^2J_{H-H}$ =12.0 Hz), 4.62-4.66 (m, 2H, OCH_2, H-2), 4.81 (dd, 1H, H-3, $^3J_{H-H}$ =5.6 Hz, $^3J_{H-H}$ =2.8 Hz), 5.07 (s, 2H, H-1, NH-Boc), 7.23 (bs, 1H, NH), 7.28-7.35 (m, 5H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=18.6 (CH_3), 24.4 (CH_3), 26.0 (CH_3), 28.3 (CH_3, ^{t}Bu), 50.9 (CH), 51.7 (C-5), 62.6 (C-6), 69.1 (OCH_2), 77.4 (C-4), 80.3 (C-3), 80.5 (C, ^{t}Bu), 85.1 (C-2), 105.0 (C-1), 112.5 ($\underline{C}Me_2$), 127.9 (CH=), 128.0 (CH=), 128.5 (CH=), 137.2 (C), 155.6 (C=O, NHBoc), 173.1 (C=O). MS HR-ESI [found 503.2359, $C_{24}H_{36}N_2O_8$ $(M\text{-}Na)^+$ requires 503.2364].

***N*-(*tert*-Butoxycarbonyl)-L-valine-(5-amido-1-*O*-benzyl-5-deoxy-2,3-*O*-isopropylidene-β-L-gulofuranose) (L70a)**. Yield: 712 mg (59%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.92 (d, 3H, CH_3 ^{i}Pr, $^3J_{H-H}$ =6.8 Hz), 0.99 (d, 3H, CH_3 ^{i}Pr, $^3J_{H-H}$ =7.2 Hz), 1.28 (s, 3H, CH_3), 1.42 (s, 9H, CH_3, ^{t}Bu), 1.44 (s, 3H, CH_3), 2.06-2.15 (m, 1H, CH, ^{i}Pr), 3.10 (bs, 1H, OH), 3.74-3.86 (m, 2H, H-6), 3.90-3.94 (dd, 1H, $^3J_{H-H}$ =8.4 Hz, $^3J_{H-H}$ =6.0 Hz), 4.24 (bs, 2H, H-5, H-4), 4.46 (d, 1H, OCH_2, $^2J_{H-H}$ =11.6 Hz), 4.60 (d, 1H, OCH_2, $^2J_{H-H}$ =12.0 Hz), 4.65 (1H, H-2, $^3J_{H-H}$ =5.6 Hz), 4.75 (dd, 1H, H-3, $^3J_{H-H}$ =6.0 Hz, $^3J_{H-H}$ =2.4 Hz), 5.06 (s, 1H, H-1), 5.19 (bs, 1H, NH-Boc), 6.63 (bs, 1H, NH), 7.27-7.36 (m, 5H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=18.1 (CH_3, ^{i}Pr), 19.4 (CH_3, ^{i}Pr), 24.7 (CH_3), 26.0 (CH_3), 28.3 (CH_3, ^{t}Bu), 31.0 (CH, ^{i}Pr), 51.8 (C-5), 60.4 (CH), 62.0 (C-6), 69.0 (OCH_2), 78.4 (C-4), 79.3 (C-3), 80.1 (^{t}Bu), 85.4 (C-2), 106.0 (C-1), 112.7 ($\underline{C}Me_2$), 127.9 (CH=), 128.0 (CH=),

128.5 (CH=), 137.4 (C), 156.2 (C=O, NHBoc), 172.3 (C=O). MS HR-ESI [found 531.2670, $C_{26}H_{40}N_2O_8$ $(M\text{-}Na)^+$ requires 531.2677].

***N*-(*tert*-Butoxycarbonyl)-L-alanine-(5-amido-1-*O*-benzyl-5-deoxy-2,3-*O*-isopropylidene-β-L-gulofuranose) (L70f)**. Yield: 452 mg (47%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.28 (s, 3H, CH_3), 1.36 (d, 3H, CH_3, $^3J_{H\text{-}H}$ =7.2 Hz), 1.43 (s, 9H, CH_3, ^{t}Bu), 1.44 (s, 3H, CH_3), 2.63 (bs, 1H, OH), 3.77 (dd, 1H, H-6, $^2J_{H\text{-}H}$ =11.6 Hz, $^3J_{H\text{-}H}$ =3.6 Hz), 3.83 (dd, 1H, H-6, $^2J_{H\text{-}H}$ =12.0 Hz, $^3J_{H\text{-}H}$ =4.0 Hz), 4.14 (bs, 2H, CH, H-5), 4.24 (dd, 1H, H-4, $^3J_{H\text{-}H}$ =8.0 Hz, $^3J_{H\text{-}H}$ =3.6 Hz), 4.48 (d, 1H, OCH_2, $^2J_{H\text{-}H}$ =12.4 Hz), 4.61 (d, 1H, OCH_2, $^2J_{H\text{-}H}$ =12.0 Hz), 4.65 (d, 1H, H-2, $^3J_{H\text{-}H}$ =6.0 Hz), 4.75 (dd, 1H, H-3, $^3J_{H\text{-}H}$ =6.0 Hz, $^3J_{H\text{-}H}$ =3.6 Hz), 5.05 (bs, 1H, NH-Boc), 5.08 (s, 1H, H-1), 6.61 (bs, 1H, NH), 7.28-7.37 (m, 5H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=18.1 (CH_3), 24.6 (CH_3), 26.0 (CH_3), 28.3 (CH_3, ^{t}Bu), 50.5 (CH), 52.0 (C-5), 61.9 (C-6), 69.2 (OCH_2), 77.8 (C-4), 79.3 (C-3), 80.3 (C, ^{t}Bu), 85.4 (C-2), 105.3 (C-1), 112.7 ($\underline{C}Me_2$), 127.8 (CH=), 128.0 (CH=), 128.4 (CH=), 137.3 (C), 155.7 (C=O, NHBoc), 173.4 (C=O). MS HR-ESI [found 503.2364, $C_{24}H_{36}N_2O_8$ $(M\text{-}Na)^+$ requires 503.2364].

***N*-(*tert*-Butoxycarbonyl)-D-valine-(5-amido-1-*O*-benzyl-5-deoxy-2,3-*O*-isopropylidene-β-L-gulofuranose) (L70h)**. Yield: 701 mg (69%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.94 (d, 3H, CH_3 ^{i}Pr, $^3J_{H\text{-}H}$ =10.8 Hz), 0.99 (d, 3H, CH_3 ^{i}Pr, $^3J_{H\text{-}H}$ =6.8 Hz), 1.29 (s, 3H, CH_3), 1.44 (s, 9H, CH_3, ^{t}Bu), 1.45 (s, 3H, CH_3), 1.92 (bs, 1H, OH), 2.12 (bs, 1H, CH, ^{i}Pr), 3.76 (dd, 1H, H-6, $^2J_{H\text{-}H}$ =11.6 Hz, $^3J_{H\text{-}H}$ =3.2 Hz), 3.89 (dd, 1H, H-6, $^2J_{H\text{-}H}$ =12.0 Hz, $^3J_{H\text{-}H}$ =4.4 Hz), 3.93 (bs, 1H, CH), 4.12 (bs, 1H, H-5), 4.27-4.29 (m, 1H, H-4), 4.47 (d, 1H, OCH_2, $^2J_{H\text{-}H}$ =12.0 Hz), 4.61-4.67 (m, 2H, OCH_2, H-2), 4.77 (dd, 1H, H-3, $^3J_{H\text{-}H}$ =6.0 Hz, $^3J_{H\text{-}H}$ =3.2 Hz), 5.08 (bs, 2H, H-1, NH-Boc), 6.40 (bs, 1H, NH), 7.28-7.38 (m, 5H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=18.0 (CH_3, ^{i}Pr), 19.5 (CH_3, ^{i}Pr), 24.7 (CH_3), 26.1 (CH_3), 28.5 (CH_3, ^{t}Bu), 31.4 (CH, ^{i}Pr), 52.7 (C-5), 60.3 (CH), 62.4 (C-6), 69.4 (OCH_2), 77.9 (C-4), 79.5 (C-3), 80.2 (C, ^{t}Bu), 85.5 (C-2), 105.4 (C-1), 112.9 ($\underline{C}Me_2$), 128.1 (CH=), 128.2 (CH=), 128.7 (CH=), 137.4 (C), 156.0 (C=O, NHBoc), 172.5 (C=O). MS HR-ESI [found 531.2683, $C_{26}H_{40}N_2O_8$ $(M\text{-}Na)^+$ requires 531.2677].

***N*-(*tert*-Butoxycarbonyl)-D-alanine-(5-amido-1-*O*-benzyl-5-deoxy-2,3-*O*-isopropylidene-β-L-gulofuranose) (L70j)**. Yield: 702 mg (73%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.29 (s, 3H, CH_3), 1.38 (d, 3H, CH_3, $^3J_{H\text{-}H}$ =6.8 Hz), 1.44 (s, 9H, CH_3, ^{t}Bu), 1.45 (s, 3H, CH_3), 3.78 (dd, 1H, H-6, $^2J_{H\text{-}H}$ =11.6 Hz, $^3J_{H\text{-}H}$ =2.8 Hz), 3.86 (dd, 1H, H-6, $^2J_{H\text{-}H}$ =12.0 Hz, $^3J_{H\text{-}H}$ =4.4 Hz), 4.12 (bs, 2H, CH, H-5), 4.26 (dd, 1H, H-4, $^3J_{H\text{-}H}$ =2.4 Hz, $^3J_{H\text{-}H}$ =7.2 Hz), 4.48 (d, 1H, OCH_2, $^2J_{H\text{-}H}$ =11.6 Hz), 4.63 (d, 1H, OCH_2, $^2J_{H\text{-}H}$ =12.0 Hz), 4.65 (d, 1H, H-2, $^3J_{H\text{-}H}$ =6.0 Hz), 4.76 (dd, 1H, H-3, $^3J_{H\text{-}H}$ =6.0 Hz, $^3J_{H\text{-}H}$ =3.2 Hz), 5.03 (bs, 1H, NH-Boc), 5.08 (s, 1H, H-1), 6.53 (bs, 1H, NH), 7.30-7.36 (m, 5H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=18.8 (CH_3), 24.5 (CH_3), 26.0 (CH_3), 28.3 (CH_3, ^{t}Bu), 50.5 (CH), 52.3 (C-5), 62.1 (C-6), 69.2 (OCH_2), 77.6 (C-4), 79.3 (C-3), 80.2 (C, ^{t}Bu), 85.3 (C-2), 105.2 (C-1), 112.7 ($\underline{C}Me_2$), 127.9 (CH=), 128.0 (CH=), 128.5 (CH=), 137.3 (C),155.4 (C=O, NHBoc), 173.4 (C=O). MS HR-ESI [found 503.2378, $C_{24}H_{36}N_2O_8$ $(M\text{-}Na)^+$ requires 503.2364].

4.2.4.3. Typical procedure for the benzoylation of L68-L70a-j

Benzoyl chloride (1.1 mmol, 128 μL) was slowly added to a cooled solution (0 °C) in dichloromethane (2 mL) of the desired hydroxyamide (1 mmol) in triethylamine (7.2 mmol, 1 mL) and DMAP (0.11 mmol, 13.4 mg). The reaction mixture was stirred overnight. Then water was added and the mixture was extracted with dichloromethane (3x20 mL), the

extract was dried over MgSO4, evaporated to dryness and the residue was purified by SiO_2-flash chromatography (petroleum ether/ethyl acetate: 3/1 for compounds **9a**-**e** and **9h**-**i** or petroleum ether/ethyl acetate: 1/1 for ligands **9f**-**g**,**j**, **10a**-**h** and **11a**-**j**) to produce the corresponding benzoylated product as white solids.

***N*-(*tert*-Butoxycarbonyl)-L-valine-(6-amido-5-*O*-benzoyl-1-*O*-benzyl-6-deoxy-2,3-*O*-isopropylidene-α-D-mannofuranose) (9a)**. Yield: 423 mg (69%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.81 (d, 3H, CH_3 ^{i}Pr, $^3J_{H-H}$ =7.2 Hz), 0.86 (d, 3H, CH_3 ^{i}Pr, $^3J_{H-H}$ =8.0 Hz), 1.23 (s, 3H, CH_3), 1.41 (s, 9H, CH_3, ^{t}Bu), 1.43 (s, 3H, CH_3), 2.05-2.09 (m, CH, ^{i}Pr), 3.77-3.80 (m, 2H, H-6), 3.86-3.90 (m, 1H, CH), 4.21 (dd, 1H, H-4, $^3J_{H-H}$ =7.6 Hz, $^3J_{H-H}$ =3.6 Hz), 4.52 (d, 1H, OCH_2, $^2J_{H-H}$ =11.6 Hz), 4.65-4.70 (m, 2H, OCH_2, H-2), 4.78 (dd, 1H, H-3, $^3J_{H-H}$ =6.0 Hz, $^3J_{H-H}$ =3.6 Hz), 5.03 (bs, 1H, NHBoc), 5.13 (s, 1H, H-1), 5.42-5.46 (m, 1H, H-5), 6.41 (bs, 1H, NH), 7.27-7.32 (m, 1H, CH=), 7.33 (d, 4H, CH=, $^4J_{H-H}$ =4.0 Hz), 7.44 (pt, 2H, CH=, $^3J_{H-H}$ =8.0 Hz), 7.55-7.59 (m, 1H, CH=), 8.00 (d, 2H, CH=, $^3J_{H-H}$ =7.6 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=17.6 (CH_3, ^{i}Pr), 19.2 (CH_3, ^{i}Pr), 24.7 (CH_3), 25.9 (CH_3), 28.3 (CH_3, ^{t}Bu), 30.7 (CH, ^{i}Pr), 41.2 (C-6), 60.1 (CH), 69.3 (OCH_2), 70.6 (C-5), 79.3 (C-4), 79.5 (C-3), 79.9 (C, ^{t}Bu), 84.7 (C-2), 105.5 (C-1), 112.9 ($\underline{C}Me_2$), 127.9 (CH=), 128.1 (CH=), 128.4 (CH=), 128.5 (CH=), 129.8 (CH=), 133.2 (C), 137.2 (C), 155.8 (C=O, NHBoc), 166.0 (C=O, OBz), 171.6 (C=O).

***N*-(*tert*-Butoxycarbonyl)-L-leucine-(6-amido-5-*O*-benzoyl-1-O-benzyl-6-deoxy-2,3-*O*-isopropylidene-α-D-mannofuranose) (9c)**. Yield: 395 mg (63%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.82 (d, 6H, CH_3 ^{i}Bu, $^3J_{H-H}$ =5.8 Hz), 1.22 (s, 3H, CH_3), 1.32-1.38 (m, 1H, CH_2, ^{i}Bu), 1.38 (s, 9H, CH_3, ^{t}Bu), 1.43 (s, 3H, CH_3), 1.52-1.59 (m, 2H, CH, CH_2, ^{i}Bu), 3.77-3.81 (m, 2H, H-6), 4.06 (bs, 1H, CH), 4.22 (dd, 1H, H-4, $^3J_{H-H}$ =7.6 Hz, $^3J_{H-H}$ =3.2 Hz), 4.51 (d, 1H, OCH_2, $^2J_{H-H}$ =11.6 Hz), 4.64 (d, 1H, H-2, $^2J_{H-H}$ =6.0 Hz), 4.69 (d, 1H, OCH_2, $^2J_{H-H}$ =12.0 Hz), 4.77 (dd, 1H, H-3, $^3J_{H-H}$ =6.0 Hz, $^3J_{H-H}$ =4.0 Hz), 4.92 (bs, 1H, NH-Boc), 5.13 (s, 1H, H-1), 5.43-5.48 (m, 1H, H-5), 6.58 (bs, 1H, NH), 7.27-7.30 (m, 1H, CH=), 7.32 (d, 2H, CH=, $^4J_{H-H}$ =2.8 Hz), 7.34 (s, 2H, CH=), 7.43 (pt, 2H, CH=, $^3J_{H-H}$ =8.0 Hz), 7.56 (pt, 1H, CH=, $^3J_{H-H}$ =7.2 Hz), 8.01 (d, 2H, CH=, $^3J_{H-H}$ =7.2 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=21.9 (CH_3, ^{i}Bu), 22.8 (CH_3, ^{i}Bu), 24.6 (CH_3, CH ^{i}Bu), 26.0 (CH_3), 28.3 (CH_3, ^{t}Bu), 41.0 (C-6), 41.3 (CH_2, ^{i}Bu), 53.1 (CH), 69.2 (OCH_2), 70.5 (C-5), 79.1 (C-4), 79.5 (C-3), 79.8 (C, ^{t}Bu), 84.7 (C-2), 105.4 (C-1), 112.8 ($\underline{C}Me_2$), 127.9 (CH=), 128.2 (CH=), 128.4 (CH=), 129.7 (CH=), 129.8 (CH=), 133.3 (C), 137.2 (C), 155.6 (C=O, NHBoc), 165.9 (C=O, OBz), 172.7 (C=O).

***N*-(*tert*-Butoxycarbonyl)-L-phenylalanine-(6-amido-5-O-benzoyl-1-O-benzyl-6-deoxy-2,3-O-isopropylidene-α-D-mannofuranose) (9d)**. Yield: 284 mg (43%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.22 (s, 3H, CH_3), 1.36 (s, 9H, CH_3, ^{t}Bu), 1.42 (s, 3H, CH_3), 3.00 (bs, 2H, CH_2), 3.62-3.68 (m, 1H, H-6), 3.78-3.84 (m, 1H, H-6), 4.09-4.14 (m, 1H, H-4), 4.30 (bs, 1H, CH), 4.51 (d, 1H, OCH_2, $^2J_{H-H}$ =12.0 Hz), 4.63-4.69 (m, 2H, OCH_2, H-2), 4.71-4.74 (m, 1H, H-3), 5.06 (bs, 1H, NH-Boc), 5.09 (s, 1H, H-1), 5.32-5.36 (m, 1H, H-5), 6.33 (bs, 1H, NH), 7.11-7.32 (m, 6H, CH=), 7.33 (d, 2H, CH=, $^4J_{H-H}$ =2.0 Hz), 7.34 (s, 2H, CH=), 7.44 (pt, 2H, CH=, $^3J_{H-H}$ =8.0 Hz), 7.57 (pt, 1H, CH=, $^3J_{H-H}$ =11.6 Hz), 7.97 (d, 2H, CH=, $^3J_{H-H}$ =11.6 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=24.7 (CH_3), 26.0 (CH_3), 28.3 (CH_3, ^{t}Bu), 38.6 (CH_2), 40.9 (C-6), 56.0 (CH), 69.2 (OCH_2), 70.7 (C-5), 78.9 (C-4), 79.5 (C-3), 80.0 (C, ^{t}Bu), 84.7 (C-2), 105.4 (C-1), 112.8 ($\underline{C}Me_2$), 126.8 (CH=), 127.9 (CH=), 128.1 (CH=), 128.4 (CH=), 128.5 (CH=), 128.6 (CH=), 129.2 (CH=), 129.8 (CH=), 133.3 (C), 136.8 (C), 137.2 (C), 155.3 (C=O, NHBoc), 165.8 (C=O, OBz), 171.3 (C=O).

***N*-(*tert*-Butoxycarbonyl)-L-phenylglycine-(6-amido-5-O-benzoyl-1-O-benzyl-6-deoxy-2,3-O-isopropylidene-α-D-mannofuranose) (9e)**. Yield: 291 mg (45%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.22 (s, 3H, CH_3), 1.40 (s, 9H, CH_3, ^{t}Bu), 1.41 (s, 3H, CH_3), 3.75-3.81 (m, 2H, H-6), 4.08 (dd, 1H, H-4, $^{3}J_{H-H}$=8.0 Hz, $^{3}J_{H-H}$=3.6 Hz), 4.51 (d, 1H, OCH_2, $^{2}J_{H-H}$=12.0 Hz), 4.62-4.71 (m, 3H, OCH_2, H-2, H-3), 5.09 (s, 1H, H-1), 5.12 (bs, 1H, CH), 5.37-5.40 (m, 1H, H-5), 5.90 (bs, 1H, NH-Boc), 6.31 (bs, 1H, NH), 7.20-7.22 (m, 3H, CH=), 7.27-7.32 (m, 3H, CH=), 7.36 (d, 4H, CH=, $^{4}J_{H-H}$=4.8 Hz), 7.44 (pt, 2H, CH=, $^{3}J_{H-H}$=7.6 Hz), 7.57 (pt, 1H, CH=, $^{3}J_{H-H}$=7.2 Hz), 7.90 (d, 2H, CH=, $^{3}J_{H-H}$=8.0 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=24.7 (CH_3), 25.9 (CH_3), 28.3 (CH_3, ^{t}Bu), 41.3 (C-6), 58.7 (CH), 69.2 (OCH_2), 70.4 (C-5), 79.1 (C-4), 79.5 (C-3), 79.9 (C, ^{t}Bu), 84.7 (C-2), 105.4 (C-1), 112.8 ($\underline{C}Me_2$), 127.1 (CH=), 127.9 (CH=), 128.0 (CH=), 128.1 (CH=), 128.4 (CH=), 128.5 (CH=), 128.9 (CH=), 129.6 (CH=), 129.8 (CH=), 133.3 (C), 137.2 (C), 138.6 (C), 155.1 (C=O, NHBoc), 165.7 (C=O, OBz), 170.2 (C=O).

***N*-(*tert*-Butoxycarbonyl)-L-alanine-(6-amido-5-*O*-benzoyl-1-*O*-benzyl-6-deoxy-2,3-*O*-isopropylidene-α-D-mannofuranose) (9f)**. Yield: 257 mg (44%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.23 (s, 3H, CH_3), 1.26 (d, 3H, CH_3, $^{3}J_{H-H}$=7.2 Hz), 1.38 (s, 9H, CH_3, ^{t}Bu), 1.44 (s, 3H, CH_3), 3.77-3.81 (m, 2H, H-6), 4.10 (bs, 1H, CH), 4.22 (dd, 1H, H-4, $^{3}J_{H-H}$=8.0 Hz, $^{3}J_{H-H}$=3.6 Hz), 4.51 (d, 1H, OCH_2, $^{2}J_{H-H}$=12.0 Hz), 4.64 (d, 1H, H-2, $^{3}J_{H-H}$=6.0 Hz), 4.68 (d, 1H, OCH_2, $^{2}J_{H-H}$=11.6 Hz), 4.78 (dd, 1H, H-3, $^{3}J_{H-H}$=6.0 Hz, $^{3}J_{H-H}$=3.6 Hz), 5.02 (bs, 1H, NHBoc), 5.13 (s, 1H, H-1), 5.42-5.47 (m, 1H, H-5), 6.57 (bs, 1H, NH), 7.27-7.31 (m, 1H, CH=), 7.33 (d, 2H, CH=, $^{4}J_{H-H}$=1.6 Hz), 7.34 (s, 1H, CH=), 7.44 (pt, 2H, CH=, $^{3}J_{H-H}$=8.0 Hz), 7.57 (pt, 1H, CH=, $^{3}J_{H-H}$=7.2 Hz), 8.01 (d, 2H, CH=, $^{3}J_{H-H}$=7.2 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=18.5 (CH_3), 23.9 (CH_3), 24.7 (CH_3), 28.3 (CH_3, ^{t}Bu), 41.0 (C-6), 50.2 (CH), 69.3 (OCH_2), 70.7 (C-5), 79.0 (C-4), 79.6 (C-3), 79.9 (C, ^{t}Bu), 84.7 (C-2), 105.5 (C-1), 112.9 ($\underline{C}Me_2$), 127.9 (CH=), 128.1 (CH=), 128.4 (CH=), 128.5 (CH=), 129.8 (CH=), 133.3 (C), 137.2 (C), 155.4 (C=O, NHBoc), 165.9 (C=O, OBz), 172.7 (C=O).

***N*-(*tert*-Butoxycarbonyl)-glycine-(6-amido-5-*O*-benzoyl-1-*O*-benzyl-6-deoxy-2,3-*O*-isopropylidene-α-D-mannofuranose) (9g)**. Yield: 183 mg (32%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.23 (s, 3H, CH_3), 1.41 (s, 9H, CH_3, ^{t}Bu), 1.43 (s, 3H, CH_3), 3.74-3.85 (m, 4H, H-6, CH_2), 4.20 (dd, 1H, H-4, $^{3}J_{H-H}$=8.0 Hz, $^{3}J_{H-H}$=3.6 Hz), 4.52 (d, 1H, OCH_2, $^{2}J_{H-H}$=12.0 Hz), 4.64 (d, 1H, H-2, $^{3}J_{H-H}$=6.0 Hz), 4.67 (d, 1H, OCH_2, $^{2}J_{H-H}$=12.0 Hz), 4.78 (dd, 1H, H-3, $^{3}J_{H-H}$=7.6 Hz, $^{3}J_{H-H}$=3.6 Hz), 5.09 (bs, 1H, NH-Boc), 5.13 (s, 1H, H-1), 5.43-5.48 (m, 1H, H-5), 6.59 (bs, 1H, NH), 7.27-7.31 (m, 1H, CH=), 7.33 (s, 3H, CH=), 7.34 (s, 1H, CH=), 7.45 (pt, 2H, CH=, $^{3}J_{H-H}$=8.4 Hz), 7.58 (pt, 1H, CH=, $^{3}J_{H-H}$=7.2 Hz), 8.02 (d, 2H, CH=, $^{3}J_{H-H}$=7.2 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=24.7 (CH_3), 26.0 (CH_3), 28.3 (CH_3, ^{t}Bu), 41.1 (C-6), 44.4 (CH_2), 69.3 (OCH_2), 70.8 (C-5), 79.0 (C-4), 79.5 (C-3), 80.1 (C, ^{t}Bu), 84.7 (C-2), 105.5 (C-1), 112.9 ($\underline{C}Me_2$), 127.9 (CH=), 128.1 (CH=), 128.4 (CH=), 128.5 (CH=), 129.7 (CH=), 129.8 (CH=), 133.3 (C), 137.2 (C), 156.0 (C=O, NHBoc), 166.0 (C=O, OBz), 169.5 (C=O).

***N*-(*tert*-Butoxycarbonyl)-D-valine-(6-amido-5-*O*-benzoyl-1-*O*-benzyl-6-deoxy-2,3-*O*-isopropylidene-α-D-mannofuranose) (9h)**. Yield: 515 mg (84%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.81 (d, 3H, CH_3 ^{i}Pr, $^{3}J_{H-H}$=6.4 Hz), 0.90 (d, 3H, CH_3 ^{i}Pr, $^{3}J_{H-H}$=6.8 Hz), 1.23 (s, 3H, CH_3), 1.40 (s, 9H, CH_3, ^{t}Bu), 1.43 (s, 3H, CH_3), 2.05-2.12 (m, 1H, CH, ^{i}Pr), 3.68-3.74 (m, 1H, H-6), 3.86-3.92 (m, 2H, CH, H-6), 4.19 (dd, 1H, H-4, $^{3}J_{H-H}$=7.6 Hz, $^{3}J_{H-H}$=3.6 Hz), 4.52 (d, 1H, OCH_2, $^{2}J_{H-H}$=12.0 Hz), 4.64-4.68 (m, 2H, OCH_2, H-2), 4.78 (dd, 1H, H-3, $^{3}J_{H-H}$=5.6 Hz, $^{3}J_{H-H}$=3.6 Hz), 5.01 (bs, 1H, NH-Boc), 5.13 (s, 1H, H-1), 5.41-5.45 (m, 1H, H-5), 6.40 (bs, 1H, NH), 7.27-7.34 (m,

5H, CH=), 7.44 (pt, 2H, CH=, $^{3}J_{H-H}$=7.6 Hz), 7.55-7.58 (m, 1H, CH=), 8.02 (d, 2H, CH=, $^{3}J_{H-H}$=7.2 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=17.7 (CH_3, ^{i}Pr), 19.2 (CH_3, ^{i}Pr), 24.7 (CH_3), 26.0 (CH_3), 28.3 (CH_3, ^{t}Bu), 30.8 (CH, ^{i}Pr), 40.8 (C-6), 60.0 (CH), 69.3 (OCH_2), 70.8 (C-5), 79.2 (C-4), 79.6 (C-3), 79.7 (C, ^{t}Bu), 84.7 (C-2), 105.6 (C-1), 112.9 ($\underline{C}Me_2$), 127.9 (CH=), 128.0 (CH=), 128.4 (CH=), 128.5 (CH=), 129.8 (CH=), 133.2 (C), 137.2 (C), 155.8 (C=O, NHBoc), 165.9 (C=O, OBz), 171.5 (C=O).

***N*-(*tert*-Butoxycarbonyl)-D-phenylglycine-(6-amido-5-*O*-benzoyl-1-*O*-benzyl-6-deoxy-2,3-*O*-isopropylidene-α-D-mannofuranose) (9i)**. Yield: 498 mg (77%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.25 (s, 3H, CH_3), 1.41 (s, 9H, CH_3, ^{t}Bu), 1.44 (s, 3H, CH_3), 3.68-3.75 (m, 1H, H-6), 3.85-3.89 (m, 1H, H-6), 4.10 (dd, 1H, H-4, $^{3}J_{H-H}$=7.2 Hz, $^{3}J_{H-H}$=3.6 Hz), 4.47 (d, 1H, OCH_2, $^{2}J_{H-H}$=11.6 Hz), 4.59 (d, 1H, OCH_2, $^{2}J_{H-H}$=11.6 Hz), 4.63 (d, 1H, H-2, $^{3}J_{H-H}$=6.0 Hz), 4.76 (dd, 1H, H-3, $^{3}J_{H-H}$=6.0 Hz, $^{3}J_{H-H}$=3.6 Hz), 5.09 (s, 2H, H-1, CH), 5.37-5.41 (m, 1H, H-5), 5.89 (bs, 1H, NH-Boc), 6.29 (bs, 1H, NH), 7.24-7.37 (m, 10H, CH=), 7.45 (pt, 2H, CH=, $^{3}J_{H-H}$=7.6 Hz), 7.60 (pt, 1H, CH=, $^{3}J_{H-H}$=7.6 Hz), 7.93 (d, 2H, CH=, $^{3}J_{H-H}$=8.0 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=24.6 (CH_3), 25.9 (CH_3), 28.3 (CH_3, ^{t}Bu), 41.2 (C-6), 58.7 (CH), 69.4 (OCH_2), 70.2 (C-5), 79.4 (C-4, C-3), 79.9 (C, ^{t}Bu), 84.6 (C-2), 105.4 (C-1), 112.8 ($\underline{C}Me_2$), 127.1 (CH=), 128.0 (CH=), 128.1 (CH=), 128.2 (CH=), 128.4 (CH=), 128.5 (CH=), 128.9 (CH=), 129.6 (CH=), 129.8 (CH=), 133.2 (C), 137.1 (C), 138.7 (C), 155.1 (C=O, NHBoc), 165.8 (C=O, OBz), 170.1 (C=O).

***N*-(*tert*-Butoxycarbonyl)-D-alanine-(6-amido-5-*O*-benzoyl-1-*O*-benzyl-6-deoxy-2,3-*O*-isopropylidene-α-D-mannofuranose) (9j)**. Yield: 409 mg (70%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.23 (s, 3H, CH_3), 1.25 (d, 3H, CH_3, $^{3}J_{H-H}$=7.2 Hz), 1.41 (s, 9H, CH_3, ^{t}Bu), 1.44 (s, 3H, CH_3), 3.77-3.81 (m, 2H, H-6), 4.10 (bs, 1H, CH), 4.18 (dd, 1H, H-4, $^{3}J_{H-H}$=8.0 Hz, $^{3}J_{H-H}$=3.6 Hz), 4.51 (d, 1H, OCH_2, $^{2}J_{H-H}$=12.0 Hz), 4.64 (d, 1H, H-2, $^{3}J_{H-H}$=6.0 Hz), 4.67 (d, 1H, OCH_2, $^{2}J_{H-H}$=11.6 Hz), 4.76 (dd, 1H, H-3, $^{3}J_{H-H}$=6.0 Hz, $^{3}J_{H-H}$=4.0 Hz), 4.90 (bs, 1H, NHBoc), 5.13 (s, 1H, H-1), 5.42-5.47 (m, 1H, H-5), 6.59 (bs, 1H, NH), 7.27-7.34 (m, 5H, CH=), 7.44 (pt, 2H, CH=, $^{3}J_{H-H}$=8.0 Hz), 7.56 (pt, 1H, CH=, $^{3}J_{H-H}$=7.6 Hz), 8.03 (d, 2H, CH=, $^{3}J_{H-H}$=7.2 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=18.3 (CH_3), 24.7 (CH_3), 26.0 (CH_3), 28.3 (CH_3, ^{t}Bu), 40.8 (C-6), 50.1 (CH), 69.1 (OCH_2), 70.7 (C-5), 78.9 (C-4), 79.5 (C-3), 79.9 (C, ^{t}Bu), 84.8 (C-2), 105.5 (C-1), 112.9 ($\underline{C}Me_2$), 127.9 (CH=), 128.0 (CH=), 128.4 (CH=), 128.5 (CH=), 129.8 (CH=), 133.2 (C), 137.3 (C), 155.4 (C=O, NHBoc), 165.9 (C=O, OBz), 172.6 (C=O).

***N*-(*tert*-Butoxycarbonyl)-L-valine-(5-amido-6-*O*-benzoyl-1-*O*-benzyl-5-deoxy-2,3-*O*-isopropylidene-α-D-mannofuranose) (10a)**. Yield: 404 mg (66%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.86 (d, 3H, CH_3 ^{i}Pr, $^{3}J_{H-H}$=6.8 Hz), 0.91 (d, 3H, CH_3 ^{i}Pr, $^{3}J_{H-H}$=6.4 Hz), 1.29 (s, 3H, CH_3), 1.40 (s, 9H, CH_3, ^{t}Bu), 1.55 (s, 3H, CH_3), 2.13 (bs, 1H, CH, ^{i}Pr), 3.94 (m, 1H, CH), 4.17-4.19 (m, 1H, H-4), 4.45 (d, 1H, OCH_2, $^{2}J_{H-H}$=12.0 Hz), 4.47-4.56 (m, 2H, H-6), 4.61-4.64 (m, 2H, OCH_2, H-2), 4.83 (dd, 1H, H-3, $^{3}J_{H-H}$=5.6 Hz, $^{3}J_{H-H}$=3.2 Hz), 4.85-4.89 (m, 1H, H-5), 5.09 (s, 1H, H-1), 5.14 (bs, 1H, NHBoc), 7.08 (bs, 1H, NH), 7.25-7.32 (m, 5H, CH=), 7.39 (pt, 2H, CH=, $^{3}J_{H-H}$=6.0 Hz), 7.53-7.58 (m, 1H, CH=), 8.04 (d, 2H, CH=, $^{3}J_{H-H}$=6.8 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=17.6 (CH_3, ^{i}Pr), 19.0 (CH_3, ^{i}Pr), 24.2 (CH_3), 26.1 (CH_3), 28.3 (CH_3, ^{t}Bu), 31.2 (CH, ^{i}Pr), 48.2 (C-5), 60.0 (CH), 64.2 (C-6), 69.1 (OCH_2), 76.9 (C-4), 79.7 (C, ^{t}Bu), 80.6 (C-3), 85.3 (C-2), 105.0 (C-1), 112.8 ($\underline{C}Me_2$), 127.9 (CH=), 128.0 (CH=), 128.4 (CH=), 128.5 (CH=), 129.6 (CH=), 129.7 (CH=), 133.2 (C), 137.1 (C),155.6 (C=O, NHBoc), 166.2 (C=O, OBz), 171.1 (C=O).

N-(*tert*-Butoxycarbonyl)-L-alanine-(5-amido-6-*O*-benzoyl-1-*O*-benzyl-5-deoxy-2,3-*O*-isopropylidene-α-D-mannofuranose) (10f).Yield: 427 mg (73%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.28 (s, 3H, CH_3), 1.33 (d, 3H, CH_3, $^{3}J_{H-H}$ =6.8 Hz), 1.40 (s, 9H, CH_3, ^{t}Bu), 1.54 (s, 3H, CH_3), 4.15-4.20 (m, 2H, CH, H-4), 4.44 (d, 1H, OCH_2, $^{2}J_{H-H}$ =11.6 Hz), 4.48-4.54 (m, 2H, H-6), 4.61-4.64 (m, 2H, OCH_2, H-2), 4.83 (bs, 2H, H-3, H-5), 5.09 (s, 1H, H-1), 5.15 (bs, 1H, NHBoc), 7.11 (bs, 1H, NH), 7.24-7.32 (m, 5H, CH=), 7.36-7.42 (m, 2H, CH=), 7.55 (pt, 1H, CH=, $^{3}J_{H-H}$ =8.4 Hz), 8.03 (d, 2H, CH=, $^{3}J_{H-H}$ =7.2 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=18.9 (CH_3), 24.3 (CH_3), 26.1 (CH_3), 28.3 (CH_3, ^{t}Bu), 48.2 (C-5), 50.3 (CH), 64.2 (C-6), 69.1 (OCH_2), 77.1 (C-4), 79.8 (C, ^{t}Bu), 80.5 (C-3), 85.2 (C-2), 105.0 (C-1), 112.8 ($\underline{C}Me_2$), 127.9 (CH=), 128.0 (CH=), 128.3 (CH=), 128.4 (CH=), 128.5 (CH=), 129.7 (CH=), 133.2 (C), 137.1 (C), 155.3 (C=O, NHBoc), 166.3 (C=O, OBz), 172.4 (C=O).

***N*-(*tert*-Butoxycarbonyl)-L-valine-(5-amido-6-*O*-benzoyl-1-*O*-benzyl-5-deoxy-2,3-*O*-isopropylidene-β-L-gulofuranose) (11a)**. Yield: 398 mg (65%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.92 (d, 3H, CH_3 ^{i}Pr, $^{3}J_{H-H}$ =6.8 Hz), 1.00 (d, 3H, CH_3 ^{i}Pr, $^{3}J_{H-H}$ =6.8 Hz), 1.30 (s, 3H, CH_3), 1.42 (s, 9H, CH_3, ^{t}Bu), 1.50 (s, 3H, CH_3), 2.17-2.22 (m, 1H, CH, ^{i}Pr), 3.95 (pt, 1H, CH, $^{3}J_{H-H}$ =6.4 Hz), 4.19 (dd, 1H, H-4, $^{3}J_{H-H}$ =8.0 Hz, $^{3}J_{H-H}$ =3.6 Hz), 4.50 (d, 1H, OCH_2, $^{2}J_{H-H}$ =12.0 Hz), 4.48-4.54 (m, 1H, H-6), 4.62 (d, 1H, OCH_2, $^{2}J_{H-H}$ =12.0 Hz), 4.65-4.70 (m, 2H, H-2, H-6), 4.72-4.79 (m, 2H, H-3, H-5), 5.09 (bs, 1H, NHBoc), 5.12 (s, 1H, H-1), 6.31 (bs, 1H, NH), 7.29-7.35 (m, 5H, CH=), 7.46 (pt, 2H, CH=, $^{3}J_{H-H}$ =7.2 Hz), 7.59 (pt, 1H, CH=, $^{3}J_{H-H}$ =6.8 Hz), 8.04 (d, 2H, CH=, $^{3}J_{H-H}$ =7.2 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=17.6 (CH_3, ^{i}Pr), 19.3 (CH_3, ^{i}Pr), 24.6 (CH_3), 26.0 (CH_3), 28.3 (CH_3, ^{t}Bu), 30.8 (CH, ^{i}Pr), 48.6 (C-5), 60.1 (CH), 64.2 (C-6), 69.2 (OCH_2), 78.3 (C-4), 79.7 (C-3), 79.8 (C, ^{t}Bu), 85.3 (C-2), 105.3 (C-1), 112.9 ($\underline{C}Me_2$), 127.9 (CH=), 128.0 (CH=), 128.4 (CH=), 128.5 (CH=), 129.7 (CH=), 129.8 (CH=), 133.2 (C), 137.3 (C), 155.8 (C=O, NHBoc), 166.4 (C=O, OBz), 171.5 (C=O).

***N*-(*tert*-Butoxycarbonyl)-D-valine-(5-amido-6-*O*-benzoyl-1-*O*-benzyl-5-deoxy-2,3-*O*-isopropylidene-β-L-gulofuranose) (11h)**. Yield: 502 mg (82%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.89 (d, 3H, CH_3 ^{i}Pr, $^{3}J_{H-H}$ =6.8 Hz), 0.95 (d, 3H, CH_3 ^{i}Pr, $^{3}J_{H-H}$ =6.8 Hz), 1.29 (s, 3H, CH_3), 1.43 (s, 9H, CH_3, ^{t}Bu), 1.48 (s, 3H, CH_3), 2.07 (bs, 1H, CH, ^{i}Pr), 3.96 (pt, 1H, CH, $^{3}J_{H-H}$ =6.4 Hz), 4.10-4.15 (m, 1H, H-4), 4.46-4.49 (m, 1H, H-6), 4.51 (d, 1H, OCH_2, $^{2}J_{H-H}$ =12.0 Hz), 4.59 (d, 1H, OCH_2, $^{2}J_{H-H}$ =11.6 Hz), 4.61-4.64 (m, 1H, H-6), 4.66 (d, 1H, H-2, $^{2}J_{H-H}$ =5.6 Hz), 4.69-4.75 (m, 1H, H-5), 4.78 (dd, 1H, H-3, $^{3}J_{H-H}$ =6.0 Hz, $^{3}J_{H-H}$ =3.6 Hz), 5.15 (s, 1H, H-1), 5.21 (bs, 1H, NHBoc), 6.03 (bs, 1H, NH), 7.27-7.35 (m, 5H, CH=), 7.47 (pt, 2H, CH=, $^{3}J_{H-H}$ =7.6 Hz), 7.60 (pt, 1H, CH=, $^{3}J_{H-H}$ =7.6 Hz), 8.03 (d, 2H, CH=, $^{3}J_{H-H}$ =5.6 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=17.6 (CH_3, ^{i}Pr), 19.2 (CH_3, ^{i}Pr), 24.4 (CH_3), 25.9 (CH_3), 28.3 (CH_3, ^{t}Bu), 31.7 (CH, ^{i}Pr), 48.3 (C-5), 59.8 (CH), 64.2 (C-6), 69.5 (OCH_2), 78.0 (C-4), 79.6 (C, ^{t}Bu), 79.7 (C-3), 85.1 (C-2), 105.7 (C-1), 112.9 ($\underline{C}Me_2$), 127.8 (CH=), 128.0 (CH=), 128.4 (CH=), 128.5 (CH=), 129.7 (CH=), 133.3 (C), 137.6 (C), 155.6 (C=O, NHBoc), 166.3 (C=O, OBz), 171.2 (C=O).

4.2.4.4. Typical procedure for the preparation of thioamide ligands L71-L73a-j

To a cooled solution of the desired benzoylated product (1 mmol) in THF (4 mL), Lawesson's reagent (0.8 mmol, 317 mg) was added at 0°C. The reaction mixture was stirred for two days at 60 °C. Then, the reaction mixture was evaporated to dryness and the residue was purified by SiO_2-flash chromatography (petroleum ether/ethyl acetate: 1/4 for

ligands **L71a**-**e** and **L71h**-**i** or petroleum ether/ethyl acetate: 1/2 for ligands **L71f**,**g**,**j**, **L72a**,**f** and **L73a**-**j**) to afford the corresponding thioamide ligands as white solids.

***N*-(*tert*-Butoxycarbonyl)-L-valine-(6-thioamido-5-*O*-benzoyl-1-*O*-benzyl-6-deoxy-2,3-*O*-isopropylidene-α-D-mannofuranose) (L71a)**. Yield: 207 mg (33%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.83 (d, 3H, CH_3 ^{i}Pr, $^{3}J_{H-H}$ =5.2 Hz), 0.88 (d, 3H, CH_3 ^{i}Pr, $^{3}J_{H-H}$ =6.4 Hz), 1.23 (s, 3H, CH_3), 1.41 (s, 9H, CH_3, ^{t}Bu), 1.44 (s, 3H, CH_3), 2.22-2.26 (m, 1H, CH, ^{i}Pr), 4.11-4.15 (m, 3H, H-6, CH), 4.26 (dd, 1H, H-4, $^{3}J_{H-H}$ =7.6 Hz, $^{3}J_{H-H}$ =3.6 Hz), 4.55 (d, 1H, OCH_2, $^{2}J_{H-H}$ =11.6 Hz), 4.66 (d, 1H, H-2, $^{3}J_{H-H}$ =6.0 Hz), 4.69 (d, 1H, OCH_2, $^{2}J_{H-H}$ =12.0 Hz), 4.82 (dd, 1H, H-3, $^{3}J_{H-H}$ =6.0 Hz, $^{3}J_{H-H}$ =3.6 Hz), 5.17 (s, 1H, H-1), 5.27 (bs, 1H, NHBoc), 5.56-5.59 (m, 1H, H-5), 7.27-7.33 (m, 1H, CH=), 7.34 (s, 3H, CH=), 7.35 (s, 1H, CH=), 7.44 (pt, 2H, CH=, $^{3}J_{H-H}$ =6.0 Hz), 7.57-7.61 (m, 1H, CH=), 8.01 (d, 2H, CH=, $^{3}J_{H-H}$ =7.2 Hz), 8.55 (bs, 1H, NH). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=17.9 (CH_3, ^{i}Pr), 19.6 (CH_3, ^{i}Pr), 24.6 (CH_3), 26.0 (CH_3), 28.3 (CH_3, ^{t}Bu), 33.2 (CH, ^{i}Pr), 48.2 (C-6), 67.1 (CH), 69.5 (OCH_2), 70.2 (C-5), 79.5 (C-4, C-3), 79.9 (C, ^{t}Bu), 84.7 (C-2), 105.7 (C-1), 113.0 ($\underline{C}Me_2$), 128.0 (CH=), 128.1 (CH=), 128.4 (CH=), 128.5 (CH=), 129.4 (CH=), 129.9 (CH=), 133.5 (C), 137.1 (C), 155.6 (C=O, NHBoc), 166.4 (C=O, OBz), 204.5 (C=S). MS HR-ESI [found 651.2717, $C_{33}H_{44}N_2O_8S$ $(M\text{-}Na)^+$ requires 651.2711].

***N*-(*tert*-Butoxycarbonyl)-L-leucine-(5-*O*-benzoyl-1-*O*-benzyl-6-deoxy-2,3-*O*-isopropylidene-6-thioamido-α-D-mannofuranose) (L71c)**. Yield: 456 mg (71%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.85-0.89 (m, 6H, CH_3, ^{i}Bu), 1.23 (s, 3H, CH_3), 1.39 (s, 9H, CH_3, ^{t}Bu), 1.44 (s, 3H, CH_3), 1.52-1.60 (m, 2H, CH, CH_2, ^{i}Bu), 1.65-1.73 (m, 1H, CH_2, ^{i}Bu), 4.16 (bs, 2H, H-6), 4.26 (dd, 1H, H-4, $^{3}J_{H-H}$ =7.6 Hz, $^{3}J_{H-H}$ =3.6 Hz), 4.34-4.40 (m, 1H, CH), 4.55 (d, 1H, OCH_2, $^{2}J_{H-H}$ =12.0 Hz), 4.66 (d, 1H, H-2, $^{2}J_{H-H}$ =5.6 Hz), 4.70 (d, 1H, OCH_2, $^{2}J_{H-H}$ =11.6 Hz), 4.81 (dd, 1H, H-3, $^{3}J_{H-H}$ =6.0 Hz, $^{3}J_{H-H}$ =4.0 Hz), 5.16 (s, 2H, H-1, NH-Boc), 5.56-5.61 (m, 1H, H-5), 7.27-7.32 (m, 1H, CH=), 7.34 (s, 3H, CH=), 7.35 (s, 1H, CH=), 7.46 (pt, 2H, CH=, $^{3}J_{H-H}$ =8.0 Hz), 7.59 (pt, 1H, CH=, $^{3}J_{H-H}$ =7.6 Hz), 8.02 (d, 2H, CH=, $^{3}J_{H-H}$ =6.8 Hz), 8.61 (bs, 1H, NH). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=22.0 (CH_3, ^{i}Bu), 22.8 (CH_3, ^{i}Bu), 24.7 (CH_3, CH ^{i}Bu), 26.0 (CH_3), 28.3 (CH_3, ^{t}Bu), 44.9 (CH_2, ^{i}Bu), 48.1 (C-6), 59.8 (CH), 69.5 (OCH_2), 70.2 (C-5), 79.4 (C-4), 79.5 (C-3), 80.0 (C, ^{t}Bu), 84.7 (C-2), 105.7 (C-1), 113.0 ($\underline{C}Me_2$), 128.0 (CH=), 128.1 (CH=), 128.4 (CH=), 128.5 (CH=), 129.4 (CH=), 129.9 (CH=), 133.5 (C), 137.1 (C), 155.4 (C=O, NHBoc), 166.4 (C=O, OBz), 205.7 (C=S). MS HR-ESI [found 643.3050, $C_{34}H_{46}N_2O_8S$ $(M\text{-}H)^+$ requires 643.3048].

***N*-(*tert*-Butoxycarbonyl)-L-phenylalanine-(5-*O*-benzoyl-1-*O*-benzyl-6-deoxy-2,3-*O*-isopropylidene-6-thioamido-α-D-mannofuranose) (L71d)**. Yield: 447 mg (66%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.21 (s, 3H, CH_3), 1.38 (s, 9H, CH_3, ^{t}Bu), 1.41 (s, 3H, CH_3), 3.12 (bs, 2H, CH_2), 3.84-3.89 (m, 1H, H-6), 4.09-4.21 (m, 2H, H-6, H-4), 4.52 (d, 1H, OCH_2, $^{2}J_{H-H}$ =12.0 Hz), 4.53-4.59 (m, 1H, CH), 4.63 (d, 1H, H-2, $^{3}J_{H-H}$ =6.0 Hz), 4.67 (d, 1H, OCH_2, $^{2}J_{H-H}$ =12.0 Hz), 4.71-4.73 (m, 1H, H-3), 5.11 (s, 1H, H-1), 5.36-5.40 (m, 2H, H-5, NH-Boc), 6.99 (bs, 1H, CH=), 7.13-7.16 (m, 4H, CH=), 7.27-7.32 (m, 1H, CH=), 7.34 (s, 3H, CH=), 7.35 (s, 1H, CH=), 7.47 (pt, 2H, CH=, $^{3}J_{H-H}$ =8.4 Hz), 7.58-7.62 (m, 1H, CH=), 7.96 (d, 2H, CH=, $^{3}J_{H-H}$ =6.8 Hz), 8.28 (bs, 1H, NH). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=24.6 (CH_3), 25.9 (CH_3), 28.3 (CH_3, ^{t}Bu), 42.1 (CH_2), 47.8 (C-6), 63.1 (CH), 69.5 (OCH_2), 70.3 (C-5), 79.1 (C-4), 79.5 (C-3), 80.1 (C, ^{t}Bu), 84.7 (C-2), 105.6 (C-1), 112.9 ($\underline{C}Me_2$), 126.8 (CH=), 127.9 (CH=), 128.0 (CH=), 128.4 (CH=), 128.5 (CH=), 129.1 (CH=), 129.3 (CH=), 129.4 (CH=), 130.0 (CH=), 133.5 (C), 136.7 (C), 137.1 (C), 155.0 (C=O, NHBoc),

166.2 (C=O, OBz), 203.3 (C=S). MS HR-ESI [found 677.2889, $C_{37}H_{44}N_2O_8S$ $(M-H)^+$ requires 677.2891].

***N*-(*tert*-Butoxycarbonyl)-L-phenylglycine-(5-*O*-benzoyl-1-*O*-benzyl-6-deoxy-2,3-*O*-isopropylidene-6-thioamido-α-D-mannofuranose) (L71e)**. Yield: 219 mg (33%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.14 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 1.32 (s, 9H, CH_3, ^{t}Bu), 1.88 (bs, 1H, OH), 3.99-4.57 (m, 3H, H-6, H-4), 4.45 (d, 1H, OCH_2, $^2J_{H-H}$ =12.4 Hz), 4.56-4.60 (m, 2H, OCH_2, H-2), 4.69 (dd, 1H, H-4, $^3J_{H-H}$ =5.6 Hz, $^3J_{H-H}$ =4.0 Hz), 5.03 (s, 1H, H-1), 5.32 (bs, 1H, CH), 5.47 (bs, 1H, H-5), 6.15 (bs, 1H, NH-Boc), 7.09-7.11 (m, 3H, CH=), 7.19-7.28 (m, 7H, CH=), 7.37 (pt, 2H, CH=, $^3J_{H-H}$ =7.6 Hz), 7.52 (pt, 1H, CH=, $^3J_{H-H}$ =7.6 Hz), 7.86 (d, 2H, CH=, $^3J_{H-H}$ =7.2 Hz), 8.47 (bs, 1H, NH). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=24.6 (CH_3), 25.9 (CH_3), 28.3 (CH_3, ^{t}Bu), 48.6 (C-6), 64.0 (CH), 69.5 (OCH_2), 70.1 (C-5), 79.5 (C-4, C-3), 80,1 (C, ^{t}Bu), 84.6 (C-2), 105.6 (C-1), 113.0 ($\underline{C}Me_2$), 126.9 (CH=), 128.0 (CH=), 128.2 (CH=), 128.5 (CH=), 128.6 (CH=), 128.8 (CH=), 129.2 (CH=), 129.9 (CH=), 133.6 (C), 137.1 (C), 139.6 (C), 154.7 (C=O, NHBoc), 166.4 (C=O, OBz), 202.1 (C=S). MS HR-ESI [found 663.2742, $C_{36}H_{42}N_2O_8S$ $(M-H)^+$ requires 663.2735].

***N*-(*tert*-Butoxycarbonyl)-L-alanine-(5-*O*-benzoyl-1-*O*-benzyl-6-deoxy-2,3-*O*-isopropylidene-6-thioamido-α-D-mannofuranose) (L71f)**. Yield: 426,5 mg (71%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.23 (s, 3H, CH_3), 1.38 (s, 9H, CH_3, ^{t}Bu), 1.41 (d, 3H, CH_3, $^3J_{H-H}$ =7.2 Hz), 1.44 (s, 3H, CH_3), 4.19 (bs, 2H, H-6), 4.26 (dd, 1H, H-4, $^3J_{H-H}$ =7.6 Hz, $^3J_{H-H}$ =3.6 Hz), 4.22-4.49 (m, 1H, CH), 4.55 (d, 1H, OCH_2, $^2J_{H-H}$ =12.0 Hz), 4.66 (d, 1H, H-2, $^3J_{H-H}$ =6.0 Hz), 4.69 (d, 1H, OCH_2, $^2J_{H-H}$ =12.0 Hz), 4.81 (dd, 1H, H-3, $^3J_{H-H}$ =6.0 Hz, $^3J_{H-H}$ =4.0 Hz), 5.16 (s, 1H, H-1), 5.25 (bs, 1H, NHBoc), 5.55-5.59 (m, 1H, H-5), 7.26-7.33 (m, 1H, CH=), 7.33 (s, 3H, CH=), 7.34 (s, 1H, CH=), 7.45 (pt, 2H, CH=, $^3J_{H-H}$ =8.0 Hz), 7.56-7.61 (m, 1H, CH=), 8.02 (d, 2H, CH=, $^3J_{H-H}$ =7.2 Hz), 8.67 (bs, 1H, NH). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=21.8 (CH_3), 24.6 (CH_3), 26.0 (CH_3), 28.3 (CH_3, ^{t}Bu), 47.9 (C-6), 56.8 (CH), 69.5 (OCH_2), 70.3 (C-5), 79.3 (C-4), 79.5 (C-3), 80.1 (C, ^{t}Bu), 84.7 (C-2), 105.7 (C-1), 113.0 ($\underline{C}Me_2$), 128.0 (CH=), 128.1 (CH=), 128.5 (CH=), 129.4 (CH=), 129.9 (CH=), 133.5 (C), 137.2 (C), 155.1 (C=O, NHBoc), 166.3 (C=O, OBz), 205.6 (C=S). MS HR-ESI [found 601.2562, $C_{31}H_{40}N_2O_8S$ $(M-H)^+$ requires 601.2578].

***N*-(*tert*-Butoxycarbonyl)-glycine-(5-*O*-benzoyl-1-*O*-benzyl-6-deoxy-2,3-*O*-isopropylidene-6-thioamido-α-D-mannofuranose) (L71g)**. Yield: 223 mg (38%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.23 (s, 3H, CH_3), 1.43 (s, 9H, CH_3, ^{t}Bu), 1.44 (s, 3H, CH_3), 4.10-4.21 (m, 4H, H-6, CH_2), 4.25 (dd, 1H, H-4, $^3J_{H-H}$ =7.6 Hz, $^3J_{H-H}$ =3.6 Hz), 4.54 (d, 1H, OCH_2, $^2J_{H-H}$ =11.6 Hz), 4.66 (d, 1H, H-2, $^3J_{H-H}$ =6.0 Hz), 4.69 (d, 1H, OCH_2, $^2J_{H-H}$ =12.0 Hz), 4.81 (dd, 1H, H-3, $^3J_{H-H}$ =5.6 Hz, $^3J_{H-H}$ =3.6 Hz), 5.12 (bs, 1H, NH-Boc), 5.16 (s, 1H, H-1), 5.55-5.59 (m, 1H, H-5), 7.27-7.33 (m, 1H, CH=), 7.34 (s, 3H, CH=), 7.35 (s, 1H, CH=), 7.47 (pt, 2H, CH=, $^3J_{H-H}$ =8.0 Hz), 7.57-7.62 (m, 1H, CH=), 8.04 (d, 2H, CH=, $^3J_{H-H}$ =7.2 Hz), 8.86 (bs, 1H, NH). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=24.7 (CH_3), 26.0 (CH_3), 28.3 (CH_3, ^{t}Bu), 47.9 (C-6), 52.4 (CH_2), 69.4 (OCH_2), 70.3 (C-5), 79.1 (C-4), 79.5 (C-3), 80.6 (C, ^{t}Bu), 84.7 (C-2), 105.6 (C-1), 113.0 ($\underline{C}Me_2$), 127.9 (CH=), 128.0 (CH=), 128.5 (CH=), 129.5 (CH=), 129.9 (CH=), 133.5 (C), 137.2 (C), 156.2 (C=O, NHBoc), 166.3 (C=O, OBz), 200.1 (C=S). MS HR-ESI [found 587.2408, $C_{30}H_{38}N_2O_8S$ $(M-H)^+$ requires 587.2422].

***N*-(*tert*-Butoxycarbonyl)-D-valine-(5-*O*-benzoyl-1-*O*-benzyl-6-deoxy-2,3-*O*-isopropylidene-6-thioamido-α-D-mannofuranose) (L71h)**. Yield: 327 mg (52%). ^{1}H NMR

(400 MHz, $CDCl_3$): δ=0.85 (d, 3H, CH_3 ^{i}Pr, $^{3}J_{H-H}$ =5.6 Hz), 0.94 (d, 3H, CH_3 ^{i}Pr, $^{3}J_{H-H}$ =6.8 Hz), 1.24 (s, 3H, CH_3), 1.39 (s, 9H, CH_3, ^{t}Bu), 1.43 (s, 3H, CH_3), 2.33 (bs, 1H, CH, ^{i}Pr), 4.02-4.10 (m, 2H, H-6), 4.25 (dd, 1H, H-4, $^{3}J_{H-H}$ =7.2 Hz, $^{3}J_{H-H}$ =3.6 Hz), 4.32 (bs, 1H, CH), 4.53 (d, 1H, OCH_2, $^{2}J_{H-H}$ =12.0 Hz), 4.66 (d, 1H, H-2, $^{3}J_{H-H}$ =5.6 Hz), 4.68 (d, 1H, OCH_2, $^{2}J_{H-H}$ =12.0 Hz), 4.82 (dd, 1H, H-3, $^{3}J_{H-H}$ =5.6 Hz, $^{3}J_{H-H}$ =3.6 Hz), 5.16 (s, 1H, H-1), 5.25 (bs, 1H, NHBoc), 5.54-5.59 (m, 1H, H-5), 7.28-7.34 (m, 5H, CH=), 7.44 (pt, 2H, CH=, $^{3}J_{H-H}$ =8.0 Hz), 7.58 (pt, 1H, CH=, $^{3}J_{H-H}$ =7.6 Hz), 8.02 (d, 2H, CH=, $^{3}J_{H-H}$ =7.2 Hz), 8.53 (bs, 1H, NH). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=17.6 (CH_3, ^{i}Pr), 19.7 (CH_3, ^{i}Pr), 24.6 (CH_3), 25.9 (CH_3), 28.3 (CH_3, ^{t}Bu), 33.1 (CH, ^{i}Pr), 47.9 (C-6), 66.9 (CH), 69.5 (OCH_2), 70.4 (C-5), 79.5 (C-4, C-3), 79.9 (C, ^{t}Bu), 84.7 (C-2), 105.7 (C-1), 113.0 ($\underline{C}Me_2$), 128.0 (CH=), 128.1 (CH=), 128.4 (CH=), 128.5 (CH=), 129.4 (CH=), 129.9 (CH=), 133.5 (C), 137.1 (C), 155.6 (C=O, NHBoc), 166.5 (C=O, OBz), 204.4 (C=S). MS HR-ESI [found 629.2883, $C_{33}H_{44}N_2O_8S$ $(M-H)^+$ requires 629.2891].

***N*-(*tert*-Butoxycarbonyl)-D-phenylglycine-(5-*O*-benzoyl-1-*O*-benzyl-6-deoxy-2,3-*O*-isopropylidene-6-thioamido-α-D-mannofuranose) (L71i)**. Yield: 510 mg (77%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.31 (s, 3H, CH_3), 1.48 (s, 9H, CH_3, ^{t}Bu), 1.49 (s, 3H, CH_3), 4.10 (bs, 1H, H-6), 4.24 (dd, 1H, H-4, $^{3}J_{H-H}$ =6.8 Hz, $^{3}J_{H-H}$ =2.6 Hz), 4.36 (m, 1H, H-6), 4.56 (d, 1H, OCH_2, $^{2}J_{H-H}$ =12.0 Hz), 4.66 (d, 1H, OCH_2, $^{2}J_{H-H}$ =12.4 Hz), 4.72 (d, 1H, H-2, $^{3}J_{H-H}$ =5.6 Hz), 4.87 (dd, 1H, H-3, $^{3}J_{H-H}$ =5.6 Hz, $^{3}J_{H-H}$ =3.6 Hz), 5.21 (s, 1H, H-1), 5.45 (bs, 1H, CH), 5.56-5.60 (m, 1H, H-5), 6.35 (bs, 1H, NH-Boc), 7.31-4.43 (m, 7H, CH=), 7.48-7.53 (m, 5H, CH=), 7.65-7.69 (m, 1H, CH=), 7.98 (d, 2H, CH=, $^{3}J_{H-H}$ =7.6 Hz), 8.61 (bs, 1H, NH). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=24.5 (CH_3), 25.9 (CH_3), 28.3 (CH_3, ^{t}Bu), 48.3 (C-6), 64.1 (CH), 69.6 (OCH_2), 70.0 (C-5), 79.4 (C-4), 79.7 (C-3), 80.1 (C, ^{t}Bu), 84.6 (C-2), 105.6 (C-1), 112.9 ($\underline{C}Me_2$), 126.9 (CH=), 128.1 (CH=), 128.3 (CH=), 128.5 (CH=), 128.6 (CH=), 128.8 (CH=), 128.9 (CH=), 129.3 (CH=), 129.9 (CH=), 133.5 (C), 137.0 (C), 139.7 (C), 154.7 (C=O, NHBoc), 166.4 (C=O, OBz), 202.0 (C=S). MS HR-ESI [found 663.2727, $C_{36}H_{42}N_2O_8S$ $(M-H)^+$ requires 663.2735].

***N*-(*tert*-Butoxycarbonyl)-D-alanine-(5-*O*-benzoyl-1-*O*-benzyl-6-deoxy-2,3-*O*-isopropylidene-6-thioamido-α-D-mannofuranose) (L71j)**. Yield: 493 mg (82%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.24 (s, 3H, CH_3), 1.41 (s, 12H, CH_3 ^{t}Bu, CH_3), 1.44 (s, 3H, CH_3), 4.11-4.17 (m, 1H, H-6), 4.23-4.27 (m, 2H, H-4, H-6), 4.42-4.49 (m, 1H, CH), 4.53 (d, 1H, OCH_2, $^{2}J_{H-H}$ =11.6 Hz), 4.66 (d, 1H, H-2, $^{3}J_{H-H}$ =6.0 Hz), 4.68 (d, 1H, OCH_2, $^{2}J_{H-H}$ =12.0 Hz), 4.81 (dd, 1H, H-3, $^{3}J_{H-H}$ =5.6 Hz, $^{3}J_{H-H}$ =3.6 Hz), 5.16 (s, 1H, H-1), 5.23 (bs, 1H, NHBoc), 5.56-5.60 (m, 1H, H-5), 7.28-7.35 (m, 5H, CH=), 7.45 (pt, 2H, CH=, $^{3}J_{H-H}$ =8.0 Hz), 7.59 (pt, 1H, CH=, $^{3}J_{H-H}$ =7.2 Hz), 8.04 (d, 2H, CH=, $^{3}J_{H-H}$ =7.2 Hz), 8.71 (bs, 1H, NH). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=21.8 (CH_3), 24.7 (CH_3), 26.0 (CH_3), 28.3 (CH_3, ^{t}Bu), 47.8 (C-6), 56.5 (CH), 69.4 (OCH_2), 70.3 (C-5), 79.2 (C-4), 79.5 (C-3), 80.2 (C, ^{t}Bu), 84.7 (C-2), 105.6 (C-1), 113.0 ($\underline{C}Me_2$), 127.9 (CH=), 128.0 (CH=), 128.4 (CH=), 128.5 (CH=), 129.5 (CH=), 129.9 (CH=), 133.4 (C), 137.1 (C), 155.3 (C=O, NHBoc), 166.4 (C=O, OBz), 205.5 (C=S). MS HR-ESI [found 601.2574, $C_{31}H_{40}N_2O_8S$ $(M-H)^+$ requires 601.2578].

***N*-(*tert*-Butoxycarbonyl)-L-valine-(6-*O*-benzoyl-1-*O*-benzyl-5-deoxy-2,3-*O*-isopropylidene-5-thioamido-α-D-mannofuranose) (L72a)**. Yield: 63 mg (10%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.88 (d, 3H, CH_3 ^{i}Pr, $^{3}J_{H-H}$ =7.2 Hz), 0.91 (d, 3H, CH_3 ^{i}Pr, $^{3}J_{H-H}$ =4.0 Hz), 1.33 (s, 3H, CH_3), 1.41 (s, 9H, CH_3, ^{t}Bu), 1.64 (s, 3H, CH_3), 2.28 (bs, 1H, CH, ^{i}Pr), 4.14 (pt, 1H, CH, $^{3}J_{H-H}$ =7.2 Hz), 4.29 (pt, 1H, H-4, $^{3}J_{H-H}$ =3.2 Hz), 4.48 (d, 1H, OCH_2, $^{2}J_{H-H}$ =11.6 Hz), 4.59 (dd, 1H, H-6,

$^{2}J_{H-H}$ =12.0 Hz, $^{3}J_{H-H}$ =4.0 Hz), 4.66-4.69 (m, 2H, OCH_2, H-2), 4.77 (bs, 1H, H-6), 4.94 (dd, 1H, H-3, $^{3}J_{H-H}$ =6.0 Hz, $^{3}J_{H-H}$ =3.2 Hz), 5.11 (s, 1H, H-1), 5.37 (bs, 1H, NHBoc), 5.53-5.55 (m, 1H, H-5), 7.28-7.36 (m, 5H, CH=), 7.43 (pt, 2H, CH=, $^{3}J_{H-H}$ =8.4 Hz), 7.56-7.61 (m, 1H, CH=), 8.06 (d, 2H, CH=, $^{3}J_{H-H}$ =7.2 Hz), 9.10 (bs, 1H, NH). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=17.2 (CH_3, ^{i}Pr), 19.9 (CH_3, ^{i}Pr), 23.3 (CH_3), 26.3 (CH_3), 28.5 (CH_3, ^{t}Bu), 34.1 (CH, ^{i}Pr), 54.1 (C-5), 62.6 (C-6), 66.9 (CH), 69.5 (OCH_2), 77.4 (C-4), 81.1 (C-3), 85.6 (C-2), 105.1 (C-1), 113.2 ($\underline{C}Me_2$), 128.1 (CH=), 128.3 (CH=), 128.6 (CH=), 128.7 (CH=), 129.7 (CH=), 130.0 (CH=), 133.5 (C), 137.2 (C), 155.5 (C=O, NHBoc), 166.4 (C=O, OBz), 204.3 (C=O). MS HR-ESI [found 651.2723, $C_{33}H_{44}N_2O_8S$ $(M-Na)^+$ requires 651.2711].

***N*-(*tert*-Butoxycarbonyl)-L-alanine-(6-*O*-benzoyl-1-*O*-benzyl-5-deoxy-2,3-*O*-isopropylidene-5-thioamido-α-D-mannofuranose) (L72f)**. Yield: 366 mg (61%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.29 (s, 3H, CH_3), 1.39 (s, 9H, CH_3, ^{t}Bu), 1.43 (d, 3H, CH_3, $^{3}J_{H-H}$ =6.8 Hz), 1.59 (s, 3H, CH_3), 4.28 (pt, 1H, H-4, $^{3}J_{H-H}$ =4.0 Hz), 4.39-4.46 (m, 1H, CH), 4.47 (d, 1H, OCH_2, $^{2}J_{H-H}$ =11.6 Hz), 4.57 (dd, 1H, H-6, $^{2}J_{H-H}$ =12.0 Hz, $^{3}J_{H-H}$ =4.4 Hz), 4.64-4.67 (m, 2H, OCH_2, H-2), 4.73 (bs, 1H, H-6), 4.92 (dd, 1H, H-3, $^{3}J_{H-H}$ =3.2 Hz, $^{3}J_{H-H}$ =6.0 Hz), 5.10 (s, 1H, H-1), 5.41 (bs, 1H, NHBoc), 5.49-5.52 (m, 1H, H-5), 7.26-7.34 (m, 5H, CH=), 7.42 (pt, 2H, CH=, $^{3}J_{H-H}$ =8.0 Hz), 7.56 (pt, 1H, CH=, $^{3}J_{H-H}$ =7.6 Hz), 8.04 (d, 2H, CH=, $^{3}J_{H-H}$ =7.2 Hz), 9.08 (bs, 1H, NH). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=22.3 (CH_3), 24.1 (CH_3), 26.0 (CH_3), 28.3 (CH_3, ^{t}Bu), 53.9 (C-5), 64.2 (C-6), 69.1 (OCH_2), 76.9 (C-4), 79.7 (C, ^{t}Bu), 80.6 (C-3), 85.3 (C-2), 105.0 (C-1), 112.8 ($\underline{C}Me_2$), 127.9 (CH=), 128.1 (CH=), 128.4 (CH=), 128.5 (CH=), 129.5 (CH=), 129.8 (CH=), 133.3 (C), 137.0 (C), 154.8 (C=O, NHBoc), 166.2 (C=O, OBz), 205.5 (C=S). MS HR-ESI [found 601.2384, $C_{31}H_{40}N_2O_8S$ $(M-Na)^+$ requires 601.2398].

***N*-(*tert*-Butoxycarbonyl)-L-valine-(6-*O*-benzoyl-1-*O*-benzyl-5-deoxy-2,3-*O*-isopropylidene-5-thioamido-β-L-gulofuranose) (L73a)**. Yield: 94 mg (15%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.93 (bs, 3H, CH_3, ^{i}Pr), 0.97 (d, 3H, CH_3 ^{i}Pr, $^{3}J_{H-H}$ =6.8 Hz), 1.29 (s, 3H, CH_3), 1.39 (s, 9H, CH_3, ^{t}Bu), 1.49 (s, 3H, CH_3), 2.37 (bs, 1H, CH, ^{i}Pr), 4.06 (m, 1H, CH), 4.34 (dd, 1H, H-4, $^{3}J_{H-H}$ =7.2 Hz, $^{3}J_{H-H}$ =3.2 Hz), 4.47 (d, 1H, OCH_2, $^{2}J_{H-H}$ =12.0 Hz), 4.59 (d, 1H, OCH_2, $^{2}J_{H-H}$ =12.0 Hz), 4.65 (d, 1H, H-2, $^{3}J_{H-H}$ =5.6 Hz), 4.66 (bs, 1H, H-6), 4.77-4.81 (m, 2H, H-6, H-3), 5.11 (s, 1H, H-1), 5.19 (bs, 1H, NHBoc), 5.38 (bs, 1H, H-5), 7.25-7.33 (m, 5H, CH=), 7.44 (pt, 2H, CH=, $^{3}J_{H-H}$ =8.0 Hz), 7.55-7.59 (m, 1H, CH=), 7.99 (bs, 1H, NH), 8.03 (d, 2H, CH=, $^{3}J_{H-H}$ =7.2 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=17.8 (CH_3, ^{i}Pr), 19.1 (CH_3, ^{i}Pr), 24.6 (CH_3), 26.1 (CH_3), 28.3 (CH_3, ^{t}Bu), 32.9 (CH, ^{i}Pr), 53.8 (C-5), 62.8 (C-6), 67.3 (CH), 69.4 (OCH_2), 77.4 (C-4), 79.8 (C-3), 80.0 (C, ^{t}Bu), 85.2 (C-2), 105.5 (C-1), 113.1 ($\underline{C}Me_2$), 128.0 (CH=), 128.4 (CH=), 128.5 (CH=), 129.7 (CH=), 129.8 (CH=), 133.2 (C), 137.2 (C), 155.7 (C=O, NHBoc), 166.4 (C=O, OBz), 204.7 (C=S). MS HR-ESI [found 629.2887, $C_{33}H_{44}N_2O_8S$ $(M-H)^+$ requires 629.2891].

***N*-(*tert*-Butoxycarbonyl)-D-valine-(6-*O*-benzoyl-1-*O*-benzyl-5-deoxy-2,3-*O*-isopropylidene-5-thioamido-β-L-gulofuranose) (L73h)**. Yield: 75 mg (12%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.89 (d, 3H, CH_3, ^{i}Pr, $^{3}J_{H-H}$ =6.4 Hz), 0.94 (d, 3H, CH_3 ^{i}Pr, $^{3}J_{H-H}$ =6.8 Hz), 1.28 (s, 3H, CH_3), 1.41 (s, 9H, CH_3, ^{t}Bu), 1.45 (s, 3H, CH_3), 2.15 (bs, 1H, CH, ^{i}Pr), 4.09 (bs, 1H, CH), 4.32 (dd, 1H, H-4, $^{3}J_{H-H}$ =5.6 Hz, $^{3}J_{H-H}$ =3.6 Hz), 4.45 (d, 1H, OCH_2, $^{2}J_{H-H}$ =11.6 Hz), 4.56 (d, 1H, OCH_2, $^{2}J_{H-H}$ =12.0 Hz), 4.62 (m, 1H, H-6), 4.74 (d, 1H, H-2, $^{3}J_{H-H}$ =4.4 Hz), 4.77-4.80 (m, 2H, H-6, H-3), 5.15 (s, 1H, H-1), 5.35 (bs, 1H, H-5), 5.47 (bs, 1H, NHBoc), 7.24-7.33 (m, 5H, CH=), 7.45 (pt, 2H, CH=, $^{3}J_{H-H}$ =8.0 Hz), 7.56-7.60 (m, 1H, CH=), 7.91 (bs, 1H, NH), 8.04 (d, 2H, CH=,

$^{3}J_{H-H}$ =7.2 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=18.3 (CH_3, ^{i}Pr), 19.5 (CH_3, ^{i}Pr), 24.3 (CH_3), 25.9 (CH_3), 28.3 (CH_3, ^{t}Bu), 34.4 (CH, ^{i}Pr), 53.3 (C-5), 62.8 (C-6), 66.8 (CH), 69.5 (OCH_2), 77.2 (C-4), 79.7 (C, ^{t}Bu), 79.9 (C-3), 84.9 (C-2), 105.6 (C-1), 113.0 ($\underline{C}Me_2$), 127.9 (CH=), 128.0 (CH=), 128.4 (CH=), 128.5 (CH=), 129.6 (CH=), 129.7 (CH=), 133.3 (C), 137.4 (C), 155.3 (C=O, NHBoc), 166.3 (C=O, OBz), 204.1 (C=S). MS HR-ESI [found 629.2885, $C_{33}H_{44}N_2O_8S$ $(M-H)^+$ requires 629.2891].

4.2.4.5. Synthesis of 6-amino-1-*O*-benzyl-6-deoxy-2,3-*O*-isopropylidene-α-D-mannofuranose (6)

Synthesis of 1-O-benzyl-2,3-O-isopropylidene-6-O-tosyl-α-D-mannofuranose. A solution of *p*-toluenesulfonyl chloride (1.6 g, 8.4 mmol) in dichloromethane (10 mL) was slowly added to a cooled solution (-15 °C) of diol **5** (2.6 g, 8.4 mmol) in pyridine (49.7 mmol, 4 mL). The reaction was allowed to stir overnight at room temperature. Then, water was added and the product was extracted with dichloromethane (x3) and washed with a solution of HCl 0.1 M (x1). The organic layer was dried over $MgSO_4$, evaporated to dryness and purified by SiO_2-flash chromatography (ethyl acetate/petroleum ether: 2/3) to produce the product as a white solid. Yield: 2.8 g, 72%. ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.30 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 2.43 (s, 3H, CH_3, OTs), 2.69 (bs, 1H, OH), 3.93 (dd, 1H, H-4, $^{3}J_{H-H}$ =7.6 Hz, $^{3}J_{H-H}$ =3.6 Hz), 4.12-4.17 (m, 2H, H-5, H-6), 4.25-4.29 (m, 1H, H-6), 4.41 (d, 1H, OCH_2, $^{2}J_{H-H}$ =11.6 Hz), 4.57 (d, 1H, OCH_2, $^{2}J_{H-H}$ =12.0 Hz), 4.63 (d, 1H, H-2, $^{3}J_{H-H}$ =5.6 Hz), 4.81 (dd, 1H, H-3, $^{3}J_{H-H}$ =6.4 Hz, $^{3}J_{H-H}$ =4.0 Hz), 5.05 (s, 1H, H-1), 7.28-7.34 (m, 7H, CH=), 7.82 (d, 2H, CH=, $^{3}J_{H-H}$ =8.4 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=21.7 (CH_3, OTs), 24.5 (CH_3), 25.9 (CH_3), 68.1 (C-5), 69.1 (OCH_2), 71.6 (C-6), 78.2 (C-4), 79.7 (C-3), 84.8 (C2), 105.2 (C-1), 112.8 ($\underline{C}Me_2$), 127.9 (CH=), 128.0 (CH=), 128.2 (CH=), 128.5 (CH=), 129.6 (CH=), 129.9 (CH=), 132.7 (C), 137.1 (C), 145.0 (C).

Synthesis of 6-azide-1-O-benzyl-6-deoxy-2,3-O-isopropylidene-α-D-mannofuranose. To a solution of 1-*O*-benzyl-2,3-*O*-isopropylidene-6-*O*-tosyl-α-D-mannofuranose (2.8 g, 6.0 mmol) in DMF (30 mL), sodium azide (12 mmol, 781.9 mg) was added. The solution was stirred at 90 °C overnight. Then, water was added and the product was extracted three times with diethyl ether. The organic phase was dried over $MgSO_4$. The dried extract was evaporated and purified by SiO_2-flash chromatography (ethyl acetate/petroleum ether: 1/2) to give the corresponding azido-alcohol as a white solid. Yield: 1.7 g, 85%. ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.33 (s, 3H, CH_3), 1.47 (s, 3H, CH_3), 3.36-3.41 (m, 2H, H-6, OH), 3.49 (dd, 1H, H-6, $^{2}J_{H-H}$ =13.2 Hz, $^{3}J_{H-H}$ =2.8 Hz), 3.94 (1H, H-4, $^{3}J_{H-H}$ =8.8 Hz, $^{3}J_{H-H}$ =4.0 Hz), 4.09-4.13 (m, 1H, H-5), 4.47 (d, 1H, OCH_2, $^{2}J_{H-H}$ =12.0 Hz), 4.63 (d, 1H, OCH_2, $^{2}J_{H-H}$ =11.6 Hz), 4.67 (d, 1H, H-2, $^{3}J_{H-H}$ =6.0 Hz), 4.84 (dd, 1H, H-3, $^{3}J_{H-H}$ =5.6 Hz, $^{3}J_{H-H}$ =4.0 Hz), 5.11 (s, 1H, H-1), 7.29-7.35 (m, 5H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=24.6 (CH_3), 25.9 (CH_3), 54.5 (C-6), 69.0 (C-5), 69.1 (OCH_2), 79.6 (C-3), 79.7 (C-4), 84.9 (C2), 105.5 (C-1), 112.7 ($\underline{C}Me_2$), 127.9 (CH=), 128.1 (CH=), 128.5 (CH=), 137.3 (C).

*Synthesis of 6-amino-1-O-benzyl-6-deoxy-2,3-O-isopropylidene-α-D-mannofuranose (**6**).* $LiAlH_4$ (345.8 mg, 9.1 mmol) was poured into a two neck flask connected to a reflux and was solved in Et_2O (20 mL). The solution was cooled at 0 °C and a solution of 6-azide-1-O-benzyl-6-deoxy-2,3-O-isopropylidene-α-D-mannofuranose (1.7 g, 6.0 mmol) in Et_2O (10 mL) was added slowly. The solution was stirred at room temperature for 3h. Then, drops of

water were carefully added and a white precipitate appeared which was filtered and clean three times with ethyl acetate. The organic phase was dried over $MgSO_4$ and evaporated to give the corresponding amino-alcohol as a white solid. Yield: 1.6 g, quantitative yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.24 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 2.39 (bs, 3H, OH, NH_2), 2.63 (dd, 1H, H-6, $^2J_{H-H}$ =13.2 Hz, $^3J_{H-H}$ =2.8 Hz), 2.88 (dd, 1H, H-6, $^2J_{H-H}$ =11.6 Hz), 3.72-3.78 (m, 1H, H-4, H-5), 4.39 (d, 1H, OCH_2, $^2J_{H-H}$ =12.0 Hz), 4.52 (d, 1H, OCH_2, $^2J_{H-H}$ =12.0 Hz), 4.56 (d, 1H, H-2, $^3J_{H-H}$ =5.6 Hz), 4.75-4.77 (m, 1H, H-3), 5.00 (s, 1H, H-1), 7.18-7.28 (m, 5H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=24.6 (CH_3), 26.0 (CH_3), 45.0 (C-6), 69.2 (OCH_2), 70.1 (C-5), 80.1 (C-4), 80.6 (C-3), 84.8 (C2), 105.6 (C-1), 112.5 ($\underline{C}Me_2$), 127.9 (CH=), 128.0 (CH=), 128.5 (CH=), 137.4 (C).

4.2.4.6. Synthesis of 5-amino-1-*O*-benzyl-5-deoxy-2,3-*O*-isopropylidene-α-D-mannofuranose (7)

Synthesis of 1-O-benzyl-2,3-O-isopropylidene-5,6-di-O-mesyl-α-D-mannofuranose.[30] Mesyl chloride (7.8 mL, 94.8 mmol) was added to a cooled solution (0 °C) of diol **5** (4.90 g, 15.8 mmol) in dichloromethane (14 mL) in the presence of triethylamine (6.5 mL, 47.4 mmol). The reaction mixture was allowed to stir at room temperature overnight. Then the reaction was quenched with water and extracted with dichloromethane (x3). The organic phase was washed with water and dried over $MgSO_4$ and concentrated. The resulting residue was purified by SiO_2-flash chromatography (ethyl acetate/petroleum ether: 1/1) to yield the product as a white solid. Yield: 6.4 g, 91%. ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.30 (s, 3H, CH_3), 1.47 (s, 3H, CH_3), 3.08 (s, 3H, CH_3, OMs), 3.13 (s, 3H, CH_3, OMs), 4.27 (dd, 1H, H-4, $^3J_{H-H}$ =8.4 Hz, $^3J_{H-H}$ =4.0 Hz), 4.46-4.53 (m, 2H, H-6, OCH_2), 4.65-4.70 (m, 3H, H-6, H-2, OCH_2), 4.78 (dd, 1H, H-3, $^3J_{H-H}$ =6.0 Hz, $^3J_{H-H}$ =4.0 Hz), 5.01-5.05 (m, 1H, H-5), 5.09 (s, 1H, H-1), 7.29-7.37 (m, 5H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=24.7 (CH_3), 25.9 (CH_3), 37.6 (CH_3, OMs), 38.6 (CH_3, OMs), 68.7 (C-6), 69.3 (OCH_2), 76.2 (C-5), 76.6 (C-4), 78.8 (C-3), 84.9 (C2), 105.2 (C-1), 113.1 ($\underline{C}Me_2$), 128.1-136.8 128.1 (CH=), 128.3 (CH=), 128.6 (CH=), 136.8 (C).

Synthesis of 5,6-di-O-acetyl-1-O-benzyl-2,3-O-isopropylidene-β-L-gulofuranose.[30] The dimesylated derivative 1-*O*-benzyl-2,3-*O*-isopropylidene-5,6-di-*O*-mesyl-α-D-mannofuranose was solved in 40 mL of dry DMF and NaOAc (7.10 g, 86.4 mmol) and Ac_2O (13.3 mL, 140.0 mmol) were added. The reaction mixture was allowed to stir at 140°C for 3 days under a reflux. Then, after cooling down the mixture to room temperature, water was added and the product was extracted with diethyl ether (x3). The organic phase was washed with water, dried over $MgSO_4$ and concentrated. The resulting residue was purified by SiO_2-flash chromatography (ethyl acetate/petroleum ether: 1/3) to yield the product as a yellow oil. Yield: 2.7 g, 47%. ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.27 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 2.06 (s, 3H, CH_3, OAc), 2.11 (s, 3H, CH_3, OAc), 4.17 (dd, 1H, H-4, $^3J_{H-H}$ =8.4 Hz, $^3J_{H-H}$ =3.2 Hz), 4.28 (dd, 1H, H-6, $^2J_{H-H}$ =12.4 Hz, $^3J_{H-H}$ =4.0 Hz), 4.46-4.50 (m, 2H, H-6, OCH_2), 4.64-4.67 (m, 2H, H-2, OCH_2), 4.71-4.73 (m, 1H, H-3), 5.11 (s, 1H, H-1), 5.38-5.41 (m, 1H, H-5), 7.26-7.36 (m, 5H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=20.8 (CH_3, OAc), 21.1 (CH_3, OAc), 24.8 (CH_3), 26.1 (CH_3), 62.9 (C-6), 69.1 (OCH_2), 70.7 (C-5), 78.2 (C-4), 79.4 (C-3), 85.3 (C2), 105.4 (C-1), 113.0 ($\underline{C}Me_2$), 127.9 (CH=), 128.0 (CH=), 128.5 (CH=), 137.2 (C) 170.3 (C=O, OAc), 170.7 (C=O, OAc).

Synthesis of 1-O-benzyl-2,3-O-isopropylidene-β-L-gulofuranose. The diacetylated derivative 5,6-di-*O*-acetyl-1-*O*-benzyl-2,3-*O*-isopropylidene-β-L-gulofuranose (2.70 g, 6.8 mmol) was solved in a mixture of H_2O/MeOH (1/1) (60.6 mL) and K_2CO_3 (2.83 g, 20.5 mmol). The reaction mixture was allowed to stir at room temperature overnight. Then, brine was added to the mixture and the product was extracted with ethyl acetate (x3). The organic phase wad dried over $MgSO_4$ and concentrated giving a pale-yellow solid, which was used in the next step without further purification. Yield: 1.9 g, 90%. ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.30 (s, 3H, CH_3), 1.47 (s, 3H, CH_3), 3.72 (d, 1H, H-6, $^3J_{H\text{-}H}$ =5.2 Hz), 3.99 (dd, 1H, H-4, $^3J_{H\text{-}H}$ =4.8 Hz, $^3J_{H\text{-}H}$ =3.6 Hz), 4.11 (q, 1H, H-5, $^3J_{H\text{-}H}$ =5.2 Hz), 4.51 (s, 1H, OCH_2, $^2J_{H\text{-}H}$ =12.0 Hz), 4.63-4.68 (m, 2H, H-2, OCH_2), 4.78 (dd, 1H, H-3, $^3J_{H\text{-}H}$ =6.0 Hz, $^3J_{H\text{-}H}$ =3.6 Hz), 5.16 (s, 1H, H-1), 7.29-7.35 (m, 5H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=24.4 (CH_3), 25.9 (CH_3), 63.6 (C-6), 69.3 (OCH_2), 70.7 (C-5), 79.2 (C-4), 80.3 (C-3), 85.4 (C2), 105.3 (C-1), 112.8 ($\underline{C}Me_2$), 127.9 (CH=), 128.1 (CH=), 128.5 (CH=), 137.3 (C).

Synthesis of 1-O-benzyl-2,3-O-isopropylidene-6-O-trityl-β-L-gulofuranose.[31] Tritylchloride (2.5 g, 7.1 mmol) was added to a solution of 1-*O*-benzyl-2,3-*O*-isopropylidene-β-L-gulofuranose (1.9 g, 6.1 mmol) in pyridine (131.9 mmol, 10.6 ml). The reaction mixture was allowed to stir at room temperature for 36 h. Then dichloromethane was added and the solution was washed with a saturated aqueous $CuSO_4$ solution. The aqueous phase was extracted with dichloromethane once. All organic phases were washed with water, dried over $MgSO_4$ and concentrated. The resulting residue was purified by SiO_2-column chromatography (ethyl acetate/petroleum ether: 1/4) to yield the product as a colorless oil. Yield: 2.6 g, 76%. ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.28 (s, 3H, CH_3), 1.47 (s, 3H, CH_3), 3.16 (bs, 1H, OH), 3.41 (d, 2H, H-6, $^3J_{H\text{-}H}$ =3.2 Hz), 4.31 (bs, 2H, H-4, H-5), 4.46 (d, 1H, OCH_2, $^2J_{H\text{-}H}$ =11.6 Hz), 4.67-4.71 (m, 3H, H-2, H-3, OCH_2), 5.17 (s, 1H, H-1), 7.25-7.38 (m, 14H, CH=), 7.51 (d, 6H, CH=, $^3J_{H\text{-}H}$ =8.0 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=24.3 (CH_3), 25.9 (CH_3), 64.1 (C-6), 68.9 (OCH_2), 69.7 (C-5), 78.9 (C-4), 80.8 (C-3), 85.5 (C2), 86.7 (C, OTr), 104.9 (C-1), 112.6 ($\underline{C}Me_2$), 127.1 (CH=), 127.9 (CH=), 128.0 (CH=), 128.3 (CH=), 128.5 (CH=), 128.7 (CH=), 137.2 (C), 143.9 (C).

Synthesis of 5-azido-1-O-benzyl-5-deoxy-2,3-O-isopropylidene-6-O-trityl-α-D-mannofuranose.[31] Pyridine (9.2 mmol, 0.7 mL) and trifluoromethanesulfonic anhydride (1.1 mL, 6.6 mmol) were added to a cooled solution (-25 °C) of 1-*O*-benzyl-2,3-*O*-isopropylidene-6-*O*-trityl-β-L-gulofuranose (2.62 g, 4.7 mmol) in dichloromethane (20 mL). The reaction mixture was allowed to reach room temperature and after stirring for 1 h, the mixture was diluted with dichloromethane, washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$ and concentrated. The resulting crude triflate was dissolved in dry DMF (12 mL) and NaN_3 was added (3.1 g, 32.9 mmol) at 0°C in the presence of 18-crown-6 ether (2.1 g). The reaction mixture was allowed to stir at room temperature for 2.5 h. Water was added to the reaction mixture and extracted with Et_2O (x3). The organic phase was dried over $MgSO_4$ and evaporated. The resulting crude was purified by SiO_2-column chromatography (ethyl acetate/petroleum ether: 1/8) to afford the product as a colorless oil. Yield: 1.96 g, 72%. ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.33 (s, 3H, CH_3), 1.41 (s, 3H, CH_3), 3.35 (dd, 1H, H-6, $^2J_{H\text{-}H}$ =9.6 Hz, $^3J_{H\text{-}H}$ =5.6 Hz), 3.55 (dd, 1H, H-6, $^2J_{H\text{-}H}$ =10.0 Hz, $^3J_{H\text{-}H}$ =2.0 Hz), 3.78-3.82 (m, 1H, H-5), 4.10-4.14 (m, 1H, H-4), 4.32 (d, 1H, OCH_2, $^2J_{H\text{-}H}$ =12.0 Hz), 4.49 (d, 1H,

OCH_2, $^2J_{H-H}$ =11.6 Hz), 4.63 (d, 1H, H-2, $^3J_{H-H}$ =6.0 Hz), 4.82 (dd, 1H, H-3, $^3J_{H-H}$ =6.0 Hz, $^3J_{H-H}$ =3.6 Hz), 4.97 (s, 1H, H-1), 7.24-7.34 (m, 14H, CH=), 7.49-7.52 (m, 6H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=24.8 (CH_3), 26.0 (CH_3), 59.9 (C-5), 63.6 (C-6), 69.0 (OCH_2), 77.7 (C-4), 79.7 (C-3), 84.7 (C2), 87.0 (C, OTr), 105.2 (C-1), 112.6 ($\underline{C}Me_2$), 127.1 (CH=), 127.9 (CH=), 128.1 (CH=), 128.3 (CH=), 128.5 (CH=), 128.8 (CH=), 136.9 (C), 143.8 (C).

Synthesis of 5-azido-1-O-benzyl-5-deoxy-2,3-O-isopropylidene-α-D-mannofuranose.[31] $BF_3.Et_2O$ (32,2 mmol, 1.3 mL) and MeOH (1.2 mL) were added to a cooled solution (0°C) of 5-azido-1-*O*-benzyl-5-deoxy-2,3-*O*-isopropylidene-6-*O*-trityl-α-D-mannofuranose (1.96 g, 3.4 mmol) in dichloromethane (22 mL). The reaction mixture was allowed to stir for 1.5 h at room temperature and then dichloromethane was added. The mixture was washed with saturated aqueous $NaHCO_3$ (x2), dried over $MgSO_4$ and concentrated. The resulting crude was purified by SiO_2-column chromatography (ethyl acetate/petroleum ether: 1/4 → 1/1) to give the product as a white solid. Yield: 592 mg, 52%. ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.33 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 1.94 (bs, 1H, OH), 3.69 (dd, 1H, H-6, $^2J_{H-H}$ =11.2 Hz, $^3J_{H-H}$ =4.8 Hz), 3.81-3.94 (m, 3H, H-4, H-5, H-6), 4.50 (d, 1H, OCH_2, $^2J_{H-H}$ =11.6 Hz), 4.59 (d, 1H, OCH_2, $^2J_{H-H}$ =11.6 Hz), 4.65 (d, 1H, H-2, $^3J_{H-H}$ =6.0 Hz), 4.81 (dd, 1H, H-3, $^3J_{H-H}$ =6.0 Hz, $^3J_{H-H}$ =3.6 Hz), 5.09 (s, 1H, H-1), 7.25-7.35 (m, 5H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=24.7 (CH_3), 26.0 (CH_3), 61.4 (C-5), 63.4 (C-6), 69.5 (OCH_2), 78.7 (C-3), 79.6 (C-4), 85.7 (C2), 105.8 (C-1), 112.8 ($\underline{C}Me_2$), 128.0 (CH=), 128.1 (CH=), 128.5 (CH=), 137.3 (C).

*Synthesis of 5-amino-1-O-benzyl-5-deoxy-2,3-O-isopropylidene-α-D-mannofuranose (**7**).* Treatment of azido-alcohol derivative 5-azido-1-*O*-benzyl-5-deoxy-2,3-*O*-isopropylidene-α-D-mannofuranose (592 mg, 1.8 mmol) as previously described for **6**, afforded the corresponding amino-alcohol as a white solid. Yield: 490.2 g, 90%. ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.30 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 2.21 (bs, 3H, OH, NH_2), 3.20 (bs, 1H, H-5), 3.53 (dd, 1H, H-6, $^2J_{H-H}$ =10.8 Hz, $^3J_{H-H}$ =6.4 Hz), 3.76-3.82 (m, 2H, H-4, H-6), 4.47 (d, 1H, OCH_2, $^2J_{H-H}$ =12.4 Hz), 4.60 (d, 1H, OCH_2, $^2J_{H-H}$ 11.6 Hz), 4.63 (d, 1H, H-2, $^3J_{H-H}$ =6.0 Hz), 4.79 (dd, 1H, H-3, $^3J_{H-H}$ =6.0 Hz, $^3J_{H-H}$ =3.6 Hz), 5.08 (s, 1H, H-1), 7.26-7.35 (m, 5H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=24.7 (CH_3), 26.0 (CH_3), 51.9 (C-5), 65.0 (C-6), 69.2 (OCH_2), 80.0 (C-3), 81.4 (C-4), 84.8 (C2), 105.5 (C-1), 112.5 ($\underline{C}Me_2$), 127.9 (CH=), 128.1 (CH=), 128.5 (CH=), 137.4 (C).

4.2.4.7. Synthesis of 5-amino-1-*O*-benzyl-5-deoxy-2,3-*O*-isopropylidene-β-L-gulofuranose (8)

Synthesis of 1-O-benzyl-2,3-O-isopropylidene-6-O-trityl-α-D-mannofuranose. Treatment of diol 1-O-benzyl-2,3-O-isopropylidene-β-L-gulofuranose (8.2 g, 26.4 mmol) as described for compound **I6** gave the corresponding crude product, which was purified by SiO_2-column chromatography (ethyl acetate/petroleum ether: 1/4) to yield the product as a colorless oil. Yield: 10.4 g, 71%. ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.35 (s, 3H, CH_3), 1.49 (s, 3H, CH_3), 2.98 (d, 1H, OH, $^3J_{H-H}$ =6.8 Hz), 3.36 (dd, 1H, H-6, $^2J_{H-H}$ =9.6 Hz, $^3J_{H-H}$ =4.4 Hz), 3.50 (dd, 1H, H-6, $^2J_{H-H}$ =9.6 Hz, $^3J_{H-H}$ =3.6 Hz), 4.13-4.16 (m, 2H, H-4, H-5), 4.43 (d, 1H, OCH_2, $^2J_{H-H}$ =9.6 Hz), 4.62 (d, 1H, OCH_2, $^2J_{H-H}$ =11.6 Hz), 4.67 (d, 1H, H-2, $^3J_{H-H}$ =6.4 Hz), 4.89 (dd, 1H, H-3, $^3J_{H-H}$ =6.0 Hz, $^3J_{H-H}$ =3.2 Hz), 5.10 (s, 1H, H-1), 7.26-7.36 (m, 14H, CH=), 7.51-7.53 (m, 6H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=24.6 (CH_3), 26.0 (CH_3), 65.0 (C-6), 68.9 (OCH_2), 69.4 (C-5), 79.1 (C-4), 80.5 (C-3), 85.0 (C2), 86.7 (C, OTr), 105.2 (C-1), 112.5 ($\underline{C}Me_2$), 127.1 (CH=), 127.9 (CH=), 128.2 (CH=), 128.5 (CH=), 128.7 (CH=), 137.2 (C), 143.9 (C).

Synthesis of 5-azide-1-O-benzyl-5-deoxy-2,3-O-isopropylidene-6-O-trityl-β-L-gulofuranose.[31] Pyridine (37.2 mmol, 3 mL) and trifluoromethanesulfonic anhydride (4.4 mL, 26.6 mmol) were added to a cooled solution (-25 °C) of 1-O-benzyl-2,3-O-isopropylidene-6-O-trityl-α-D-mannofuranose (10.5 g, 19.0 mmol) in dichloromethane (80 mL). The reaction mixture was allowed to reach room temperature and after stirring for 1 h, the mixture was diluted with dichloromethane, washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$ and concentrated. The resulting crude triflate was dissolved in dry DMF (50 mL) and NaN_3 was added (12.59 g, 133.0 mmol) at 0°C in the presence of 18-crown-6 ether (8.37 g). The reaction mixture was allowed to stir at room temperature for 2.5 h. Water was added to the reaction mixture and extracted with Et_2O (x3). The organic phase was dried over $MgSO_4$ and evaporated. The resulting crude was purified by SiO_2-column chromatography (ethyl acetate/petroleum ether: 1/8) to afford the product as a colorless oil. Yield: 7.85 g, 71%. ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.15 (s, 3H, CH_3), 1.39 (s, 3H, CH_3), 3.26 (dd, 1H, H-6, $^2J_{H-H}$=6.0 Hz, $^3J_{H-H}$=4.4 Hz), 3.58 (d, 1H, H-6, $^2J_{H-H}$=10.0 Hz), 3.82-3.84 (m, 1H, H-5), 4.28-4.30 (m, 1H, H-3), 4.35 (dd, 1H, H-4, $^3J_{H-H}$=9.2 Hz, $^3J_{H-H}$=3.6 Hz), 4.54 (d, 1H, OCH_2, $^2J_{H-H}$=11.6 Hz), 4.58 (d, 1H, H-2, $^3J_{H-H}$=8.8 Hz), 4.79 (d, 1H, OCH_2, $^2J_{H-H}$=11.6 Hz), 5.13 (s, 1H, H-1), 7.27-7.40 (m, 14H, CH=), 7.51-7.54 (m, 6H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=24.6 (CH_3), 26.0 (CH_3), 61.2 (C-5), 63.0 (C-6), 69.0 (OCH_2), 79.3 (C-3, C-4), 85.2 (C2), 87.1 (C, OTr), 105.2 (C-1), 112.5 ($\underline{C}Me_2$), 127.2 (CH=), 127.3 (CH=), 128.0 (CH=), 128.5 (CH=), 128.6 (CH=), 128.7 (CH=), 137.2 (C), 143.6 (C).

Synthesis of 5-azide-1-O-benzyl-5-deoxy-2,3-O-isopropylidene-β-L-gulofuranose.[31] $BF_3.Et_2O$ (44.5 mmol, 1.8 mL) and MeOH (4.8 mL) were added to a cooled solution (0°C) of the tritylated azido derivative 5-azide-1-*O*-benzyl-5-deoxy-2,3-*O*-isopropylidene-6-*O*-trityl-β-L-gulofuranose (4.7 mmol, 2.7 g) in dichloromethane (30 mL). The reaction mixture was allowed to stir for 1.5 h at room temperature and then dichloromethane was added. The mixture was washed with saturated aqueous $NaHCO_3$ (x2), dried over $MgSO_4$ and concentrated. The resulting crude was purified by SiO_2-column chromatography (ethyl acetate/petroleum ether: 1/4 → 1/1) to give the product as a yellowish oil. Yield: 2.63 g, 58%. ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.30 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 2.42 (bs, 1H, OH), 3.68-3.71 (bs, 1H, H-6), 3.80-3.85 (bs, 1H, H-6), 3.86-3.89 (m, 1H, H-5), 4.17 (dd, 1H, H-4, $^3J_{H-H}$=8.8 Hz, $^3J_{H-H}$=3.6 Hz), 4.52 (d, 1H, OCH_2, $^2J_{H-H}$=11.6 Hz), 4.67 (d, 1H, H-2, $^3J_{H-H}$=6.4 Hz), 4.71 (d, 1H, OCH_2, $^2J_{H-H}$=11.6 Hz), 4.72-4.74 (m, 1H, H-3), 5.13 (s, 1H, H-1), 7.34-7.37 (m, 5H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=24.7 (CH_3), 26.0 (CH_3), 62.1 (C-5), 63.3 (C-6), 69.0 (OCH_2), 79.5 (C-3), 80.0 (C-4), 85.3 (C2), 104.9 (C-1), 112.8 ($\underline{C}Me_2$), 127.9 (CH=), 128.2 (CH=), 128.5 (CH=), 137.0 (C).

*Synthesis of 5-amino-1-O-benzyl-5-deoxy-2,3-O-isopropylidene-β-L-gulofuranose (**8**).* Treatment of the azido-alcohol derivative (2.64 g, 7.84 mmol) 5-azide-1-*O*-benzyl-5-deoxy-2,3-*O*-isopropylidene-β-L-gulofuranose as previously described for **7** afforded the corresponding amino-alcohol as a white solid. Yield: 2.08 g, 86%. ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.29 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 2.17 (bs, 3H, OH, NH_2), 3.27-3.29 (m, 1H, H-5), 3.54 (dd, 1H, H-6, $^2J_{H-H}$=10.8 Hz, $^3J_{H-H}$=6.0 Hz), 3.67 (dd, 1H, H-6, $^2J_{H-H}$=10.8 Hz, $^3J_{H-H}$=4.4 Hz), 3.84 (dd, 1H, H-4, $^3J_{H-H}$=7.6 Hz, $^3J_{H-H}$=3.6 Hz), 4.50 (d, 1H, OCH_2, $^2J_{H-H}$=11.6 Hz), 4.63 (d, 1H, OCH_2, $^2J_{H-H}$=12.4 Hz), 4.65 (d, 1H, H-2, $^3J_{H-H}$=5.6 Hz), 4.72-4.73 (m, 1H, H-3), 5.09 (s, 1H, H-1), 7.29-

7.35 (m, 5H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=24.6 (CH_3), 26.0 (CH_3), 52.0 (C-5), 63.5 (C-6), 69.1 (OCH_2), 79.7 (C-3), 81.1 (C-4), 85.4 (C2), 105.0 (C-1), 112.5 ($\underline{C}Me_2$), 127.9 (CH=), 128.0 (CH=), 128.5 (CH=), 137.4 (C).

4.2.4.8. Typical procedure for the ATH of ketones

The desired ligand (0.0055 mmol), catalyst precursor ($[RuCl_2(p\text{-cymene})_2]_2$ or $[RhCl_2Cp^*_2]_2$) (0.0025 mmol), and LiCl (4.2 mg, 0.1 mmol) were treated under vacuum for 10 min. Under argon, substrate (1 mmol), propan-2-ol (2 mL) and THF (2.5 mmol) were sequentially added. The reaction was stirred for 15 min. The reaction was initiated by adding ^{t}BuOK (0.1M, 0.5 mL, 0.05 mmol) to the solution. After completion of the reaction the solution was filtered through a plug of silica and eluted with Et_2O, and the solvents were evaporated. The products were analyzed by GC (CP Chirasil DEX CB) or HPLC.[11d,13,16,25d,32]

4.2.4.9. Typical procedure for the tandem isomerization/ATH of ketones

The catalyst precursor $[RuCl_2(p\text{-cymene})_2]_2$ (6.2 mg, 0.01 mmol) and LiCl (4.4 mg, 0.10 mmol, 10 mol%) were treated under vacuum for 10 min. Dry THF (0.50 mL) and dry ethanol (0.9 mL) were added, followed by the corresponding ligand (0.011 mmol) and the resulting mixture was stirred for 15 min at 40^{o}C. The reaction was initiated by addition of a 1.0 M stock solution of K^{t}BuO in dry ethanol (0.30 mL, 0.30 mmol, 30 mol%). After 24 h at 40^{o}C, the solution was passed though a pad of silica with ethyl acetate as the eluent. The resulting solutions were analyzed by ^{1}H NMR spectroscopy. The resulting oily residue was purified by column chromatography. Enantiomeric excesses were measured by chiral GC (CP Chirasil DEX CB) or chiral HPLC.[27c,32a,33]

4.2.4.10. Typical procedure for the tandem α-alkylation/ATH of ketones

The catalyst precursor $[RuCl_2(p\text{-cymene})_2]_2$ (15.3 mg, 0.025 mmol), the corresponding ligand (0.055 mmol) and LiCl (21.2 mg, 0.50 mmol) were treated under vacuum for 10 min. Dry DMSO (1.6 mL), the corresponding alcohol (15.0 mmol), and substrate (5.0 mmol) were added. The mixture was allowed to stir for 10 min, thereafter KO^{t}Bu (280 mg, 2.5 mmol) was added. The reaction was allowed to stir at 65 °C for 30 min. Thereafter, the temperature in the bath was decreased to 40 °C, and the stirring was continued for additional 4.5 h. Brine (20 mL) was added, and the mixture was extracted with EtOAc (4x20 mL). The combined organic layers were dried with Na_2SO_4 and concentrated under reduced pressure. The resulting oily residue was purified by column chromatography. Enantiomeric excesses were measured by chiral HPLC.[28b]

4.2.5. Acknowledgements

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UNIVERSITAT ROVIRA I VIRGILI
SCREENING OF MODULAR AND READILY AVAILABLE LIGAND LIBRARIES FOR C-X (X=H, C, N AND O) BOND FORMING REACTIONS. THE USE OF DFT STUDIES FOR CATALYSTS OPTIMIZATION
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Chapter 5

Asymmetric allylic substitution reactions

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5. Asymmetric Pd-catalyzed allylic substitution

5.1. Background

Asymmetric Pd-catalyzed allylic substitution is one of the most popular catalyzed reactions in organic chemistry. A number of allylic substrates can react with a variety of carbon and heteroatom nucleophiles. In addition it usually shows high regio- and enantioselectivities.

As discussed in the introduction, heterodonor ligands (mainly phosphine/phosphinite-oxazoline ligands) have been the ligands of choice for this transformation. The electronic discrimination of the two allylic terminal carbon atoms due to the different *trans* influences of the donor groups directs the nucleophilic attack. More recently, we found that the presence of a flexible biaryl π-acceptor phosphite moiety in heterodonor ligands overcame the most common limitations of this process, such as low reaction rates and high substrate specificity.

Only few successful heterodonor ligands that incorporate more robust groups than oxazolines (e.g amine, pyridine, thioether) have been effective in this transformation and most of them are limited in terms of substrate and nucleophile scope. In this context, phosphine-thioether and, to a lesser extent, phosphinite-thioether ligands have shown their potential utility but it was not until 2014 that our group reported the first successful application of a phosphite-thioether ligand family in the Pd-allylic substitution. High yields and enantioselectivities were obtained in the addition of a variety of C-, N- and O-nucleophiles to several substrates. On the other hand, our group has also shown that phosphite-pyridine and phosphite-amine compounds are also efficient ligands for this transformation. However, further research must be done towards the search of new ligands that are easy to handle (solids and stable in air), prepared from simple available feedstocks and able to stereoselectively catalyze the allylic substitution of several nucleophiles to a wide range of substrates.

We therefore report in this chapter the use of new phosphite/phosphinite-thioether, phosphite-pyridine and phosphite-triazole ligands in Pd-allylic substitution reactions. Concretely, we report in section 5.2 the application of carbohydrate-derived phosphite-thioether/selenoether ligands (**L1**-**L23a-g**) previously described in section 3.2, in the Pd-allylic substitution of several mono- and disubstituted substrates using a wide range of C-, N- and O-nucleophiles. By correctly choosing the ligand components, we could achieve high enantioselectivities in a wide range of disubstituted substrates with different steric requirements (ee's up to 98%). In the next section (5.3), we expand the previous study of 2014 (see above) to other furanoside phosphite-thioether ligands (**L24**-**L40a**-**l**) and also the study of this family of ligands to other types of substrates and nucleophiles. By varying the ligand parameters, we achieved high enantioselectivities and activities in several hindered and unhindered substrates using a wide range of C-, N- and O-nucleophiles (ee's >99%). In this section we have also carried out DFT calculations and the synthesis and characterization of the Pd-π-allyl intermediates in order to explain the origin of enantioselectivity. In section 5.4 a readily accessible P,S-ligand family **L51**-**58a**-**g** described

in section 3.5 has been found to be very effective in the Pd-allylic substitution of a variety of C-, N- and O-nucleophiles to several substrates. High enantioselectivities (up to >99% ee) and high activities were obtained for both linear and cyclic substrates, which are comparable with the best ones reported in the literature. In addition the potential utility of the new P/S-catalytic system has been demonstrated by transforming the allylic substitution products into biologically active chiral carbocyclics using simple sequential transformations. Furthermore, these new phosphite-thioether ligands also performed well in the alternative environmentally friendly solvent propylene carbonate (PC). In section 5.5 we present the application of the carbohydrate-based phosphite-pyridine ligand family **L59**-**L60a**-**f** in the Pd-allylic substitution of several substrates. This ligand family has been previously described in section 3.6. We have been able to identify ligands that provided promising enantioselectivities in the Pd-catalyzed intermolecular allylic substitution of cyclic substrates (ee's up to 86%) and in the desymmetrization of mesocyclopent-2-ene-1,4-diol (ee's up to 94%). In the last section (5.6) we show the preliminary results in the Pd-allylic alkylation of benchmark linear and cyclic substrates using the new readily available phosphite-triazole ligand family (**L61**-**67a**-**c**) described in section 3.7.

5.2. Asymmetric Pd-catalyzed allylic substitution reactions using phosphite-thioether/selenoether ligands

Jèssica Margalef, Carlota Borràs, Sabina Alegre, Oscar Pàmies and Montserrat Diéguez in manuscript to be submitted

***Abstract**: A library of phosphite-thioether/selenoether ligands **L1**-**L23a**-**g** has been applied in the Pd-catalyzed allylic substitution reactions of several mono- and disubstituted substrates using a wide range of C-, N- and O-nucleophiles, among which are the little studied α-substituted malonates, β-diketones and benzyl alcohol. This ligand library combines the advantages of the thioether/selenoether moiety with those of the phosphite group. The extent to which the chiral information was transferred to the product can be tuned by correctly choosing the ligand components. Enantioselectivities were therefore high in a wide range of disubstituted substrates with different steric requirements using several C-, N- and O-nucleophiles.*

5.2.1. Introduction

The development of methods for enantioselective formation of carbon-carbon and carbon-heteroatom bonds is one of the key issues in organic synthesis. One of the most versatile and powerful method for achieving this is the asymmetric Pd-catalyzed allylic substitution reaction.[1] Most of the successful ligands reported to date for this process have been designed using two main strategies.[1] The first one consists in the use of C_2-symmetrical ligand scaffolds in order to restrict the number of diastereomeric transition states. The second strategy relies on the ability of the ligand to direct the approach to one of the allylic terminal atoms. This latter strategy can be achieved by means of introducing either a secondary ligand-nucleophile interaction to direct the nucleophile approach to one of the allylic terminal carbon atoms,[2] or an electronic differentiation to electronically discriminate between the two allylic terminal carbon atoms because of the different *trans* influences of the ligand's donor groups.[3] All these strategies have led to the discovery of several privileged ligands (i.e. DACH-phenyl Trost ligand, PHOX, etc.), albeit in most of them the asymmetric induction is highly dependent on the steric demands of the substrate. Thus, most of the privileged catalytic systems only afford high enantioselectivities for either hindered (i.e. PHOX-ligands) or unhindered substrates (i.e. DACH-phenyl Trost's ligands). Our group has showed that the introduction of a biaryl phosphite group in the ligand design can be of great importance to overcome this problem, since this moiety is flexible enough to accommodate the size of the catalyst's chiral pocket to the steric demands of the substrate.[1j,4]

Mixed phosphorus-oxazoline ligands have played a dominant role among heterodonor ligands in this process.[1] Heteredonor phosphorus-thioether ligands have scarcely been studied, although some of them have proved to be potentially useful for this transformation.[5] The minor role of thioether-based ligands in this process can be explained by the formation of mixtures of diastereomeric thioether complexes (because the S atom

becomes a stereogenic centre when coordinated to the metal) and the difficulty of controlling their interconversion in solution.[6] Nevertheless, if the ligand scaffold can control the S-coordination, this feature may be extremely beneficial because then the chirality moves closer to the metal. In this respect, we recently found that the furanoside backbone in phosphite-thioether ligands can control the thioether coordination to palladium and achieve therefore high enantiomeric excesses.[5g] Encouraged by this latter finding, in this chapter we report the application of phosphite-thioether/selenoether ligand library derived from L-(+)-tartaric acid and D-(+)-mannitol (**L1**-**L23a**-**g**; Figure 5.2.1). The modular ligand design allowed us to systematically investigate the effect of varying: (a) the electronic and steric properties of the thioether group (ligands **L1**-**L7**); (b) the substituents and the introduction of a new stereogenic centre in the alkyl backbone chain next to the phosphite moiety (ligands **L1**, **L7**, **L8**-**L9** and **L11**-**L18**); (c) the substituents and the introduction of a new stereogenic centre in the alkyl backbone chain next to the thioether moiety (ligands **L1**, **L2**, **L10** and **L19**); (d) the substituents and configurations in the biaryl phosphite moiety (**a**-**g**); and (e) the replacement of the thioether group by a selenoether moiety. By carefully selecting these elements, we achieved good activities and high enantioselectivities for both hindered and unhindered substrates using a wide range of C-, N- and O-nucleophiles.

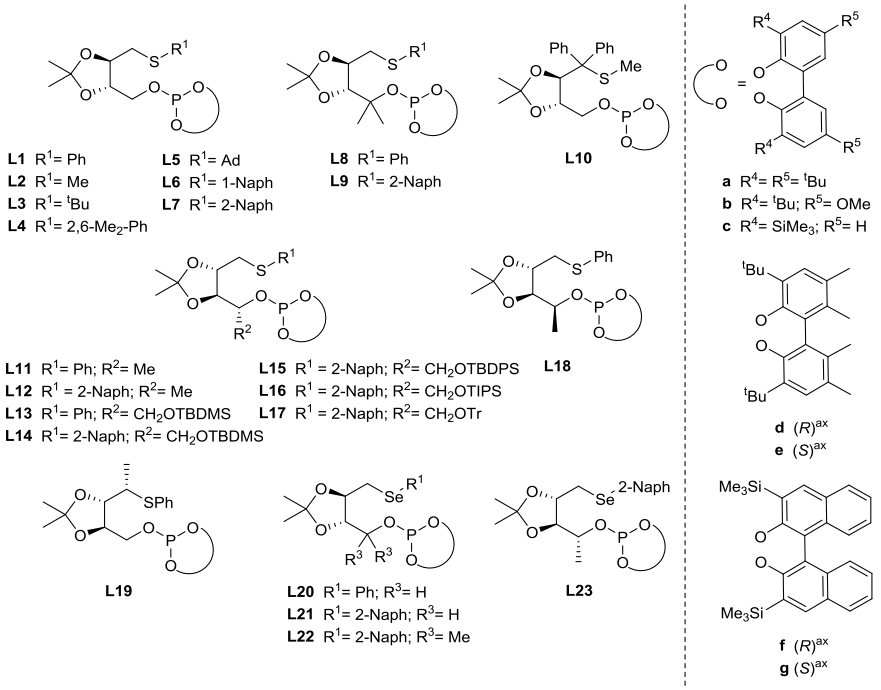
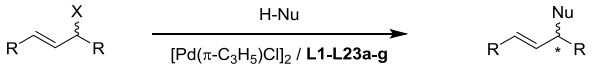


Figure 5.2.1. Phosphite-thioether/selenoether ligand library **L1**-**L23a**-**g**.

5.2.2. Results and discussion

5.2.2.1. Allylic substitution of disubstituted linear substrates

In this section, we report the use of the chiral phosphite-thioether/selenoether ligands **L1**-**L23a**-**g** in the Pd-catalyzed allylic substitution of linear substrates with different steric properties (equation 5.2.1): *rac*-1,3-diphenyl-3-acetoxyprop-1-ene **S1** (widely used as a model substrate), *rac*-(*E*)-ethyl-2,5-dimethyl-3-hex-4-enylcarbonate **S2** and *rac*-1,3-dimethyl-3-acetoxyprop-1-ene **S3**. In all the cases, the catalysts were generated in situ from π–allyl-palladium chloride dimer $[PdCl(\eta^3\text{-}C_3H_5)]_2$, the corresponding ligand and the corresponding nucleophile. Several C-, N- and O- nucleophiles were used under standard conditions.



(5.2.1)

S1 R= Ph; X= OAc
S2 R= ^{i}Pr; X= OCO_2Et
S3 R= Me; X= OAc

1 R= Ph; H-Nu= H-CH(COOMe)$_2$
2 R= Ph; H-Nu= H-CH(COOEt)$_2$
3 R= Ph; H-Nu= H-CH(COOBn)$_2$
4 R= Ph; H-Nu= H-CMe(COOMe)$_2$
5 R= Ph; H-Nu= H-CAllyl(COOMe)$_2$
6 R= Ph; H-Nu= H-CButenyll(COOMe)$_2$
7 R= Ph; H-Nu= H-CPentenyl(COOMe)$_2$
8 R= Ph; H-Nu= H-CPropargyl(COOMe)$_2$
9 R= Ph; H-Nu= H-CH(COMe)$_2$
10 R= Ph; H-Nu= H-NHCH$_2$Ph
11 R= Ph; H-Nu= H-OCH$_2$Ph
12 R= Ph; H-Nu= H-OCH$_2$(4-Me-C$_6$H$_4$)
13 R= Ph; H-Nu= H-OCH$_2$(4-CF$_3$-C$_6$H$_4$)
14 R= ^{i}Pr; H-Nu= H-CH(COOMe)$_2$
15 R= Me; H-Nu= H-CH(COOMe)$_2$
16 R= Me; H-Nu= H-CH(COOBn)$_2$
17 R= Me; H-Nu= H-CMe(COOMe)$_2$
18 R= Me; H-Nu= H-CAllyl(COOMe)$_2$
19 R= Me; H-Nu= H-CPropargyl(COOMe)$_2$

*Allylic substitution of rac-1,3-diphenyl-3-acetoxyprop-1-ene (**S1**) using several nucleophiles*

In the first set of experiments, we used the palladium-catalyzed asymmetric substitution reactions of **S1** (Eq. 5.2.1, R = Ph), with dimethyl malonate as nucleophile, to study the potential of the phosphite-thioether/selenoether ligand library **L1**-**L23a**-**g**. **S1** was chosen as a model substrate because this reaction has been performed with a wide range of ligands, which enables the efficiency of the various ligand systems to be compared directly.[1] The results, which are summarized in Table 5.2.1, indicate that enantioselectivities are highly affected by a subtle balance of the thioether/selenoether substituent, the substituents/configurations at the alkyl backbone chain next to the phosphite and thioether/selenoether moieties as well as the configuration of the biaryl phosphite moiety. By correctly choosing the ligand parameters high enantioselectivities (up to 97% ee) could be therefore achieved.

The effect of the substituents and configuration of the biaryl phosphite moiety was mainly investigated using **L1a**-**g**. The results indicated that the substituents at the biaryl phosphite moiety have little impact on enantioselectivity and that the presence of chiral biaryl moieties is necessary to achieve high enantioselectivities. The latter indicates that the chiral ligand backbone is not able to control the tropoisomerism of the biphenyl phosphite moiety.

The results using ligands **L1**-**L7** indicate that enantioselectivity is affected by the thioether substituent. Thus, ligands **L1**, containing a phenyl thioether group led to higher enantioselectivities. (i.e. entry 4 vs 8, 10, 13, 15, 17 and 19).

Table 5.2.1. Selected results for the Pd-catalyzed allylic alkylation of **S1** with dimethyl malonate using the ligand library **L1**-**L23a**-**g**.[a]

Entry	Ligand	% Conv (h)[b]	% ee[c]	Entry	Ligand	% Conv (h)[b]	% ee[c]
1	**L1a**	100 (3)	18 (*S*)	26	**L10g**	100 (3)	45 (*S*)
2	**L1b**	100 (3)	17 (*S*)	27	**L11a**	100 (3)	70 (*S*)
3	**L1c**	100 (3)	17 (*S*)	28	**L11f**	100 (3)	35 (*R*)
4	**L1d**	100 (3)	34 (*R*)	29	**L11g**	100 (3)	92 (*S*)
5	**L1e**	100 (3)	37 (*S*)	30	**L12f**	100 (3)	39 (*R*)
6	**L1f**	100 (3)	38 (*R*)	31	**L12g**	100 (3)	94 (*S*)
7	**L1g**	100 (3)	39 (*S*)	32	**L13a**	100 (3)	72 (*S*)
8	**L2a**	100 (3)	4 (*S*)	33	**L14a**	100 (3)	76 (*S*)
9	**L3a**	92 (3)	17 (*R*)	34	**L14g**	100 (3)	92 (*S*)
10	**L3d**	96 (3)	23 (*R*)	35	**L15g**	100 (3)	92 (*S*)
11	**L3e**	100 (3)	12 (*S*)	36	**L16g**	100 (3)	93 (*S*)
12	**L4a**	100 (3)	11 (*R*)	37	**L17g**	100 (3)	97 (*S*)
13	**L4d**	100 (3)	27 (*R*)	38	**L18a**	100 (3)	13 (*R*)
14	**L4e**	100 (3)	14 (*S*)	39	**L18f**	100 (3)	41 (*S*)
15	**L5d**	100 (3)	25 (*R*)	40	**L18g**	100 (3)	46 (*R*)
16	**L5e**	100 (3)	0	41	**L19a**	100 (3)	9 (*S*)
17	**L6d**	100 (3)	22 (*R*)	42	**L19f**	100 (3)	50 (*R*)
18	**L6e**	100 (3)	4 (*R*)	43	**L19g**	100 (3)	24 (S)
19	**L7d**	100 (3)	14 (*R*)	44	**L20a**	100 (3)	7 (S)
20	**L7e**	100 (3)	4 (*R*)	45	**L20f**	100 (3)	13 (*R*)
21	**L8a**	100 (3)	40 (*R*)	46	**L20g**	100 (3)	18 (*S*)
22	**L8d**	100 (3)	80 (*R*)	47	**L22f**	100 (3)	81 (*R*)
23	**L8e**	100 (3)	10 (*R*)	48	**L22g**	100 (3)	4 (*S*)
24	**L9a**	100 (3)	58 (*R*)	49	**L23f**	100 (3)	2 (*R*)
25	**L10f**	100 (3)	31 (*R*)	50	**L23g**	100 (3)	90 (*S*)

[a] 0.5 mol% $[PdCl(\eta^3\text{-}C_3H_5)]_2$, ligand (0.011 mmol), **S1** (1 mmol), CH_2Cl_2 (2 mL), BSA (3 eq), dimethyl malonate (3 eq), KOAc (pinch). [b] Conversion percentage determined by ^{1}H-NMR. [c] Enantiomeric excesses determined by HPLC on a Chiralcel-OJ column. Absolute configuration drawn in parentheses.

The results using ligands **L8** and **L9** indicated that the presence of two methyl substituents attached to the carbon close to the phosphite moiety had a positive effect on enantioselectivity (Table 5.2.1; entries 22 and 23 vs 4 and 5). Similarly, the use of ligands **L10** and **L19**, with substituents attached to the carbon next to the thioether group, also had a positive effect on enantioselectivity (entries 25, 26 and 41-43). Nevertheless, the results using ligands **L11** and **L18** indicated that there is a cooperative effect between the configuration of the carbon adjacent to the phosphite group, the ligand backbone and the configuration of the biaryl phosphite group that results in a matched combination for ligands **L11g**, with an (*R*)-configuratation at the carbon adjacent to the phosphite group and an (*S*)-configuration at the biaryl phosphite moiety (92% ee; entry 29).

With ligands **L12**-**L17**, we studied the effect of different substituents attached to the carbon adjacent to the phosphite moiety. The results indicated that the highest enantioselectivity (up to 97% ee) was achieved using Pd-**L17g** catalytic system (entry 37).

Finally, comparing the results using phosphite-selenoether ligands **L20**-**L23** with their thioether counterparts indicate that the catalytic performance is hardly affected by the replacement of the sulphur by selenium (i.e. entry 29 vs 50).

We then went on to study the allylic substitution of **S1** using other C-, N-, and O-nucleophiles, among which are the more challenging functionalized malonates, β-diketones, and alkyl alcohols. The results are summarized in Figure 5.2.2. We were pleased to note that Pd/**L17g** is very tolerant to variation of the steric properties of the ester moiety and the substituents of the malonate nucleophiles. A broad range of malonates therefore provided products **2**-**8** in high yields and enantioselectivities, comparable to those obtained with dimetyl malonate (ee's up to 98%). Of particular interest are the high enantioselectivities achieved with allyl-, butenyl-, pentenyl- and propargyl-substituted malonates, whose products are key intermediates in the synthesis of more complex chiral products.[4e,5g,7] The addition of acetylacetone (compound **9**) also proceeded with similar high enantioselectivities (ee's up to 97%). Enantiocontrol was also excellent when N-nucleophiles such as benzylamine (compound **10**) were used.

Finally, we considered the allylic substitution of **S1** using several O-nucleophiles. The asymmetric Pd-catalyzed allylic etherification has recently attracted the attention of many researchers because the resulting chiral ethers and related derivatives are important intermediates in the synthesis of biologically active compounds.[8] Despite its importance, few successful examples exist and most of them use phenols as O-nucleophiles,[9] being aliphatic alcohols[10] much less studied. The application of Pd/**L17g** to several aliphatic alcohols provided the desired products (compounds **11**-**13**) in high yields and enantioselectivities, comparable to the best ones reported in the literature.

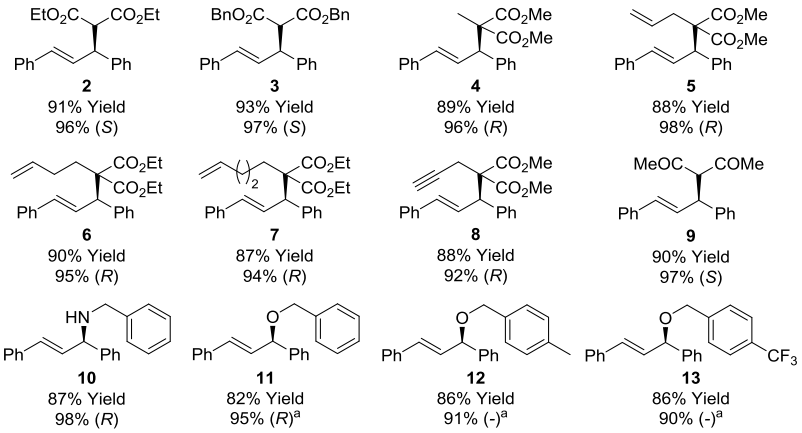


Figure 5.2.2. Allylic substitution of **S1** with C-, N- and O-nucleophiles using Pd-**L17g** catalytic system. Reactions were run at 23 °C with $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (0.5 mol %), CH_2Cl_2 as solvent, ligand (1.1 mol %), BSA (3 equiv), and KOAc. Full conversions were achieved after 4 h. [a] Reactions carried out using 2 mol % $[PdCl(\eta^3\text{-}C_3H_5)]_2$, 4 mol % ligand, and Cs_2CO_3 (3 equiv). Full conversions were achieved after 18 h.

*Allylic substitution of rac-(E)-ethyl-2,5-dimethyl-3-hex-4-enylcarbonate (**S2**) using dimethyl malonate as nucleophile*

We also screened the phosphite-thioether/selenoether ligand library **L1**-**L23a**-**g** in the allylic alkylation process of **S2** using dimethyl malonate as nucleophile (Eq 5.2.1, R = ^{i}Pr, X = OCO_2Et). This substrate is more sterically demanding than substrate **S1**, used previously.[1] If enantiomeric excesses are to be high, the ligand must create a slightly bigger chiral pocket (the chiral cavity in which the allyl is embedded) around the metal center in order to be able to accommodate the sterically demanding isopropyl substituents.[1] Due to the flexibility conferred by the biaryl phosphite moiety, we expected to obtain good enantioselectivities for this substrate, as well. Table 5.2.2 shows the most representative results.

In general, the trends were the same as for the allylic substitution of **S1**. Again, the alkylation product **14** was accessible in excellent enantioselectivity (ee's up to 99%) when catalyst precursor containing ligand **L17g** was used (Table 5.2.2, entry 37). As expected, the activities were lower than in the alkylation reaction of **S1**.[1]

Table 5.2.2. Selected results for the Pd-catalyzed allylic alkylation of **S2** with dimethyl malonate using the ligand library **L1**-**L23a**-**g**.[a]

Entry	Ligand	% Conv (h)[b]	% ee[c]	Entry	Ligand	% Conv (h)[b]	% ee[c]
1	**L1a**	100 (24)	21 (*S*)	26	**L10g**	100 (24)	49 (*S*)
2	**L1b**	100 (24)	22 (*S*)	27	**L11a**	100 (24)	74 (*S*)
3	**L1c**	100 (24)	20 (*S*)	28	**L11f**	100 (24)	38 (*R*)
4	**L1d**	100 (24)	44 (*R*)	29	**L11g**	100 (24)	95 (*S*)
5	**L1e**	100 (24)	20 (*S*)	30	**L12f**	100 (24)	43 (*R*)
6	**L1f**	100 (24)	46 (*R*)	31	**L12g**	100 (24)	94 (*S*)
7	**L1g**	100 (24)	25 (*S*)	32	**L13a**	100 (24)	78 (*S*)
8	**L2a**	100 (24)	7 (*S*)	33	**L14a**	100 (24)	77 (*S*)
9	**L3a**	99 (24)	19 (*R*)	34	**L14g**	100 (24)	95 (*S*)
10	**L3d**	100 (24)	26 (*R*)	35	**L15g**	100 (24)	93 (*S*)
11	**L3e**	100 (24)	17 (*S*)	36	**L16g**	100 (24)	97 (*S*)
12	**L4a**	100 (24)	15 (*R*)	37	**L17g**	100 (24)	99 (*S*)
13	**L4d**	100 (24)	34 (*R*)	38	**L18a**	100 (24)	18 (*R*)
14	**L4e**	100 (24)	19 (*S*)	39	**L18f**	100 (24)	44 (*S*)
15	**L5d**	100 (24)	31 (*R*)	40	**L18g**	100 (24)	53 (*R*)
16	**L5e**	100 (24)	2 (*S*)	41	**L19a**	100 (24)	11 (*S*)
17	**L6d**	100 (24)	29 (*R*)	42	**L19f**	100 (24)	54 (*R*)
18	**L6e**	100 (24)	9 (*R*)	43	**L19g**	100 (24)	31 (*S*)
19	**L7d**	100 (24)	19 (*R*)	44	**L20a**	100 (24)	12 (*S*)
20	**L7e**	100 (24)	7 (*R*)	45	**L20f**	100 (24)	18 (*R*)
21	**L8a**	100 (24)	42 (*R*)	46	**L20g**	100 (24)	23 (*S*)
22	**L8d**	100 (24)	83 (*R*)	47	**L22f**	100 (24)	82 (*R*)
23	**L8e**	100 (24)	12 (*R*)	48	**L22g**	100 (24)	11 (*S*)
24	**L9a**	100 (24)	63 (*R*)	49	**L23f**	100 (24)	8 (*R*)
25	**L10f**	100 (24)	37 (*R*)	50	**L23g**	100 (24)	92 (*S*)

[a] 0.5 mol% $[PdCl(\eta^3\text{-}C_3H_5)]_2$, ligand (0.011 mmol), **S2** (1 mmol), CH_2Cl_2 (2 mL), BSA (3 eq), dimethyl malonate (3 eq), KOAc (pinch). [b] Conversion percentage determined by ^{1}H-NMR. [c] Enantiomeric excesses determined by ^{1}H using $[Eu(hfc)_3]$. Absolute configuration drawn in parentheses.

*Allylic substitution of rac-1,3-dimethyl-3-acetoxyprop-1-ene (**S3**) using using several nucleophiles*

We also tested ligands **L1**-**L23a**-**g** in the allylic substitution of the linear substrate **S3** (Eq. 5.2.1, R = Me, X = OAc). Substrate **S3** is less sterically demanding than substrates **S1** and **S2**, used previously. There are therefore fewer successful catalyst systems for the Pd-catalyzed allylic substitution of this substrate than for the allylic substitution of hindered substrates such as **S1** and **S2**.[4b,c,,11] If enantiomeric excesses are to be high, the ligand must create a small chiral pocket around the metal center, mainly because of the presence of less sterically demanding methyl *syn* substituents.[1] Due to the flexibility conferred by the biaryl phosphite moiety in combination with the possibility of changing the parameters of the ligand, we expected to adequately modulate the chiral pocket in order to obtain good enantioselectivities for this substrate, as well.

The results, which are summarized in Table 5.2.3, indicated that we were able to fine-tune the ligands in order to obtain also high enantioselectivities in the alkylation of this demanding substrate (ee's up to 86%). The results indicate that although

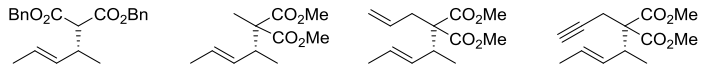
enantioselectivities are controlled by the same ligand parameters as for in the substitution of **S1**, their effect on enantioselectivity is different. Thus, for example and in contrast to the reduction of **S1**, ligands containing an (*R*)-biaryl phosphite moiety provided the highest enantioselectivities (i.e. entries 6 and 7). Thus, the highest enantioselectivity of the ligand series (ee's up to 86%) was achieved using ligand **L14f** (entry 34).

Table 5.2.3. Selected results for the Pd-catalyzed allylic alkylation of **S3** with dimethyl malonate using the ligand library **L1**-**L23a**-**g**.[a]

Entry	Ligand	% Conv (h)[b]	% ee[c]	Entry	Ligand	% Conv (h)[b]	% ee[c]
1	**L1a**	100 (6)	11 (*S*)	25	**L10f**	100 (6)	72 (*R*)
2	**L1b**	100 (6)	9 (*S*)	26	**L10g**	100 (6)	69 (*S*)
3	**L1c**	100 (6)	10 (*S*)	27	**L11a**	100 (6)	21 (*S*)
4	**L1d**	100 (6)	59 (*R*)	28	**L11f**	100 (6)	71 (*R*)
5	**L1e**	100 (6)	12 (*S*)	29	**L11g**	100 (6)	50 (*S*)
6	**L1f**	100 (6)	62 (*R*)	30	**L12f**	100 (6)	60 (*R*)
7	**L1g**	100 (6)	12 (*S*)	31	**L12g**	100 (6)	42 (*S*)
8	**L2a**	100 (6)	3 (*S*)	32	**L13a**	100 (6)	22 (*S*)
9	**L3a**	100 (6)	15 (*R*)	33	**L13f**	100 (6)	82 (*R*)
10	**L3d**	100 (6)	21 (*R*)	34	**L14f**	100 (6)	86 (*R*)
11	**L3e**	100 (6)	19 (*S*)	35	**L14g**	100 (6)	39 (*S*)
12	**L4a**	100 (6)	8 (*R*)	36	**L18a**	100 (6)	27 (*R*)
13	**L4d**	100 (6)	22 (*R*)	37	**L18f**	100 (6)	48 (*R*)
14	**L4e**	100 (6)	15 (*S*)	38	**L18g**	100 (6)	29 (*S*)
15	**L5d**	100 (6)	20 (*R*)	39	**L19a**	100 (6)	6 (*R*)
16	**L5e**	100 (6)	10 (*S*)	40	**L19f**	100 (6)	72 (*R*)
17	**L6d**	100 (6)	24 (*R*)	41	**L19g**	100 (6)	64 (*S*)
18	**L6e**	100 (6)	7 (*R*)	42	**L20a**	100 (6)	12 (*S*)
19	**L7d**	100 (6)	40 (*R*)	43	**L20f**	100 (6)	48 (*R*)
20	**L7e**	100 (6)	8 (*R*)	44	**L20g**	100 (6)	9 (*S*)
21	**L8a**	100 (6)	8 (*R*)	45	**L22f**	100 (6)	59 (*R*)
22	**L8d**	100 (6)	64 (*R*)	46	**L22g**	100 (6)	39 (*S*)
23	**L8e**	100 (6)	29 (*R*)	47	**L23f**	100 (6)	49 (*R*)
24	**L9a**	100 (6)	13 (*R*)	48	**L23g**	100 (6)	15 (*S*)

[a] 0.5 mol% $[PdCl(\eta^3\text{-}C_3H_5)]_2$, ligand (0.011 mmol), **S1** (1 mmol), CH_2Cl_2 (2 mL), BSA (3 eq), dimethyl malonate (3 eq), KOAc (pinch). [b] Conversion percentage determined by ^{1}H-NMR. [c] Enantiomeric excesses determined by GC. Absolute configuration drawn in parentheses.

We next studied the allylic substitution of **S3** using several carbon nucleophiles. The most notable results are shown in Figure 5.2.3. Again, the catalyst precursor containing ligand **L14f** provided the best enantioselectivities (ee's ranging from 82% to 86%). In all cases, enantioselectivities were similar to those obtained using dimethyl malonate.



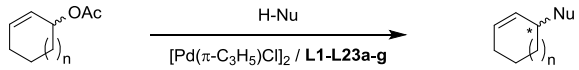
16 88% Yield 85% (*R*) | **17** 86% Yield 84% (*R*) | **18** 90% Yield 86% (*R*) | **19** 84% Yield 82% (*R*)

Figure 5.2.3. Allylic substitution of **S3** with several C-nucleophiles using Pd-**L14f** catalytic system. Reactions were run at 23 °C with $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (0.5 mol %), CH_2Cl_2 as solvent, ligand (1.1 mol %), BSA (3 equiv), and KOAc. Full conversions were achieved after 4 h.

5.2.2.2. Allylic substitution of disubstituted cyclic substrates

As for the unhindered linear substrate **S3**, enantioselectivity in cyclic substrates is difficult to control, mainly because of the presence of less sterically *anti* substituents. These *anti* substituents are thought to play a crucial role in the enantioselection observed with cyclic substrates in the corresponding Pd-allyl intermediates.

In this section, we report the use of the chiral phosphite-thioether/selenoether ligands **L1**-**L23a**-**g** in the Pd-catalyzed allylic substitution of cyclic substrates with different ring sizes (equation 5.2.2): *rac*-3-acetoxycyclohexene (**S4**) (which is widely used as a model substrate), *rac*-3-acetoxycyclopentene (**S5**) and *rac*-3-acetoxycycloheptene (**S6**). In all the cases, the catalysts were generated in situ from π–allyl-palladium chloride dimer $[PdCl(\eta^3\text{-}C_3H_5)]_2$, the corresponding ligands and nucleophiles. Several C-nucleophiles were used under standard conditions.



(5.2.2)

S4 n= 1
S5 n= 0
S6 n= 2

20 n= 1; H-Nu= H-CH(COOMe)$_2$
21 n= 1; H-Nu= H-CMe(COOMe)$_2$
22 n= 1; H-Nu= H-CAllyl(COOMe)$_2$
23 n= 1; H-Nu= H-CPropargyl(COOMe)$_2$
24 n= 1; H-Nu= H-CH(COMe)$_2$
25 n= 0; H-Nu= H-CH(COOMe)$_2$
26 n= 0; H-Nu= H-CPropargyl(COOMe)$_2$
27 n= 2; H-Nu= H-CH(COOMe)$_2$
28 n= 2; H-Nu= H-CPropargyl(COOMe)$_2$

*Allylic substitution of rac-3-acetoxycyclohexene (**S4**) using several C-nucleophiles*

We initially used the palladium-catalyzed asymmetric substitution reactions of **S4** (Eq. 5.2.2, n= 1), with dimethyl malonate as nucleophile, to study the potential of the phosphite-thioether/selenoether ligand library **L1-L23a-g**. **S4** was chosen as a model substrate because this reaction has been performed with a wide range of ligands, which enables the efficiency of the various ligand systems to be compared directly.[1] The results, which are summarized in Table 5.2.4, indicate that enantioselectivities are highly affected by a subtle balance of the thioether/selenoether substituent, the substituents/configurations at the alkyl backbone chain next to the phosphite a thioether/selenoether moieties as well as the configuration of the biaryl phosphite moiety. By correctly choosing the ligand parameters we could therefore obtain both enantiomers of the alkylated product in good enantioselectivities (up to 89% ee).

The effect of the substituents and configuration of the biaryl phosphite moiety was mainly investigated using **L1a**-**g**. In contrast to the alkylation of linear disubstituted substrates **S1**-**S3**, enantioselectivities are better when bulky trimethylsilyl substituents are

present at the *ortho* positions of the biaryl phosphite moiety. (i.e. entry 3 vs 1-2). The results also indicated that the sense of enantioselectivity is mainly controlled by the configuration of the biaryl phosphite group. Thus, while the use of ligands containing (*R*)-biaryl phosphite groups (**d** and **f**) provide (*R*)-**20**, (*S*)-**20** is achieved when using ligands with (*S*)-biaryl phosphite moieties (**e** and **g**).

The results using ligands **L1**-**L7** again indicate that the highest enantioselectivity is achieved with ligands containing a phenyl thioether moiety (ligands **L1**; entry 4 vs 8, 10, 13, 15, 17 and 19).

In contrast to linear substrates, the presence of two methyl substituents attached to the carbon close to the phosphite moiety (ligands **L8** and **L9**) didn't show much improvement on enantioselectivity (Table 5.2.4; entries 22 and 23 vs 4 and 5). Similarly, the use of ligands **L10** and **L19**, with substituents attached to the carbon next to the thioether group, didn't improved the enantioselectivities achieved (entries 25, 26 and 41-43). As for **S1**-**S3**, the results using ligands **L11** and **L18** indicated that there is a cooperative effect between the configuration of the carbon adjacent to the phosphite group, the ligand backbone and the configuration of the biaryl phosphite group. However, this cooperative effect results in a matched combination for ligands **L11g** and ligands **L18f** (ee's up to 85%; entries 29 and 40 vs 28 and 41). So, in contrast to **S1**-**S3**, this matched combination provides access to both enantiomers of alkylated product **20** in high ee's.

The results using ligands **L12**-**L17** indicated that enantioselectivities could be further improved to up to 89% ee by introducing bulkier groups attached to the carbon adjacent to the phosphite moiety. The highest enantioselectivities were achieved using ligands **L16g** and **L17g** (entries 37 and 38).

Finally, as observed for **S1**, comparison between the results achieved using phosphite-selenoether ligands **L20**-**L23** with their thioether counterparts indicate that the catalytic performance is hardly affected by the replacement of the sulphur by selenium (i.e. entry 28 vs 46).

Table 5.2.4. Selected results for the Pd-catalyzed allylic alkylation of **S4** with dimethyl malonate using the ligand library **L1**-**L23a**-**g**.[a]

Entry	Ligand	% Conv (h)[b]	% ee[c]	Entry	Ligand	% Conv (h)[b]	% ee[c]
1	**L1a**	100 (6)	9 (*S*)	27	**L11a**	100 (6)	24 (*S*)
2	**L1b**	100 (6)	9 (*S*)	28	**L11f**	100 (6)	72 (*R*)
3	**L1c**	100 (6)	14 (*S*)	29	**L11g**	100 (6)	82 (*S*)
4	**L1d**	100 (6)	55 (*R*)	30	**L12f**	100 (6)	75 (*R*)
5	**L1e**	100 (6)	66 (*S*)	31	**L12g**	100 (6)	87 (*S*)
6	**L1f**	100 (6)	80 (*R*)	32	**L13a**	100 (6)	23 (*S*)
7	**L1g**	100 (6)	77 (*S*)	33	**L13f**	100 (6)	82 (*R*)
8	**L2a**	100 (6)	3 (*S*)	34	**L14a**	100 (6)	37 (*S*)
9	**L3a**	100 (6)	11 (*S*)	35	**L14g**	100 (6)	82 (*S*)
10	**L3d**	100 (6)	22 (*R*)	36	**L15g**	100 (6)	87 (*S*)
11	**L3e**	100 (6)	14 (*S*)	37	**L16g**	100 (6)	89 (*S*)
12	**L4a**	100 (6)	8 (*S*)	38	**L17g**	100 (6)	89 (*S*)
13	**L4d**	100 (6)	42 (*R*)	39	**L18a**	100 (6)	52 (*R*)
14	**L4e**	100 (6)	25 (*S*)	40	**L18f**	100 (6)	85 (*R*)
15	**L5d**	100 (6)	24 (*R*)	41	**L18g**	100 (6)	82 (*S*)
16	**L5e**	100 (6)	17 (*S*)	42	**L19a**	100 (6)	20 (*S*)
17	**L6d**	100 (6)	34 (*R*)	43	**L19f**	100 (6)	77 (*R*)
18	**L6e**	100 (6)	19 (*S*)	44	**L19g**	100 (6)	79 (*S*)
19	**L7d**	100 (6)	40 (*R*)	45	**L20a**	100 (6)	2 (*S*)
20	**L7e**	100 (6)	12 (*S*)	46	**L20f**	100 (6)	78 (*R*)
21	**L8a**	100 (6)	8 (*R*)	47	**L20g**	100 (6)	78 (*S*)
22	**L8d**	100 (6)	59 (*R*)	48	**L22f**	100 (6)	71 (*R*)
23	**L8e**	100 (6)	41 (*S*)	49	**L22g**	100 (6)	85 (*S*)
24	**L9a**	100 (6)	13 (*R*)	50	**L23f**	100 (6)	75 (*R*)
25	**L10f**	100 (6)	78 (*R*)	51	**L23g**	100 (6)	72 (*S*)
26	**L10g**	100 (6)	74 (*S*)				

[a] 0.5 mol% $[PdCl(\eta^3\text{-}C_3H_5)]_2$, ligand (0.011 mmol), **S1** (1 mmol), CH_2Cl_2 (2 mL), BSA (3 eq), dimethyl malonate (3 eq), KOAc (pinch). [b] Conversion percentage determined by ^{1}H-NMR. [c] Enantiomeric excesses determined by HPLC on a Chiralcel-OJ column. Absolute configuration drawn in parentheses.

We next studied the allylic substitution of **S4** using several carbon nucleophiles other than dimethyl malonate (Figure 5.2.4). We were pleased to note that Pd/**L16g** is very tolerant to variation to the substituents of the malonate nucleophiles. A broad range of malonates therefore provided products **21**-**23** in high yields and enantioselectivities, comparable to those obtained with dimetyl malonate (ee's up to 91%). Of particular interest are the high enantioselectivities achieved with allyl- and propargyl-substituted malonates, whose products are key intermediates in the synthesis of more complex chiral products.[4e,5g,] The addition of acetylacetone (compound **24**) also proceeded with similar high enantioselectivities (ee's up to 88%).

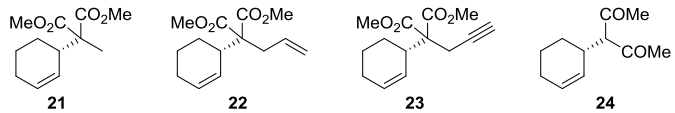
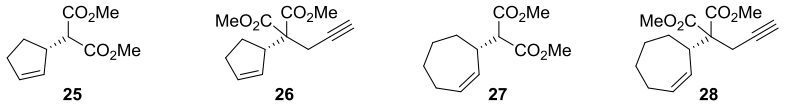


Figure 5.2.4. Allylic substitution of **S4** with several C-nucleophiles using Pd-**L16g** catalytic system. Reactions were run at 23 °C with $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (0.5 mol %), CH_2Cl_2 as solvent, ligand (1.1 mol %), BSA (3 equiv), and KOAc. Full conversions were achieved after 6 h.

*Allylic substitution of rac-3-acetoxycyclopentene (**S5**) and rac-3-acetoxycycloheptene (**S6**) using several C-nucleophiles*

The scope of the new catalytic systems Pd/**L1**-**L23a**-**g** was further studied by using other cyclic substrates than **S4**. We were pleased to see that the good performance of ligands **L16f** and **L18g** also extended to the allylic substitution of cyclic substrates with different ring sizes (*rac*-3-acetoxycyclopentene **S5** and *rac*-3-acetoxycycloheptene **S6**; Eq 5.2.2). Thus, both enantiomers of the alkylated products **25**-**28** could be achieved in enantioselectivities as high as 92% ee (Figure 5.2.5).

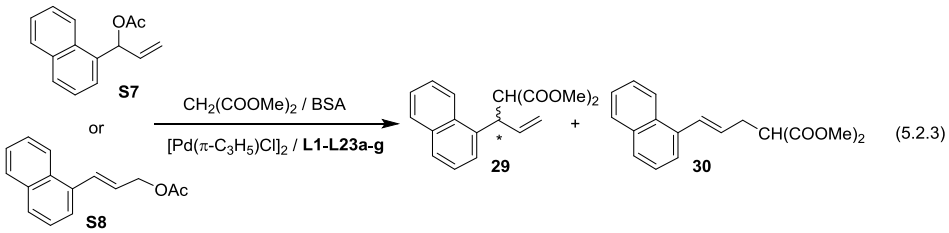


L16g: 84% Yield; 82% (-) **L16g**: 86% Yield; 80% (*S*) **L16g**: 89% Yield; 92% (*S*) **L16g**: 87% Yield; 91% (*S*)
L18f: 79% Yield; 80% (+) **L18f**: 84% Yield; 79% (*R*) **L18f**: 86% Yield; 91% (*R*) **L18f**: 91% Yield; 87% (*R*)

Figure 5.2.5. Selected results for the allylic substitution of **S5** and **S6** with several C-nucleophiles using Pd-**L1**-**L23a**-**g** catalytic system. Reactions were run at 23 °C with $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (0.5 mol %), CH_2Cl_2 as solvent, ligand (1.1 mol %), BSA (3 equiv), and KOAc. Full conversions were achieved after 6 h.

5.2.2.3. Allylic substitution of monosubstituted substrates

To further study the potential of these readily available ligands, we tested **L1**-**L23a**-**g** in the regio- and stereoselective allylic alkylation of 1-(1-naphthyl)allyl acetate (**S7**) and 1-(1-naphthyl)-3-acetoxyprop-1-ene (**S8**) with dimethyl malonate as nucleophile (Eq. 5.2.3). For these substrates, not only does the enantioselectivity of the process need to be controlled but regioselectivity is also a problem because a mixture of regioisomers can be obtained. Most Pd-catalysts developed to date favor the formation of achiral linear product **30** rather than the desired branched isomer **29**.[12] The development of highly regio- and enantioselective Pd-catalysts is therefore still important.[4b,g,11d,13]



(5.2.3)

The results, which are summarized in Table 5.2.5, indicated that regio- and enantioselectivity is highly affected the nature of thioether group, the presence of a stereogenic center at the carbon adjacent to the phosphite moiety, the configuration of the biaryl phosphite group and the introduction of a selenoether group instead of the thioether moiety. Therefore, the use of phosphite-thioether/selenoether provided high regioselectivity (up to 85%) towards the desired branched product **29**, but with moderate enantioselectivities (up to 54% ee). In addition both substrates provided similar regioselectivities, which excludes the possibility of memory effects.[14] In other words, the results indicated that the equilibration rates of isomeric allylic palladium intermediates are fast compared to the rate of nucleophilic attack.

The use of ligands **L1**-**L7** indicated that nature of the thioether substituent has an effect on enantioselectivity, but not on regioselectivity. The best catalytic performance was therefore achieved using aryl thioether groups (ee's up to 48% and regioselectivities up to 60% in favor of **29**).

The presence of substituents at the carbon close to the thioether group has almost no effect on catalytic performance; however, the presence of substituents at the carbon adjacent to the phosphite moiety has an important impact on regioselectivity. Using ligands **L11** and **L18** we have therefore found that there is a cooperative effect between the configuration of the stereocenter adjacent to the phosphite group and the configuration of the biaryl phosphite moiety. This results in a high regioselectivity (up to 80% in favor of **29**) for ligand **L11g** (entry 18), albeit the highest enantioselectivity (up to 54% ee) was achieved using ligand **L18f** (entry 24).

Table 5.2.5. Selected results for the Pd-catalyzed allylic alkylation of **S7** and **S8** with dimethyl malonate using the ligand library **L1**-**L23a**-**g**.[a]

		S7			**S8**		
Entry	Ligand	%Conv (h)[b]	% b/l[b]	% ee[c]	%Conv (h)[b]	% b/l[b]	% ee[c]
1	**L1a**	100 (2)	60/40	8 (*R*)	100 (2)	55/45	7 (*R*)
2	**L1f**	100 (2)	50/50	33 (*S*)	100 (2)	50/50	33 (*S*)
3	**L1g**	100 (2)	50/50	48 (*R*)	100 (2)	50/50	48 (*R*)
4	**L2a**	100 (2)	55/45	3 (*R*)	100 (2)	55/45	4 (*R*)
5	**L3d**	100 (2)	45/55	12 (*S*)	100 (2)	45/55	11 (*S*)
6	**L3e**	100 (2)	40/60	16 (*R*)	100 (2)	40/60	18 (*R*)
7	**L4d**	100 (2)	55/45	36 (*S*)	100 (2)	55/45	36 (*S*)
8	**L4e**	100 (2)	50/50	41 (*R*)	100 (2)	50/50	40 (*R*)
9	**L5e**	100 (2)	55/45	28 (*R*)	100 (2)	55/45	28 (*R*)
10	**L6e**	100 (2)	50/50	34 (*R*)	100 (2)	50/50	32 (*R*)
11	**L7e**	100 (2)	55/45	41 (*R*)	100 (2)	55/45	39 (*R*)
12	**L8d**	100 (2)	50/50	16 (*S*)	100 (2)	50/50	16 (*S*)
13	**L8e**	100 (2)	55/45	35 (*R*)	100 (2)	55/45	35 (*R*)
14	**L9a**	100 (2)	50/50	10 (*S*)	100 (2)	50/50	9 (*S*)
15	**L10f**	100 (2)	65/35	31 (*S*)	100 (2)	65/35	30 (*S*)
16	**L10g**	100 (2)	55/45	42 (*R*)	100 (2)	55/45	42 (*R*)
17	**L11f**	100 (2)	55/45	29 (*R*)	100 (2)	55/45	29 (*R*)
18	**L11g**	100 (2)	80/20	23 (*S*)	100 (2)	80/20	25 (*S*)
19	**L12f**	100 (2)	50/50	24 (*R*)	100 (2)	50/50	24 (*R*)
20	**L12g**	100 (2)	80/20	35 (*S*)	100 (2)	80/20	36 (*S*)
21	**L13a**	100 (2)	40/60	38 (*S*)	100 (2)	40/60	38 (*S*)
22	**L13f**	100 (2)	45/55	26 (*R*)	100 (2)	45/55	26 (*R*)
23	**L13g**	100 (2)	75/25	35 (*S*)	100 (2)	75/25	35 (*S*)
24	**L18f**	100 (2)	65/35	54 (*R*)	100 (2)	65/35	53 (*R*)
25	**L18g**	100 (2)	50/50	19 (*S*)	100 (2)	50/50	19 (*S*)
26	**L19f**	100 (2)	55/45	18 (*R*)	100 (2)	55/45	17 (*R*)
27	**L19g**	100 (2)	65/35	41 (*S*)	100 (2)	65/35	41 (*S*)
28	**L20f**	100 (2)	60/40	14 (*R*)	100 (2)	50/50	13 (*R*)
29	**L20g**	100 (2)	85/15	38 (*S*)	100 (2)	80/20	37 (*S*)
30	**L23f**	100 (2)	50/50	26 (*R*)	100 (2)	60/40	24 (*R*)
31	**L23g**	100 (2)	80/20	32 (*S*)	100 (2)	85/15	34 (*S*)

[a] 0.5 mol% $[PdCl(\eta^3\text{-}C_3H_5)]_2$, ligand (0.011 mmol), substrate (1 mmol), CH_2Cl_2 (2 mL), BSA (3 eq), dimethyl malonate (3 eq), KOAc (pinch). [b] Conversion percentage and branched-to-linear ratio determined by ^{1}H-NMR. [c] Enantiomeric excesses determined by HPLC on a Chiralcel-OJ column. Absolute configuration drawn in parentheses.

5.2.3. Conclusions

A library of phosphite-thioether/selenoether ligands **L1**-**L23a**-**g** has been applied in the Pd-catalyzed allylic substitution reactions of several mono- and disubstituted substrates using a wide range of C-, N- and O-nucleophiles, among which are the little studied α-substituted malonates, β-diketones and benzyl alcohol. This ligand library combines the advantages of the thioether/selenoether moiety with those of the phosphite group. The ligands are very stable, less sensitive to air and other oxidizing agents than phosphines and phosphinites, and easy to synthesize from readily available feedstocks. Moreover, we found that the extent to which the chiral information was transferred to the product can be

tuned by correctly choosing the ligand components. Enantioselectivities were therefore high in a wide range of disubstituted substrates using several C-, N- and O-nucleophiles.

5.2.4. Experimental section

5.2.4.1. General considerations

All reactions were carried out using standard Schlenk techniques under an argon atmosphere. Commercial chemicals were used as received. Solvents were dried by means of standard procedures and stored under argon. ^{1}H, $^{13}C\{^{1}H\}$ and $^{31}P\{^{1}H\}$ NMR spectra were recorded using a Varian Mercury-400 MHz spectrometer. Chemical shifts are relative to that of $SiMe_4$ (^{1}H and $^{13}C\{^{1}H\}$) as an internal standard. Racemic substrates **S1**-**S8** were prepared as previously reported.[15] The synthesis of ligands **L1**-**L23a**-**g** is described in section 3.2 (Chapter 3).

5.2.4.2. Typical procedure for the allylic alkylation of disubstituted linear (S1-S3) and cyclic (S4-S6) substrates

A degassed solution of $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (0.9 mg, 0.0025 mmol) and the corresponding phosphite-thioether/selenoether ligand (0.0055 mmol) in dichloromethane (0.5 mL) was stirred for 30 min. Subsequently, a solution of the corresponding substrate (0.5 mmol) in dichloromethane (1.5 mL), nucleophile (1.5 mmol), *N*,*O*-bis(trimethylsilyl)-acetamide (370 μL, 1.5 mmol) and KOAc (3mg, 003 mmol) was added. The reaction mixture was stirred at room temperature. After the desired reaction time the reaction mixture was diluted with Et_2O (5 mL) and saturated NH_4Cl (aq) (25 mL) was added. The mixture was extracted with Et_2O (3 x 10 mL) and the extract dried over $MgSO_4$. For compounds **1**-**13**, **16**, **18**-**19**, **21** and **22**, the solvent was removed, conversions were measured by ^{1}H NMR and enantiomeric excesses were determined by HPLC.[4g] For compounds **15**, **17**, **20, 23**-**24** and **26**-**28**, conversion and enantiomeric excesses were determined by GC.[4g] For compounds **14** and **25**, conversion were measured by ^{1}H NMR and ee's were determined by ^{1}H NMR using $[Eu(hfc)_3]$.[4g]

5.2.4.3. Typical procedure for the allylic alkylation of monosubstituted substrates (S7 and S8)

A degassed solution of $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (1.8 mg, 0.005 mmol) and the corresponding phosphite-thioether/selenoether ligand (0.011 mmol) in dichloromethane (0.5 mL) was stirred for 30 min at room temperature. Subsequently, a solution of substrate (0.5 mmol) in dichloromethane (1.5 mL), dimethyl malonate (171 μL, 1.5 mmol), *N*,*O*-bis(trimethylsilyl)-acetamide (370 μL, 1.5 mmol) and KOAc (3mg, 003 mmol) was added. After 2 hours at room temperature, the reaction mixture was diluted with Et_2O (5 mL) and saturated NH_4Cl (aq) (25 mL) was added. The mixture was extracted with Et_2O (3 x 10 mL) and the extract dried over $MgSO_4$. The solvent was removed, conversions and regioselectivities were measured by ^{1}H NMR and enantiomeric excesses were determined by HPLC.[4g]

5.2.4.4. Typical procedure for the allylic amination of disubstituted linear substrate S1

A degassed solution of $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (0.9 mg, 0.0025 mmol) and the corresponding phosphite-thioether/selenoether (0.0055 mmol) in dichloromethane (0.5 mL) was stirred for 30 min. Subsequently, a solution of the corresponding substrate (0.5 mmol) in dichloromethane (1.5 mL) and benzylamine (131 μL, 1.5 mmol) were added. The reaction mixture was stirred at room temperature. After the desired reaction time, the reaction mixture was diluted with Et_2O (5 mL) and saturated NH_4Cl (aq) (25 mL) was added. The mixture was extracted with Et_2O (3 x 10 mL) and the extract dried over $MgSO_4$. The solvent was removed, conversions were measured by ^1H NMR and enantiomeric excesses were determined by HPLC.[4b]

5.2.4.5. Typical procedure for the allylic etherification of disubstituted linear substrate S1

A degassed solution of $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (0.9 mg, 0.0025 mmol) and the corresponding phosphite-thioether/selenoether (0.0055 mmol) in dichloromethane (0.5 mL) was stirred for 30 min. Subsequently, a solution of the corresponding substrate (31.5 mg, 0.125 mmol) in dichloromethane (1.5 mL) was added. After 10 minutes, Cs_2CO_3 (122 mg, 0.375 mmol) and benzyl alcohol (40 μL, 0.375 mmol) were added. The reaction mixture was stirred at room temperature. After the desired reaction time, the reaction mixture was diluted with Et_2O (5 mL) and saturated NH_4Cl (aq) (25 mL) was added. The mixture was extracted with Et_2O (3 x 10 mL) and the extract dried over $MgSO_4$. The solvent was removed, conversions were measured by ^1H NMR and enantiomeric excesses were determined by HPLC.[4g]

5.2.5. Acknowledgements

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5.3. Asymmetric catalyzed allylic substitution using a Pd/P-S catalyst library with exceptional high substrate and nucleophile versatility. DFT and Pd-π-allyl key intermediates studies

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Abstract: *A large library of furanoside phosphite/phosphinite/phosphine-thioether-ligands* ***L24-L40a-I*** *has been applied in the Pd-catalyzed allylic substitution reactions of several substrate types using a wide range of nucleophiles. These ligands, which are prepared from inexpensive D-xylose, also incorporate the advantages of the heterodonor, the robustness of the thioether moiety and the extra control provided by the flexibility of the chiral pocket through the presence of a biaryl phosphite group and a modular sugar backbone. By selecting the ligand components we have been able to identify catalytic systems that can create new C-C, C-N and C-O bonds, in several substrate types (hindered and unhindered) using a wide range of nucleophiles in high yields and enantioselectivities (ee's up to >99%). Of particular note are the excellent enantioselectivities obtained in the etherification of linear and cyclic substrates, which represents the first example of successful etherification of both substrate types. The DFT computational study is in agreement with an early transition state. Further studies on the Pd-π-allyl intermediates provided a deep understanding of the effect of ligand structure in the origin of enantioselectivity.*

5.3.1. Introduction

Transition-metal based asymmetric catalysis is recognized as one of the most reliable strategies to access a wide range of optically pure compounds because of its high selectivity and atom-economic nature. In this respect, remarkable efforts have been dedicated to asymmetric Pd-catalyzed allylic substitution reaction as one of the most relevant method for the synthesis of C-C and C-heteroatom bonds.[1] Over the last decades a great number of ligands have been specially designed and successfully applied in this process. Most of these ligands are equipped with strong and weak donor heteroatom pairs (e.g. P-N, P-S, P-P', etc) which take advantage of the different *trans* influence of the two coordinative groups.[1] In this context, our group has contributed with an advanced generation of ligands. We have found that the presence of biaryl π-acceptor groups (phosphite or phosphoroamidite moieties) into the ligands has an extremely positive effect on substrate versatility and activity.[1j,2] Despite all the relevant advancements achieved in catalysts design still most of the ligands rarely tolerate a broad range of substrates and different ligands are needed for each type of substrate to optimize enantiopurity. Moreover, more efforts are required to enlarge the range of nucleophiles. Many important nucleophiles still provide inadequate results with known catalysts. The discovery of more efficient catalysts (good for a broad range of substrate and nucleophiles) constitutes a key issue for achieving a sustainable production of all sorts of C-C and C-heteroatom bonds suitable for synthesizing more

complex organic reactions in near future. Mixed P-oxazoline ligands have played a dominant role among heterodonor ligands. To a lesser extent, P-thioether ligands have also demonstrated their potential utility in Pd-catalyzed asymmetric allylic substitution.[3] The early pioneering works of the groups of Pregosin and Evans among others with the successful use of P-thioether ligands in Pd-allylic substitution and other relevant asymmetric processes made them a promising type of ligands for catalysis. Despite the design of new P-S became the focus of many research group only a few of them were successfully applied and these are limited in substrate scope (enantioselectivities are only high in the allylic substitution of hindered standard substrate *rac*-1,3-diphenyl-3-acetoxyprop-1-ene). The minor role of thioether-based ligands in this process can be found in the formation of mixtures of diastereomeric thioether complexes (because the S atom becomes a stereogenic center when coordinated to the metal) and the difficulty of controlling their interconversion in solution.[4] Nevertheless, if the ligand scaffold can control the S-coordination, this feature may be extremely beneficial because then the chirality moves closer to the metal. In this respect, recently we identified a simple ligand's backbones that can control the thioether coordination in Pd/thioether-phosphite catalysts. Xylofuranoside thioether-phosphite ligands have been successfully applied in the Pd-catalyzed allylic substitution reaction of several substrates types using several nucleophiles.[3g] Despite this success, the use of other phosphorus-thioether ligands in the same process remains unexplored, and a systematic study of the scope of P,S-ligands is still needed. No mechanistic studies have been made using this type of ligands in order to enable *a priori* prediction of the right ligand needed to obtain high enantioselectivity. Therefore, more research is also needed to discern the role of ligand parameters in the origin of enantioselectivity.

To fully investigate these possibilities, in this paper we expand the previous study of 2014[3g] to other furanoside phosphite-thioether ligands (Figure 5.3.1) and also the study of this family of ligands to other types of substrates and nucleophiles. To do this, we have taken advantage of the high modularity of these ligands and have synthesized and screened a library of 44 furanoside phosphite-thioether ligands with the same underlying structure (Figure 5.3.1). We have therefore extended the Pd-P,S catalyst library by adding two new ligands backbones (ligands **L37**-**L38** and **L39**-**L40**). We have also enlarged the catalyst library by adding furanoside ligands with new substituents in the thioether and biaryl phosphite group. Finally, we also compare the effectiveness of these phosphite-thioether ligands with their related phosphinite-thioethers (**L24**-**L40i**-**k**) and phosphine-thioethers (**L24**-**L40l**). By varying these ligand parameters, we achieved high enantioselectivities and activities in several hindered and unhindered substrates using a wide range of C-, N- and O-nucleophiles, including the less studied α-substituted malonates, β-diketones and alkyl alcohols. In this paper we have also carried out DFT calculations and the synthesis and characterization of the Pd-π-allyl intermediates in order to explain the origin of enantioselectivity.

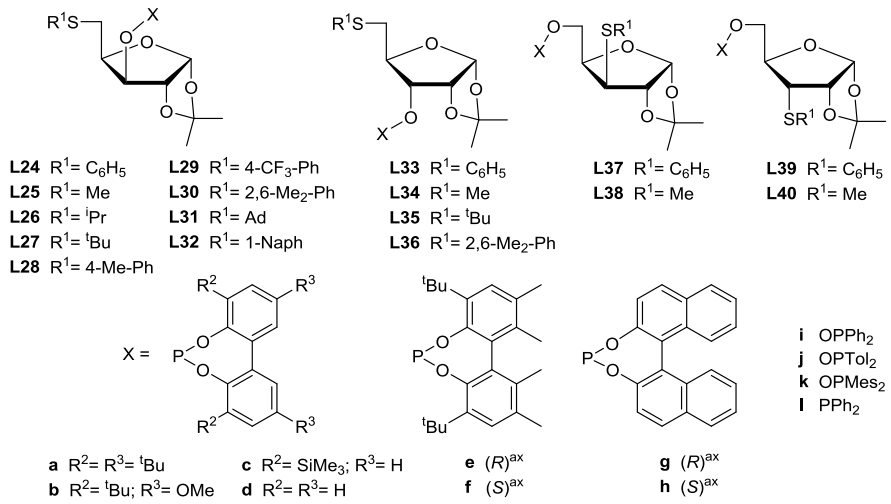


Figure 5.3.1. Phosphite/phosphinite/phosphine-thioether ligand library **L24**-**L40a**-**l**.

5.3.2. Results and discussion

5.3.2.1. Allylic substitution of disubstituted substrates S1-S3 using dimethyl malonate as nucleophile

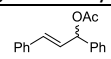
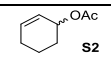
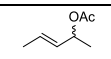
Bearing in mind that the stereochemical outcome of this reaction is highly dependent on the steric demands of the substrate, in this section, we report the use of the chiral ligand library **L24**-**L40a**-**l** in the Pd-catalyzed allylic substitution of linear substrates with different steric properties: *rac*-1,3-diphenyl-3-acetoxyprop-1-ene **S1** (widely used as a model substrate), *rac*-3-acetoxycyclohexene **S2** and *rac*-1,3-dimethyl-3-acetoxyprop-1-ene **S3**. In all the cases, the catalysts were generated in situ from π–allyl-palladium chloride dimer $[PdCl(\eta^3\text{-}C_3H_5)]_2$, the corresponding ligand and nucleophile. The results, which are shown in Table 5.3.1, indicate that enantioselectivities are highly affected by the position of the thioether group at either C-5 or C-3 of the furanoside backbone, the configuration of C-3, the thioether substituents, the substituents/configuration in the biaryl phosphite moiety (**a**-**h**) and the replacement of the phosphite moiety by a phosphinite (**i**-**k**) or a phosphine (**l**) group.

The results indicate a cooperative effect between the position of the thioether group and the configuration of carbon atom C-3 of the furanoside backbone (Table 5.3.1, entries 1, 12, 31, 34, 36, 39, 43 and 44). While for substrates **S1** and **S2**, the matched combination is therefore achieved with 5-deoxy-xylofuranoside derived ligands **L24**-**L32**, which have the thioether moiety attached to C-5 and an (*S*)-configuration of carbon atom C-3, for substrate **S3** the matched combination is achieved with 5-deoxy-ribofuranoside derived ligands **L33**-**L36**. It should be pointed out that ligands containing the thioether group attached to C-3 led to lower enantioselectivities than ligands with the thioether moiety attached to C-5. This suggests that the furanoside backbone controls better the thioether inversion when the thioether group is attached to C-5 (flexible primary carbon) rather to the sterogenic secondary carbon C-3.

The effects of the phosphite moiety were studied using 5-deoxy xylofuranoside ligands **L24a**-**h** (Table 5.3.1, entries 1-8). We found that bulky substituents need to be present in the *ortho* positions of the biaryl phosphite moieties if enantioselectivities are to be high (i.e. Table 5.3.1, entries 1-3 vs 4). However, the nature of the substituents at the *para* positions of the biaryl phosphite group has little effect on enantioselectivity (entries 1-3). The results also show a cooperative effect between the configuration of the bulky biphenyl moiety and the configuration of the ligand backbone on enantioselectivity. This led to a matched combination for ligand **L24f**, which contains an (*S*)-biaryl moiety (Table 5.3.1, entry 6). Nevertheless, the cooperative effect using 5-deoxy ribofuranoside ligands **L36e**-**f**, led to a matched combination for ligand **L36e**, containing an (*R*)-biaryl moiety (entry 37).

The effect of the phosphinite moiety was studied with ligands **L24i**-**k**, containing several phosphinite groups. The results indicated that enantioselectivities are hardly affected by the steric bulk of the phosphinite group (entries 9-11). Moreover, if we compare these results with those achieved with the phosphite (**L24a**-**h**) and phosphine (**L24l**; entry 12) counterparts, we can conclude that the best enantioselectivities are obtained with ligands containing a bulky (*S*)-biaryl phosphite moiety (ligand **L24f**).

Table 5.3.1. Selected results for the Pd-catalyzed allylic alkylation of **S1**-**S3** with dimethyl malonate using the ligand library **L24**-**L40a**-**l.**[a]

		 **S1**		 **S2**		 **S3**	
Entry	Ligand	% Conv (h)[b]	% ee[c]	% Conv (h)[b]	% ee[c]	% Conv (h)[b]	% ee[c]
1	**L24a**	100 (3)	58 (*S*)	100 (3)	78 (*S*)	100 (3)	57 (*S*)
2	**L24b**	100 (3)	63 (*S*)	100 (3)	77 (*S*)	100 (3)	55 (*S*)
3	**L24c**	100 (3)	54 (*S*)	100 (3)	78 (*S*)	100 (3)	56 (*S*)
4	**L24d**	100 (3)	2 (*R*)	100 (3)	3 (*S*)	100 (3)	4 (*R*)
5	**L24e**	100 (3)	20 (*R*)	100 (3)	63 (*S*)	100 (3)	19 (*S*)
6	**L24f**	100 (3)	95 (*S*)	100 (3)[d]	96 (*S*)	100 (3)	68 (*S*)
7	**L24g**	100 (3)	10 (*R*)	100 (3)	4 (*R*)	100 (3)	2 (*R*)
8	**L24h**	100 (3)	9 (*S*)	100 (3)[d]	5 (*S*)	100 (3)	4 (*S*)
9	**L24i**	100 (3)	63 (*S*)	100 (3)	4 (*R*)	100 (3)	7 (*R*)
10	**L24j**	100 (3)	63 (*S*)	100 (3)[d]	45 (*S*)	100 (3)	24 (*S*)
11	**L24k**	100 (3)	54 (*S*)	100 (3)	28 (*S*)	100 (3)	29 (*S*)
12	**L25a**	100 (3)	63 (*S*)	100 (3)	68 (*S*)	100 (3)	47 (*S*)
13	**L26a**	100 (3)	54 (*S*)	100 (3)	52 (*S*)	100 (3)	34 (*S*)
14	**L27a**	100 (3)	49 (*S*)	100 (3)	44 (*S*)	100 (3)	4 (*R*)
15	**L27i**	100 (3)	86 (*S*)	100 (3)	75 (*S*)	100 (3)	33 (*R*)
16	**L27j**	100 (3)	70 (*S*)	100 (3)	48 (*R*)	100 (3)	9 (*S*)
17	**L28a**	100 (3)	59 (*S*)	100 (3)	77 (*S*)	100 (3)	56 (*S*)
18	**L29a**	100 (3)[d]	57 (S)	100 (3)	75 (*S*)	100 (3)	54 (*S*)
19	**L30a**	100 (3)	69 (*S*)	100 (3)	63 (*S*)	100 (3)	63 (*S*)
20	**L30e**	100 (3)	52 (*R*)	100 (3)	63 (*S*)	100 (3)	16 (*S*)
21	**L30f**	100 (3)	98 (*S*)	100 (3)	92 (*S*)	100 (3)	72 (*S*)
22	**L30l**	100 (3)	15 (*S*)	100 (3)	5 (*R*)	100 (3)	4 (*R*)
23	**L31a**	100 (3)	78 (*S*)	100 (3)	48 (*S*)	100 (3)	7 (*S*)
24	**L31e**	100 (3)[d]	35 (*R*)	100 (3)	40 (*R*)	100 (3)	3 (*S*)
25	**L31f**	100 (3)	84 (*S*)	100 (3)	86 (*S*)	100 (3)	35 (*S*)
26	**L31i**	100 (3)	58 (*S*)	100 (3)	60 (*R*)	100 (3)	44 (*S*)
27	**L32a**	100 (3)	78 (*S*)	100 (3)	75(*S*)	100 (3)	68 (*S*)
28	**L32e**	100 (3)[d]	33 (*R*)	100 (3)	32 (*S*)	100 (3)	17 (*S*)
29	**L32f**	100 (3)	>99 (*S*)	100 (3)	96 (*S*)	100 (3)	76 (*S*)
30	**L32i**	100 (3)	60 (*S*)	100 (3)	27 (*S*)	100 (3)	55 (*S*)
31	**L33a**	100 (3)	53 (*R*)	100 (3)	41 (*R*)	100 (3)	39 (*S*)
32	**L33e**	100 (3)[d]	51 (*R*)	100 (3)	49 (*R*)	100 (3)	88 (*S*)
33	**L33f**	100 (3)	24 (*S*)	100 (3)	19 (*S*)	100 (3)	8 (*S*)
34	**L34a**	100 (3)	52 (*R*)	100 (3)	41 (*R*)	100 (3)	49 (*S*)
35	**L35a**	100 (30)[d]	13 (*S*)	100 (3)	9 (*R*)	100 (3)	12 (*R*)
36	**L36a**	100 (3)	60 (*R*)	100 (3)	66 (*S*)	100 (3)	48 (*S*)
37	**L36e**	100 (3)[d]	64 (*R*)	100 (3)	62 (*R*)	100 (3)	96 (*S*)
38	**L36f**	100 (3)	11 (*S*)	100 (3)	24 (*S*)	100 (3)	7 (*S*)
39	**L37a**	100 (3)[d]	12 (*S*)	100 (3)	24 (*S*)	100 (3)	18 (*S*)
40	**L37e**	100 (3)[d]	36 (*S*)	100 (3)	24 (*S*)	100 (3)	9 (*S*)
41	**L37f**	100 (3)	29 (*R*)	100 (3)	57 (*S*)	100 (3)	32 (*S*)
42	**L38a**	100 (3)	32 (*R*)	100 (3)	40 (*R*)	100 (3)	20 (*R*)
43	**L39a**	100 (3)[d]	9 (*R*)	100 (3)	4 (*S*)	100 (3)	8 (*S*)
44	**L40a**	100 (3)	4 (*R*)	100 (3)	3 (*S*)	100 (3)	3 (*S*)

[a] 0.5 mol% $[PdCl(\eta^3\text{-}C_3H_5)]_2$, ligand (0.011 mmol), **S1**-**S3** (1 mmol), CH_2Cl_2 (2 mL), BSA (3 eq), dimethyl malonate (3 eq), KOAc (pinch). [b] Conversion percentage determined by ^{1}H-NMR (for **S1**) or GC (for **S2** and **S3**). [c] Enantiomeric excesses determined by HPLC (for **S1**) and GC (for **S2**-**S3**). Absolute configuration drawn in parentheses. [d] Isolated yields >90% in all cases.

The effect of the thioether substituent was studied using ligands **L24**-**L32** (Table 5.3.1). Results showed that the presence of aryl thioether substituents is needed for high enantioselectivity. Thus, in general the highest enantioselectivities were achieved using a phenyl (ligands **L24**), 2,6-dimethylphenyl (ligands **L30**) or a 1-naphthyl (ligands **L32**) thioether groups.

In summary, alkylated products dimethyl 2-(1,3-diphenylallyl)malonate **1** and dimethyl 2-(cyclohex-2-en-1-yl)malonate **2** were obtained in high enantioselectivities (up to >99% ee) using 5-deoxy-xylofuranoside ligand **L32f** (entry 29) while for the alkylated product dimethyl 2-(pent-3-en-2-yl)malonate **3**, the highest ee's (up to 96%) were achieved using 5-deoxy-ribofuranoside ligand **L36e** (entry 37). These results compare favourably with the best ones reported in the literature.

5.3.2.2. Allylic substitution of disubstituted substrates S1-S10 using several nucleophiles. Scope and limitations.

With the best catalytic systems in hand (Pd-**L32f**, for hindered linear substrate **S1** and cyclic substrate **S2**; and Pd-**L36e**, for unhindered linear substrate **S3**), we next decided to study their scope by applying several C-, N- and O-nucleophiles as well as increasing the range of substrates (Figure 5.3.2).

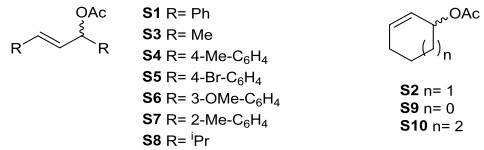


Figure 5.3.2. Substrates **S1**-**S10** used in this study.

We initially considered the allylic substitution of **S1** with Pd-**L32f** catalyst using a range C-, N- and O-nucleophiles, among which are the more challenging functionalized malonates, β-diketones and alkyl alcohols (Figure 5.3.3). Several malonates, including those substituted with allyl-, butenyl, pentenyl- and propargyl-groups, reacted cleanly to **S1** to afford products **4**-**10** in high yields and enantioselectivities (ee's ranging from 92% to 99%). The reaction also worked well when acetylacetone (compound **11**) and benzylamine (compound **12**) were used as nucleophiles (ee's up to >99%).

The excellent enantiocontrol also extends to the use of several aliphatic alcohols (compounds **13-17**, ee's up to >99%). The effective allylic substitution with this type of O-nucleophiles opens up a patch for the construction of aliphatic chiral ethers which are important for the synthesis of biologically active targets.[5] However, although the Pd-allylic etherification is currently studied by relevant research groups, few successful examples have been reported and most of them are phenols,[6] while aliphatic alcohols have been less studied.[7] Our results surpass the best results achieved using Pd-(*R*,*R*)-FerroNPS[7c] and Pd-CycloN2P2-Phos[7d] catalytic systems, specifically designed for this purpose.

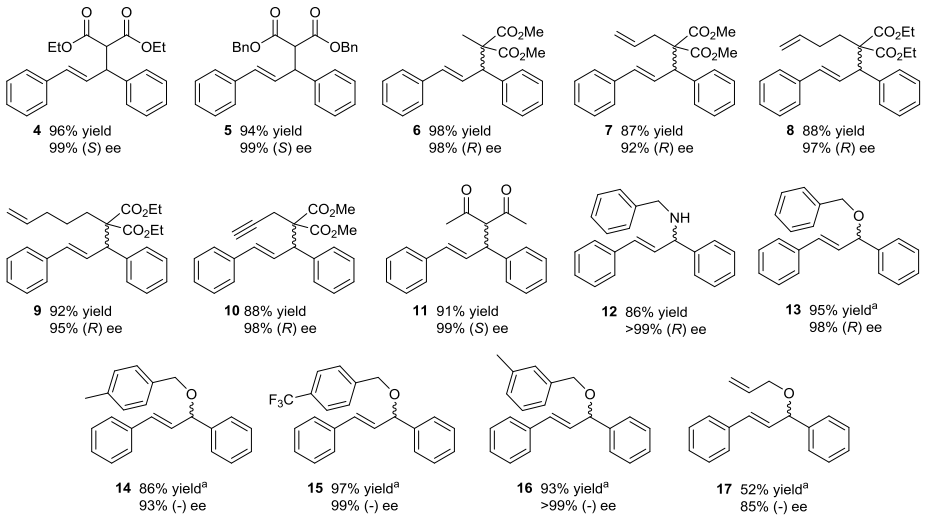


Figure 5.3.3. Allylic substitution of **S1** with C-, N- and O-nucleophiles using Pd-**L32f** catalytic system. Reactions were run at 23 °C with $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (0.5 mol %), CH_2Cl_2 as solvent, ligand (1.1 mol %), BSA (3 equiv), and KOAc. Full conversions were achieved after 4 h. [a] Reactions carried out using 2 mol % $[PdCl(\eta^3\text{-}C_3H_5)]_2$, 4 mol % ligand, and Cs_2CO_3 (3 equiv). Full conversions were achieved after 18 h.

The scope of these new catalytic systems was further studied by using other linear substrates **S3**-**S8** with different steric and electronic requirements (Figure 5.3.4). Advantageously, we found that the catalytic performance is unaffected by the introduction of *ortho*- and *metha*-substituents at the phenyl groups of the substrate, as well as by the introduction of electron withdrawing and electron donating groups. Also, the Pd-allylic alkylation of substrate **S8**, which is more sterically demanding and is usually substituted much less enantioselectively than **S1**, also proceeded with high enantioselectivity (>95% ee).

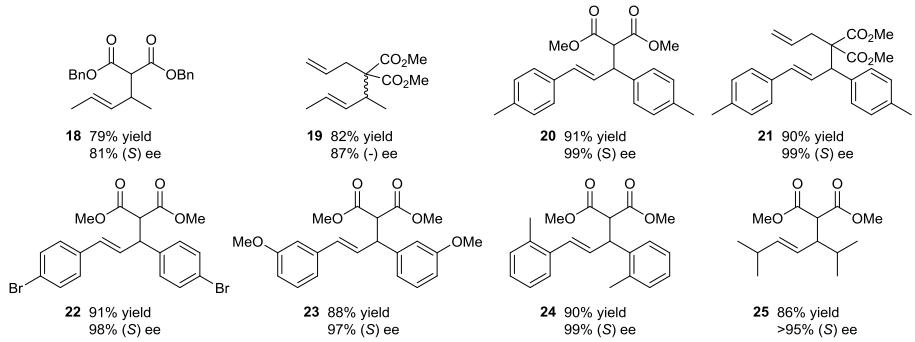


Figure 5.3.4. Allylic substitution of **S3**-**S8** with C-nucleophiles using Pd-**L36e** (compounds **18** and **19**) or Pd-**L32f** (compounds **20**-**25**) catalytic system. Reactions were run at 23 °C with $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (0.5 mol %), CH_2Cl_2 as solvent, ligand (1.1 mol %), BSA (3 equiv), and KOAc. Full conversions were achieved after 4 h.

Finally, we completed the scope's study by applying Pd-**L32f** in the allylic substitution of several cyclic substrates (**S2**, **S9** and **S10**) with a range of C, N- and O-nucleophiles (Figure 5.3.5). In all cases, enantioselectivities in the allylic alkylation of **S2** were as high as those obtained using dimethyl malonate (ee's up to 98%), except when dimethyl methylmalonate was used as nucleophile, which led to slightly lower enantioselectivity (compound **26**; 87% ee). Excellent ee's were therefore obtained using allyl- and propargyl-substituted nucleophiles (compounds **27** and **28**), acetylacetone (compound **29**) and benzylamine (compound **20**). High yields and enantioselectivities were also achieved in the etherification of **S2** (compound **32**). Pd-**L36f** is the first catalytic system that can etherificate both substrate types linear **S1** (Figure 5.3.3, compounds **13**-**17**) and cyclic **S2** with high ee's,[7a] and therefore, could be used for the stereoselective construction of an ether linkage adjacent to a stereogenic carbon center, which is of great importance for the synthesis of many biologically active targets.

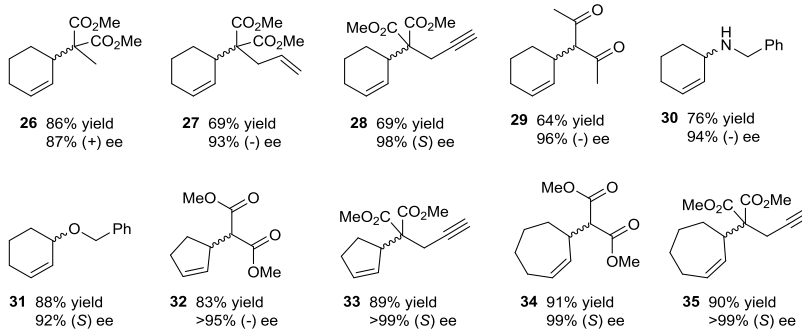


Figure 5.3.5. Allylic substitution of **S2**, **S9**-**S10** with C, N and O-nucleophiles using Pd-**L32f** catalytic system. Reactions were run at 23 °C with $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (0.5 mol %), CH_2Cl_2 as solvent, ligand (1.1 mol %), BSA (3 equiv), and KOAc. Full conversions were achieved after 6 h.

The good performance also extended to the allylic substitution of other cyclic substrates with different ring size. It should be noted that the enantiocontrol was excellent in both cases, but especially in the allylic substitution of *rac*-3-acetoxycyclopentene (compounds **32** and **33**), which is usually substituted less enantioselectively than the 6-membered cyclic substrate **S2**.

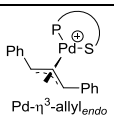
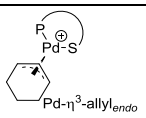
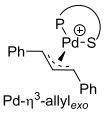
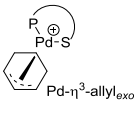
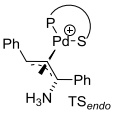
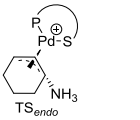
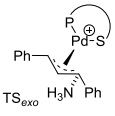
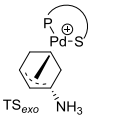
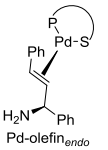
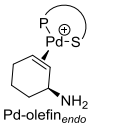
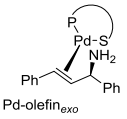
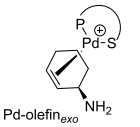
5.3.2.3. Origin of enantioselectivity

Initially, we performed a DFT computational study of the key intermediates and transition states involved in the enantiocontrol of the Pd-catalyzed allylic substitution of substrates **S1** and **S2**, using ligands **L32e** and **L32f** as models. The mechanistic studies found in the literature have shown that enantioselectivity is controlled in the effectively irreversible nucleophilic attack, but transition state (TS) for this step can be either early or late depending on the nature of the nucleophile, ligands, and reaction conditions. In an early transition state, the interactions leading to stereochemical differentiation can be understood from the structure of the Pd-allyl intermediate,[8] whereas the late transition state is more reminiscent of the Pd-alkene product complex.[9] For the early TS case, stereochemistry is governed by both the population of the Pd-η^3-allyl intermediates and

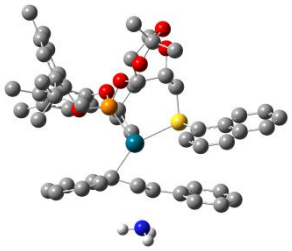
the relative electrophilicity of the allylic carbon atoms, with an allyl terminus *trans* to a phosphorus atom generally being more reactive than one *trans* to the thioether group. When the TS is late, the formation of the most stable Pd-olefin complex controls enantioselectivity. Previous experience has shown that ammonia can be used as a good model nucleophile,[10] avoiding the problems related to charge separation in conjunction with a continuum solvent model. Note that the use of ammonia as nucleophile instead of dimethyl malonate results in the inversion of the CIP descriptor in the 1,3-diphenylallyl case, due to the change in priority of the groups, although the sense of stereoselectivity is maintained.

We therefore calculated the relative stability of the two *syn-syn* η^3-allyl complexes (named Pd-η^3-allyl$_{endo}$ and the Pd-η^3-allyl$_{exo}$), the transition states TS$_{endo}$ and TS$_{exo}$, using NH_3 as nucleophile and the Pd-olefin intermediates (Pd-olefin$_{endo}$ and Pd-olefin$_{exo}$). Calculations were performed using the B3LYP functional,[11] the 6-31G*/LANL2DZ basis set,[12] and the PCM solvent model with parameters for CH_2Cl_2,[13] as implemented in Gaussian 09.[14] The energies were further refined by performing single point calculations at the 6-311+G** level,[15] and by dispersion correction with the DFT-D3 model.[16] Table 5.3.2 shows the relative energies of the most stable *endo*/*exo* isomers which are the result of varying between the two possible configurations at the sulphur center and rotating the 1-naphtyl thioether group on its own axis. The energy differences of the calculated TSs agree with the catalytic results and therefore they are in agreement with an early transition state (Figure 5.3.6). The structural elucidation of the Pd-allyl intermediates and the determination of their relative reactivity towards the nucleophile are therefore crucial to understand their catalytic behaviour.

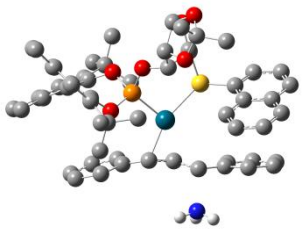
Table 5.3.2. Calculated energies for the *endo* and *exo* Pd-η^3-allyl intermediates, TSs and Pd-π-olefin complexes using **S1** and **S2** and NH_3 as nucleophile[a]

	L32e	**L32f**		**L32e**	**L32f**
 Pd-η^3-allyl$_{endo}$	5.3	8.9	 Pd-η^3-allyl$_{endo}$	9.2	0
 Pd-η^3-allyl$_{exo}$	2.3	0	 Pd-η^3-allyl$_{exo}$	11.9	10.5
 TS$_{endo}$	5	18.7	 TS$_{endo}$	7.6	0
 TS$_{exo}$	7.9	0	 TS$_{exo}$	10.3	5.7
 Pd-olefin$_{endo}$	0	14.7	 Pd-olefin$_{endo}$	6.8	0
 Pd-olefin$_{exo}$	10.1	2.3	 Pd-olefin$_{exo}$	8.2	3.6

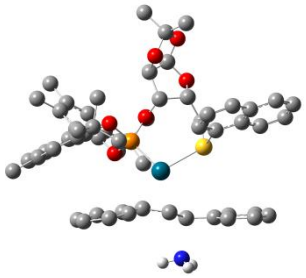
[a] Relative energies in kJ/mol.



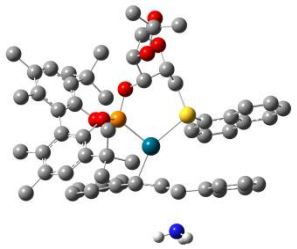
L36e/TS_{endo} (linear)



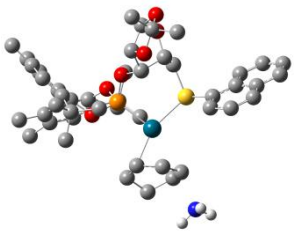
L36e/TS_{exo} (linear)



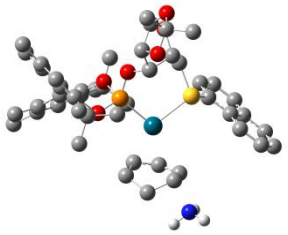
L36f/TS_{endo} (linear)



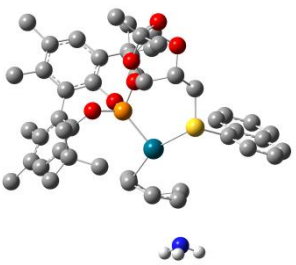
L36f/TS_{exo} (linear)



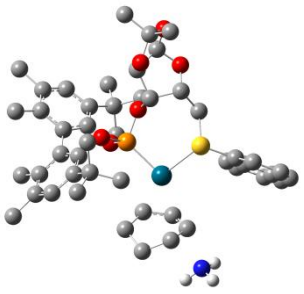
L36e/TS_{endo} (cyclic)



L36e/TS_{exo} (cyclic)



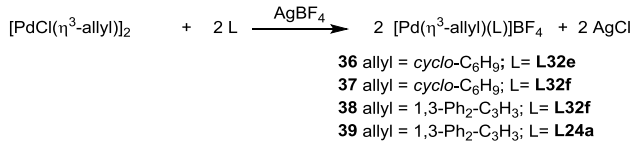
L36f/TS_{endo} (cyclic)



L36f/TS_{exo} (cyclic)

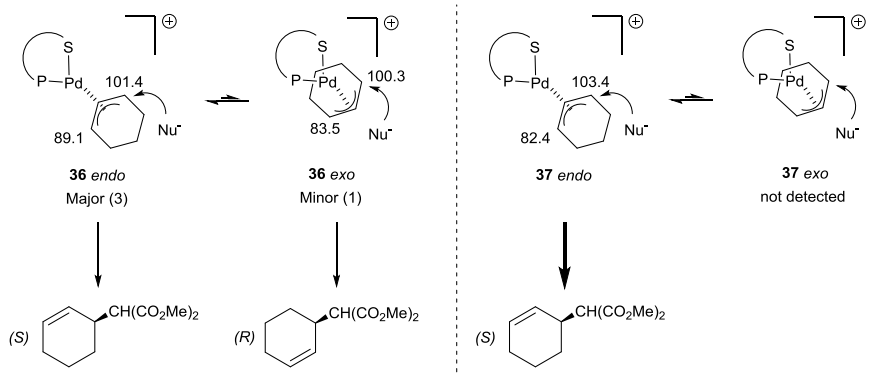
Figure 5.3.6. Calculated transition states using ligands **L36e** and **L36f**. Hydrogens of Pd-allyl complexes have been omitted for clarity.

To provide further insight into how ligand parameters affect catalytic performance, we therefore studied the Pd-π-allyl compounds **36**-**39** [Pd(η^3-allyl)(L)]BF_4 (L = **L24**-**L40a**-**l**). These ionic palladium complexes, which contain cyclohexenyl or 1,3-diphenyl allyl groups, were prepared using the previously reported method from the corresponding Pd-allyl dimer and the appropriate ligand in the presence of silver tetrafluoroborate (Scheme 5.3.1).[17] The complexes were characterized by ^1H, ^{13}C and ^{31}P NMR spectroscopy. The spectral assignments were based on information from ^1H-^1H, ^{31}P-^1H and ^{13}C-^1H correlation measurements in combination with ^1H-^1H NOESY experiments. Unfortunately, we were unable to obtain crystal of sufficient quality to perform X-ray diffraction measurements.



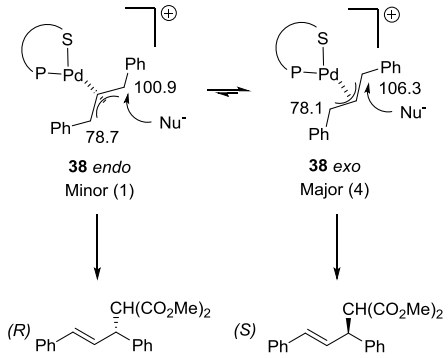
Scheme 5.3.1. Preparation of [Pd(η^3-allyl)(**L**)]BF_4 complexes **36**-**39**.

The VT-NMR study (30 °C to -80 °C) of Pd-1,3-cyclohexenyl allyl intermediates **36** and **39**, which respectively contains ligands **L32e** and **L32f**, showed a mixture of two isomers in equilibrium at a ratio of 3:2 and >20:1, respectively (Scheme 5.3.2). The major isomers were unambiguously assigned by NOE to Pd-η^3-*endo* isomers. The carbon NMR chemical shifts indicated that the most electrophilic allylic terminus carbon is *trans* to the phosphite moiety. For complexes **36**, the fact that the electrophilicities of the allylic terminal carbon atom *trans* to the phosphite are rather similar in both complexes ($\Delta\delta(^{13}C) \approx 1.1$ ppm) suggests that both isomers reacts at a similar rate. So, the enantioselectivity is mainly affected by the population of the *endo* and *exo* isomers. The much higher enantioselectivity obtained using Pd-**L32f** can be therefore attributed to the fact that only the *endo* isomer is detected.



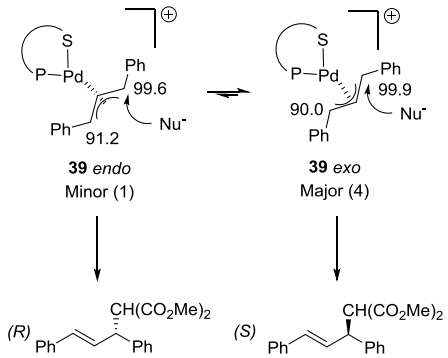
Scheme 5.3.2. Diastereoisomer Pd-allyl intermediates for **S2** with ligands **L32e** (isomers **36**) and **L32f** (isomers **37**) The relative amounts of each isomer are shown in parentheses. The chemical shifts (in ppm) of the allylic terminal carbons are also shown.

The VT-NMR study (30 °C to -80 °C) of Pd-1,3-diphenyl allyl intermediates **38**, which contains ligand **L32f**, showed a mixture of two isomers in equilibrium at a ratio of 1:4 (Scheme 5.3.3). Both isomers were unambiguously assigned by NMR to the two *syn*/*syn* Pd-η^3-*endo* and *exo* isomer. The carbon chemicals shifts indicate that the most electrophilic allylic terminal carbon is located *trans* to the phosphite moiety in the major isomer ($\Delta\delta(^{13}C)$ ≈ 5.4 ppm). The excellent enantioselectivities obtained for this catalytic system can be therefore explained by the fact that the major isomer is also the fast reacting one.



Scheme 5.3.3. Diastereoisomer Pd-allyl intermediates for **S1** with ligands **L32f** (isomers **38**). The relative amounts of each isomer are shown in parentheses. The chemical shifts (in ppm) of the allylic terminal carbons are also shown.

Finally, we also studied the Pd-1,3-diphenyl allyl intermediates **39** containing ligand **L24a** (Scheme 5.3.4) As for intermediate **38**, a mixture of two isomers in equilibrium at a ratio of 1:4, was observed. However, the electrophilicities of the allylic terminal carbon atom *trans* to the phosphite are rather similar in both complexes ($\Delta\delta(^{13}C)$ ≈ 0.3 ppm), which indicates that both species reacts at similar rate. This fact fully explains the lower enantioselectivities obtained with the Pd-**L24a** compared to the ones achieved with Pd-**L32f**.



Scheme 5.3.4. Diastereoisomer Pd-allyl intermediates for **S1** with ligands **L24a** (isomers **39**). The relative amounts of each isomer are shown in parentheses. The chemical shifts (in ppm) of the allylic terminal carbons are also shown.

5.3.3. Conclusions

A large library of furanoside phosphite/phosphinite/phosphine-thioether-ligands **L24**-**L40a**-**l** has been applied in the Pd-catalyzed allylic substitution reactions of several substrate types using a wide range of nucleophiles. These ligands, which are prepared from inexpensive D-xylose, also incorporate the advantages of the heterodonor, the robustness of the thioether moiety and the extra control provided by the flexibility of the chiral pocket through the presence of a biaryl phosphite group and a modular sugar backbone. The modular nature of this ligand library allowed us to investigate the effect of systematically varying the position of the thioether group at either C-5 or C-3 of the furanoside backbone and the effect of the configuration at C-3 of the furanoside backbone on catalytic performance. We also studied the effect of the substituents in the thioether group, the effect of the substituents and configurations in the biaryl phosphite moiety and replacing the phosphite moiety by a phosphinite group or a phosphine group. By selecting the ligand components we have been able to identify catalytic systems that can create new C-C, C-N and C-O bonds, in several substrate types (hindered and unhindered) using a wide range of nucleophiles in high yields and enantioselectivities (ee's up to >99%). Of particular note are the excellent enantioselectivities obtained in the etherification of linear and cyclic substrates, which represent the first example of successful etherification of both substrate types. So, the exceptional ligand family presented here competes very well with a few other ligand series that also provide high ee in several substrate types using a wide range of C-, N- and O-nucleophiles, among which are the little studied α-substituted malonates and alkyl alcohols.

A DFT computational study of the key intermediates and transition states involved in the enantiocontrol are in agreement with an early transition state. Further studies on the Pd-π-allyl intermediates provided a deep understanding of the effect of the ligand parameters on the origin of the enantioselectivity.

5.3.4. Experimental section

5.3.4.1. General considerations

All reactions were carried out using standard Schlenk techniques under an argon atmosphere. Commercial chemicals were used as received. Solvents were dried by means of standard procedures and stored under argon. ^{1}H, $^{13}C\{^{1}H\}$ and $^{31}P\{^{1}H\}$ NMR spectra were recorded using a Varian Mercury-400 MHz spectrometer. Chemical shifts are relative to that of $SiMe_4$ (^{1}H and $^{13}C\{^{1}H\}$) as an internal standard. Racemic substrates **S1**-**S10** were prepared as previously reported.[18] Ligands **L24**-**L40a**-**l** were prepared as previously described.[19]

5.3.4.2. Typical procedure for the allylic alkylation

A degassed solution of $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (0.9 mg, 0.0025 mmol) and the corresponding ligand (0.0055 mmol) in dichloromethane (0.5 mL) was stirred for 30 min. Subsequently, a solution of the corresponding substrate (0.5 mmol) in dichloromethane (1.5 mL), nucleophile (1.5 mmol), *N*,*O*-bis(trimethylsilyl)-acetamide (370 μL, 1.5 mmol) and KOAc (3mg, 003 mmol) was added. The reaction mixture was stirred at room temperature. After

the desired reaction time the reaction mixture was diluted with Et_2O (5 mL) and saturated NH_4Cl (aq) (25 mL) was added. The mixture was extracted with Et_2O (3 x 10 mL) and the extract dried over $MgSO_4$. For compounds **1**, **4**-**11**, **20**-**24**, **26**-**27**, the solvent was removed, conversions were measured by ^{1}H NMR and enantiomeric excesses were determined by HPLC.[2g] For compounds **2**-**3**, **18**-**19**, **28**-**29** and **33**-**35**, conversion and enantiomeric excesses were determined by GC.[2g] For compounds **25** and **32**, conversion were measured by ^{1}H NMR and ee's were determined by ^{1}H NMR using $[Eu(hfc)_3]$.[2g]

5.3.4.3. Typical procedure for the allylic amination

A degassed solution of $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (0.9 mg, 0.0025 mmol) and the corresponding ligand (0.0055 mmol) in dichloromethane (0.5 mL) was stirred for 30 min. Subsequently, a solution of the corresponding substrate (0.5 mmol) in dichloromethane (1.5 mL) and benzylamine (131 μL, 1.5 mmol) were added. The reaction mixture was stirred at room temperature. After the desired reaction time, the reaction mixture was diluted with Et_2O (5 mL) and saturated NH_4Cl (aq) (25 mL) was added. The mixture was extracted with Et_2O (3 x 10 mL) and the extract dried over $MgSO_4$. The solvent was removed, conversions were measured by ^{1}H NMR and enantiomeric excesses of compounds were determined by HPLC.[2b]

5.3.4.4. Typical procedure for the allylic etherification

A degassed solution of $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (0.9 mg, 0.0025 mmol) and the corresponding ligand (0.0055 mmol) in dichloromethane (0.5 mL) was stirred for 30 min. Subsequently, a solution of the corresponding substrate (31.5 mg, 0.125 mmol) in dichloromethane (1.5 mL) was added. After 10 minutes, Cs_2CO_3 (122 mg, 0.375 mmol) and benzyl alcohol (40 μL, 0.375 mmol) were added. The reaction mixture was stirred at room temperature. After the desired reaction time, the reaction mixture was diluted with Et_2O (5 mL) and saturated NH_4Cl (aq) (25 mL) was added. The mixture was extracted with Et_2O (3 x 10 mL) and the extract dried over $MgSO_4$. The solvent was removed, conversions were measured by ^{1}H NMR and enantiomeric excesses were determined by HPLC.[2g]

5.3.4.5. Computational details

Geometries of all transition states and intermediates were optimized using the Gaussian 09 program,[14] employing the B3LYP[11] density functional and the LANL2DZ[12d] basis set for iridium and the 6-31G*[12a-c] basis set for all other elements. Solvation correction was applied in the course of the optimizations using the PCM model with the default parameters for dichloromethane.[13] The complexes were treated with charge +1 and in the singlet state. No symmetry constraints were applied. Normal mode analysis of all transition states revealed a single imaginary mode corresponding to the expected nucleophilic attack of ammonia to one of the two allylic termini. The energies were further refined by performing single point calculations using the above mentioned parameters, with the exception that the 6-311+G**[15] basis set was used for all elements except for palladium, and by applying dispersion correction using the DFT-D3[16] model. All energies reported are Gibbs free energies at 298.15 K and calculated as $G_{reported} = G_{6\text{-}31G^*} + E_{6\text{-}311+G^{**}} - E_{6\text{-}31G^*} + E_{DFT\text{-}D3}$.

5.3.4.6. Typical procedure for preparation of [Pd(η³-allyl)(L)]BF_4 complexes 36-39

The corresponding ligand (0.05 mmol) and the complex [Pd(μ-Cl)(η3-1,3-allyl)]2 (0.025 mmol) were dissolved in CD_2Cl_2 (1.5 mL) at room temperature under argon. $AgBF_4$ (9.8 mg, 0.05 mmol) was added after 30 minutes and the mixture was stirred for 30 minutes. The mixture was then filtered over celite under argon and the resulting solutions were analyzed by NMR. After the NMR analysis, the complexes were precipitated as pale yellow solids by adding hexane.

[Pd(η³-1,3-cyclohexenylallyl)(L32e)]BF_4 (36). Isomer *endo* (60%): ^{31}P NMR (161 MHz, CD_2Cl_2) δ: 139.5 (s). ^{1}H NMR (400 MHz, CD_2Cl_2) δ: 0.87-1.09 (m, 2H, CH_2), 1.20 (s, 3H, CH_3), 1.28-1.40 (m, 2H, CH_2), 1.32 (s, 3H, CH_3), 1.53 (s, 9H, CH_3, ^{t}Bu), 1.62 (s, 9H, CH_3, ^{t}Bu), 1.80-2.10 (m, 2H, CH_2), 1.83 (s, 3H, CH_3), 1.86 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 2.33 (s, 3H, CH_3), 3.21 (m, 1H, H-4), 3.77 (m, 1H, H-5'), 3.93 (m, 1H, H-5), 4.46 (d, 1H, H-2, $^3J_{2\text{-}1}$= 3.6 Hz), 4.69 (m, 1H, CH= allyl *trans* to S), 5.13 (dd, 1H, H-3, $^3J_{3\text{-}P}$= 13.2 Hz, $^3J_{3\text{-}4}$= 2.0 Hz), 5.72 (d, 1H, H-1, $^3J_{1\text{-}2}$= 3.6 Hz), 5.93 ((m, 1H, CH= allyl *trans* to P), 6.17 (m, 1H, CH= allyl central), 7.29 (d, 1H, CH=, *J*= 6 Hz), 7.6-7.8 (m, 4H, CH=), 8.0-8.2 (m, 2H, CH=), 8.50 (d, 1H, CH=, *J*= 8.4 Hz). ^{13}C NMR (100 MHz, CD_2Cl_2) δ: 16.3 (CH_3), 16.4 (CH_3), 19.3 (CH_2), 20.0 (CH_3), 20.1 (CH_3), 25.8 (CH_3), 25.9 (CH_3), 28.1 (CH_2), 29.0 (CH_2), 31.3 (CH_3, ^{t}Bu), 31.4 (CH_3, ^{t}Bu), 34.7 (C, ^{t}Bu), 35.0 (C, ^{t}Bu), 38.5 (b, C-5), 75.8 (C-4), 78.2 (d, C-3, $J_{C\text{-}P}$= 10.7 Hz), 84.2 (d, C-2, $J_{C\text{-}P}$= 9.1 Hz), 89.1 (d, CH= allyl *trans* to S, $J_{C\text{-}P}$= 6.8 Hz), 101.4 (d, CH= allyl *trans* to P, $J_{C\text{-}P}$= 34.2 Hz), 104.1 (C-1), 112.4 (CMe_2), 114.6 (d, CH= allyl central, $J_{C\text{-}P}$= 9.9 Hz), 123.5-144.9 (aromatic carbons). Isomer *exo* (40%): ^{31}P NMR (161 MHz, CD_2Cl_2) δ: 139.2 (s). ^{1}H NMR (400 MHz, CD_2Cl_2) δ: 0.87-1.09 (m, 2H, CH_2), 1.11 (s, 3H, CH_3), 1.28-1.40 (m, 2H, CH_2), 1.28 (s, 3H, CH_3), 1.50 (s, 9H, CH_3, ^{t}Bu), 1.54 (s, 9H, CH_3, ^{t}Bu), 1.80-2.10 (m, 2H, CH_2), 1.85 (s, 3H, CH_3), 1.99 (s, 3H, CH_3), 2.33 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 3.62 (m, 1H, H-4), 3.77 (m, 1H, H-5'), 3.93 (m, 1H, H-5), 4.55 (d, 1H, H-2, $^3J_{2\text{-}1}$= 3.6 Hz), 4.61 (m, 1H, CH= allyl *trans* to S), 4.52 (m, 2H, H-3, CH= allyl *trans* to P), 5.87 (d, 1H, H-1, $^3J_{1\text{-}2}$= 3.6 Hz), 5.95 (m, 1H, CH= allyl central), 7.31 (d, 1H, CH=, *J*= 6 Hz), 7.6-7.8 (m, 4H, CH=), 8.0-8.2 (m, 2H, CH=), 8.38 (d, 1H, CH=, *J*= 8.4 Hz). ^{13}C NMR (100 MHz, CD_2Cl_2) δ: 16.0 (CH_3), 16.8 (CH_3), 19.3 (CH_2), 20.0 (CH_3), 20.1 (CH_3), 25.7 (CH_3), 26.1 (CH_3), 29.3 (b, CH_2), 29.6 (CH_2), 31.7 (CH_3, ^{t}Bu), 32.2 (CH_3, ^{t}Bu), 34.9 (C, ^{t}Bu), 35.2 (C, ^{t}Bu), 38.5 (b, C-5), 76.4 (C-4), 78.0 (d, C-3, $J_{C\text{-}P}$= 7.5 Hz), 83.5 (d, CH= allyl *trans* to S, $J_{C\text{-}P}$= 6.9 Hz), 84.5 (d, C-2, $J_{C\text{-}P}$= 7.6 Hz), 100.3 (d, CH= allyl *trans* to P, $J_{C\text{-}P}$= 34.0 Hz), 104.2 (C-1), 112.8 (CMe_2), 113.6 (d, CH= allyl central, $J_{C\text{-}P}$= 9.9 Hz), 123.5-144.9 (aromatic carbons).

[Pd(η³-1,3-cyclohexenylallyl)(L32f)]BF_4 (37). ^{31}P NMR (161 MHz, CD_2Cl_2) δ: 138.5 (s). ^{1}H NMR (400 MHz, CD_2Cl_2) δ: 0.95 (m, 1H, CH_2), 1.27 (s, 3H, CH_3), 1.40 (m, 1H, CH_2), 1.42 (b, 2H, CH_2), 1.43 (s, 3H, CH_3), 1.48 (s, 9H, CH_3, ^{t}Bu), 1.57 (s, 9H, CH_3, ^{t}Bu), 1.79 (s, 3H, CH_3), 1.93 (m, 1H, CH_2), 1.94 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 3.80 (dd, 1H, H-5', $^2J_{5'\text{-}5}$= 11.6 Hz, $^3J_{5'\text{-}4}$= 4.8 Hz), 3.91 (b, 2H, H-5, CH= allyl *trans* to S), 4.54 (m, 1H, H-4), 4.71 (d, 1H, H-2, $^3J_{2\text{-}1}$= 3.6 Hz), 4.95 (dd, 1H, H-3, $^3J_{3\text{-}P}$= 15.6 Hz, $^3J_{3\text{-}4}$= 2.4 Hz), 5.03 (m, 1H, CH= allyl *trans* to P), 5.41 (m, 1H, CH= allyl central), 5.85 (d, 1H, H-1, $^3J_{1\text{-}2}$= 3.6 Hz), 7.44 (d, 2H, CH=, *J*= 6 Hz), 7.62 (m, 1H, CH=), 7.71 (m, 1H, CH=), 7.78 (m, 2H, CH=), 8.06 (m, 2H, CH=), 8.32 (d, 1H, CH=, *J*= 8.4 Hz). ^{13}C NMR (100 MHz, CD_2Cl_2) δ: 16.3 (CH_3), 16.4 (CH_3), 19.7 (CH_2), 20.0 (CH_3), 20.3 (CH_3), 25.9 (CH_3), 26.3 (CH_3), 26.5 (b, CH_2), 27.5 (CH_2), 31.3 (CH_3, ^{t}Bu), 31.4 (CH_3,

^{t}Bu), 34.9 (C, ^{t}Bu), 35.0 (C, ^{t}Bu), 37.6 (C-5), 76.5 (d, C-4, $J_{C\text{-}P}$= 2.3 Hz), 76.7 (d, C-3, $J_{C\text{-}P}$= 3.8 Hz), 82.4 (d, CH= allyl *trans* to S, $J_{C\text{-}P}$= 6.9 Hz), 83.8 (d, C-2, $J_{C\text{-}P}$= 3.8 Hz), 103.4 (d, CH= allyl *trans* to P, $J_{C\text{-}P}$= 35.9 Hz), 104.6 (C-1), 111.9 (d, CH= allyl central, $J_{C\text{-}P}$= 9.9 Hz), 113.1 (CMe_2), 123.5-144.9 (aromatic carbons).

[Pd(η^3-1,3-diphenylallyl)(32f)]BF$_4$ (38). Isomer *endo* (20%): ^{31}P NMR (161 MHz, CD_2Cl_2) δ: 137.1 (s). ^{1}H NMR (400 MHz, CD_2Cl_2) δ: 1.19 (s, 3H, CH_3), 1.32 (s, 3H, CH_3), 1.58 (s, 9H, CH_3, ^{t}Bu), 1.67 (s, 9H, CH_3, ^{t}Bu), 1.72 (s, 3H, CH_3), 1.76 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 3.21 (m, 1H, H-5'), 3.56 (dd, 1H, H-5, $^2J_{5\text{-}5'}$= 12.4 Hz, $^3J_{5\text{-}4}$= 4.8 Hz), 4.42 (m, 2H, H-4, CH= allyl *trans* to S), 4.63 (d, 1H, H-2, $^3J_{2\text{-}1}$= 3.6 Hz), 4.97 (b, 1H, H-3), 5.03 (m, 1H, CH= allyl *trans* to P), 5.71 (d, 1H, H-1, $^3J_{1\text{-}2}$= 3.6 Hz), 6.42 (m, 1H, CH= allyl central), 6.5-8.4 (m, 17H, CH=). ^{13}C NMR (100 MHz, CD_2Cl_2) δ: 16.8 (CH_3), 17.1 (CH_3), 20.6 (CH_3), 20.7 (CH_3), 26.4 (CH_3), 27.0 (CH_3), 32.2 (CH_3, ^{t}Bu), 32.3 (CH_3, ^{t}Bu), 35.2 (C, ^{t}Bu), 35.7 (C, ^{t}Bu), 41.8 (C-5), 77.0 (C-4), 78.7 (b, CH= allyl *trans* to S), 81.7 (b, C-3), 84.4 (C-2), 100.9 (d, CH= allyl *trans* to P, $J_{C\text{-}P}$= 33.2 Hz), 105.5 (C-1), 112.2 (d, CH= allyl central, $J_{C\text{-}P}$= 9.2 Hz), 113.5 (CMe_2), 124.1-143.9 (aromatic carbons). Isomer *exo* (80%): ^{31}P NMR (161 MHz, CD_2Cl_2) δ: 138.0 (s). ^{1}H NMR (400 MHz, CD_2Cl_2) δ: 1.22 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 1.38 (s, 9H, CH_3, ^{t}Bu), 1.74 (s, 3H, CH_3), 1.78 (s, 3H, CH_3), 1.81 (s, 9H, CH_3, ^{t}Bu), 2.25 (s, 3H, CH_3), 2.47 (s, 3H, CH_3), 3.39 (m, 2H, H-5', H-5), 4.21 (d, 1H, H-2, $^3J_{2\text{-}1}$= 3.6 Hz), 4.32 (m, 1H, H-4), 4.97 (m, 1H, CH= allyl *trans* to S), 5.00 (b, 1H, H-3), 5.52 (m, 1H, CH= allyl *trans* to P), 5.64 (d, 1H, H-1, $^3J_{1\text{-}2}$= 3.6 Hz), 6.24 (m, 1H, CH= allyl central), 6.5-8.4 (m, 17H, CH=). ^{13}C NMR (100 MHz, CD_2Cl_2) δ: 16.9 (CH_3), 17.3 (CH_3), 20.6 (CH_3), 20.8 (CH_3), 26.5 (CH_3), 26.8 (CH_3), 32.0 (CH_3, ^{t}Bu), 32.7 (CH_3, ^{t}Bu), 35.2 (C, ^{t}Bu), 35.8 (C, ^{t}Bu), 39.6 (C-5), 76.4 (C-4), 78.1 (b, CH= allyl *trans* to S), 81.7 (b, C-3), 84.6 (C-2), 105.1 (C-1), 106.3 (d, CH= allyl *trans* to P, $J_{C\text{-}P}$= 32.4 Hz), 110.9 (d, CH= allyl central, $J_{C\text{-}P}$= 9.5 Hz), 113.3 (CMe_2), 124.1-143.9 (aromatic carbons).

[Pd(η^3-1,3-diphenylallyl)(L24a)]BF$_4$ (39). Isomer *exo* (80%): ^{31}P NMR (161 MHz, CD_2Cl_2) δ: 143.6 (s). ^{1}H NMR (400 MHz, CD_2Cl_2) δ: 1.25 (s, 3H, CH_3), 1.28 (s, 3H, CH_3), 1.36 (s, 9H, CH_3, ^{t}Bu), 1.45 (s, 9H, CH_3, ^{t}Bu), 1.59 (s, 9H, CH_3, ^{t}Bu), 1.63 (s, 9H, CH_3, ^{t}Bu), 3.00 (dd, 1H, H-5', $^2J_{5'\text{-}5}$= 13.6 Hz, $^3J_{5'\text{-}4}$= 11.6 Hz), 3.56 (dd, 1H, H-5, $^2J_{5\text{-}5'}$= 13.6 Hz, $^3J_{5\text{-}4}$= 4.0 Hz), 4.09 (m, 1H, H-4), 4.53 (d, 1H, H-2, $^3J_{2\text{-}1}$= 4.0 Hz), 5.66 (m, 2H, H-3, CH= allyl *trans* to S), 5.73 (d, 1H, H-1, $^3J_{1\text{-}2}$= 4.0 Hz), 5.83 (m, 1H, CH= allyl *trans* to P), 6.56 (m, 1H, CH= allyl central), 6.7-7.7 (m, 19H, CH=). ^{13}C NMR (100 MHz, CD_2Cl_2) δ: 26.5 (CH_3), 26.6 (CH_3), 31.6 (CH_3, ^{t}Bu), 31.7 (CH_3, ^{t}Bu), 32.0 (CH_3, ^{t}Bu), 32.3 (CH_3, ^{t}Bu), 35.1 (C, ^{t}Bu), 35.2 (C, ^{t}Bu), 35.8 (C, ^{t}Bu), 36.5 (C, ^{t}Bu), 37.3 (b, C-5), 76.2 (C-4), 78.8 (d, C-3, $J_{C\text{-}P}$= 10.7 Hz), 85.1 (d, C-2, $J_{C\text{-}P}$= 8.4 Hz), 90.0 (b, CH= allyl *trans* to S), 99.9 (d, CH= allyl *trans* to P, $J_{C\text{-}P}$= 32.4 Hz), 104.9 (C-1), 113.0 (CMe_2), 114.4 (d, CH= allyl central, $J_{C\text{-}P}$= 10.1 Hz), 125.4-149.4 (aromatic carbons). Isomer *endo* (20%): ^{31}P NMR (161 MHz, CD_2Cl_2) δ: 140.6 (s). ^{1}H NMR (400 MHz, CD_2Cl_2) δ: 1.15 (s, 3H, CH_3), 1.18 (s, 3H, CH_3), 1.37 (s, 9H, CH_3, ^{t}Bu), 1.47 (s, 9H, CH_3, ^{t}Bu), 1.59 (s, 9H, CH_3, ^{t}Bu), 1.72 (s, 9H, CH_3, ^{t}Bu), 3.29 (m, 1H, H-5'), 3.64 (dd, 1H, H-5, $^2J_{5\text{-}5'}$= 13.6 Hz, $^3J_{5\text{-}4}$= 4.8 Hz), 3.92 (m, 1H, H-4), 4.28 (d, 1H, H-2, $^3J_{2\text{-}1}$= 3.6 Hz), 5.30 (m, 1H, CH= allyl *trans* to S), 5.44 (m, 1H, CH= allyl *trans* to P), 5.66 (m, 1H, H-3), 5.71 (d, 1H, H-1, $^3J_{1\text{-}2}$= 3.6 Hz), 6.81 (m, 1H, CH= allyl central), 6.7-7.7 (m, 19H, CH=). ^{13}C NMR (100 MHz, CD_2Cl_2) δ: 26.2 (CH_3), 26.4 (CH_3), 31.6 (CH_3, ^{t}Bu), 31.7 (CH_3, ^{t}Bu), 32.0 (CH_3, ^{t}Bu), 32.3 (CH_3, ^{t}Bu), 35.2 (C, ^{t}Bu), 35.3 (C, ^{t}Bu), 35.8 (C, ^{t}Bu), 36.2 (C, ^{t}Bu), 38.1 (b, C-5), 76.2 (C-4), 78.8 (d, C-3, $J_{C\text{-}P}$= 10.7 Hz), 84.6 (d, C-2, $J_{C\text{-}P}$= 7.8 Hz), 91.2 (b,

CH= allyl *trans* to S), 99.6 (d, CH= allyl *trans* to P, $J_{C\text{-}P}$= 33.4 Hz), 104.9 (C-1), 109.8 (d, CH= allyl central, $J_{C\text{-}P}$= 9.8 Hz), 113.0 (CMe_2), 125.4-149.4 (aromatic carbons).

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UNIVERSITAT ROVIRA I VIRGILI
SCREENING OF MODULAR AND READILY AVAILABLE LIGAND LIBRARIES FOR C-X (X=H, C, N AND O) BOND FORMING REACTIONS. THE USE OF DFT STUDIES FOR CATALYSTS OPTIMIZATION
Jèssica Margalef Pallarès

5.4. Asymmetric Pd-catalyzed allylic substitution reactions using indene-based phosphite/phosphinite-thioether ligands

Maria Biosca, Jèssica Margalef, Xisco Caldentey, Erik A. Karlsson, Carles Rodríguez-Escrich, Miquel A. Pericàs, Oscar Pàmies, and Montserrat Diéguez in manuscript to be submitted

Abstract: *A library of phosphite/phosphinite-thioether ligands has been successfully applied in the Pd-catalyzed allylic substitution reactions of a range of substrates, with different steric demands, using a wide range of C-, N- and O-nucleophiles, among which are the little studied α-substituted malonates, β-diketones, pyrroles, alkyl alcohols and silanols. The potential application of allylic substitution using functionalized malonates has been demonstrated by the practical synthesis of the chiral (poli)carbocyclic using simple sequential allylic alkylation/ring-closing metathesis and allylic alkylation/Pauson-Khand reactions. The new phosphite-thioether ligands not only perform well in traditional organic solvents but also in propylene carbonate which is an alternative environmentally friendly solvent.*

5.4.1. Introduction

The development and improvement of catalysts constitutes a key issue for achieving the sustainable production of all sorts of chemicals. Chirality is a fundamental property of a large number of technologically and biologically appealing compounds. Among the enantioselective catalytic reactions leading to chiral products, asymmetric Pd-catalyzed allylic substitution creates new chiral C-C and C-heteroatom bonds in simple molecules, which can be further transformed into more complex ones by taking advantage of the alkene functionality of the substrate. Other advantages of the Pd-catalyzed allylic substitution are the high functional group tolerance and mild reaction conditions.[1] Heterodonor compounds are among the most successful ligands reported to date. Their success derives from the different *trans* influence of the donor groups that allow an efficient electronic differentiation between the two allylic terminal carbon atoms so that the nucleophilic attack takes place predominantly trans to the donor group with stronger trans influence. Among the heterodonor compounds, phosphine/phosphinite-oxazoline ligands have been studied the most.[1,2] Our group has also contributed improvements in catalyst performance with mixed ligands that have biaryl phosphite moieties.[1j,3]

Despite all these advances, ligands are rarely suitable for a wide range of substrates so that different ligands are required for different substrates to optimize enantiopurity. Additional efforts are still needed to extent the range of nucleophiles since many of them still give unsatisfactory results with known catalysts. Ligands with a wide substrate scope and suitable for a large number of nucleophiles are desirable in order to limit time-consuming ligand design and preparation, and synthesize more complex chiral organic molecules. The discovery of "privileged ligands" that are easy to handle (solid, robust and stable in air), prepared from simple starting materials and good for a broad range of substrates and nucleophiles is a relevant topic.[4] To solve these problems, we recently

started synthesizing ligands with more robust groups than oxazoline. In this respect, in 2014 we identified a Pd/thioether-phosphite catalyst that creates C-C, C-N and C-O bonds in different substrates and with a variety of nucleophiles in high yields and enantioselectivities.[5] Although other researchers have developed heterodonor P,S-ligands, only a few of them have been successfully applied and these are limited in substrate and nucleophile scope (enantioselectivities are mainly high in the allylic substitution of the hindered standard substrate *rac*-1,3-diphenyl-3-acetoxyprop-1-ene **S1** using dimethylmalonate as nucleophile).[6] The performance of this new class of P,S-ligands must be further studied for this process by screening new readily accessible thioether-containing ligands.

For this purpose, in this chapter we took one step further and applied phosphite/phosphinite-thioether ligand library (**L51**-**L58a**-**g**; Figure 5.4.1) for the Pd-catalyzed allylic substitution of a broad range of substrates and nucleophiles. These ligands are synthesized in only three steps from commercially accessible indene. They also benefit from the robustness of the thioether group and the control of the chiral cavity by the tuning of the thioether and phosphite/phosphinite moieties. With these ligands we studied the catalytic performance by systematically varying: (a) the electronic and steric proprieties of the thioether (**L51**-**L58**) group, (b) the configuration of the biaryl phosphite moiety (**a**-**c**), and (c) the phosphorous group (phosphite versus phosphinite groups, **d**-**g**). By thoroughly selecting these ligand parameters, we achieved high enantioselectivities and activities in several linear and cyclic substrates using a broad range of C-, N- and O-nucleophiles, including the less studied α-substituted malonates, β-diketones, pyrroles, alkyl alcohols and silanols. We have also demonstrated the potential application of the allylic substitution products by conveniently transforming them into biologically active chiral carbocyclics using a simple sequential allylic alkylation/ring-closing metathesis and allylic alkylation/Pauson-Khand reactions. Finally, we have also extended the use of these new catalytic systems to alternative environmentally friendly solvents such as propylene carbonate and ionic liquids.

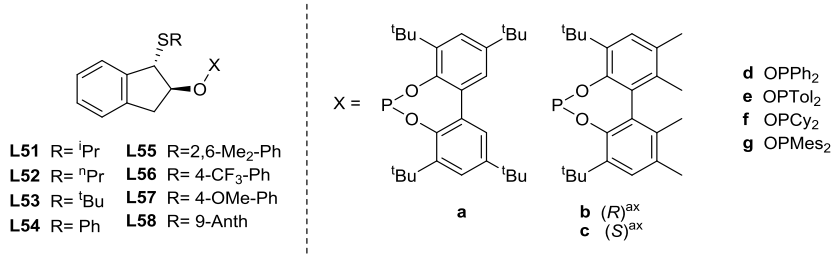


Figure 5.4.1. Phosphite-thioether/selenide ligand library **L51**-**L58a**-**g**.

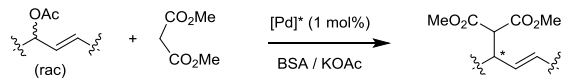
5.4.2. Results and discussion

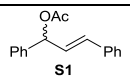
5.4.2.1. Allylic substitution of model 1,3-disubstituted allylic substrates

As already mentioned, the catalyst's ability to self-adapt to the steric demands of the substrate decisively affects its effectiveness in transferring the chirality to the alkylated

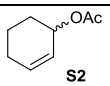
product. To assess the potential of the new phosphite/phosphinite-thioether ligand library in the allylic substitution, we first tested them in substrates with different steric requirements. Namely, in the asymmetric Pd-catalyzed allylic substitution of model substrate **S1** and the more demanding cyclic **S2** (Table 5.4.1). In all cases excellent yields were achieved under mild reaction conditions (i.e. 1 mol% Pd, ligand-to-palladium ratio of 1.1 at room temperature). In addition, we found high enantioselectivities for both substrate types (ee's up to 99% in dimethyl 2-(1,3-diphenylallyl)malonate **1** and 94% in dimethyl 2-(cyclohex-2-en-1-yl)malonate **2**) by combining into the ligand an aryl thioether group with a chiral biaryl phosphite group.

Table 5.4.1. Selected results for the Pd-catalyzed allylic alkylation of model substrates **S1** and **S2** with dimethyl malonate using the ligand library **L51**-**L58a**-**g**.[a]





S1



S2

Entry	L	% Conv (h)[b]	%ee[c]	% Conv (h)[b]	%ee[c]
1	**L51a**	100 (0.5)	17 (*R*)	100 (2)	15 (*S*)
2	**L51b**	100 (0.5)	90 (*R*)	100 (2)	66 (*R*)
3	**L51c**	100 (0.5)	75 (*S*)	100 (2)	61 (*S*)
4	**L51d**	100 (0.5)	50 (*R*)	100 (2)	28 (*S*)
5	**L51e**	100 (0.5)	25 (*R*)	100 (2)	11 (*S*)
6	**L51f**	5 (0.5)	32 (*R*)	10 (2)	28 (*S*)
7	**L51g**	100 (0.5)	4 (*R*)	100 (2)	14 (*R*)
8	**L52b**	100 (0.5)	90 (*R*)	100 (2)	62 (*R*)
9	**L53b**	100 (0.5)	84 (*R*)	100 (2)	60 (*R*)
10	**L53e**	100 (0.5)	63 (*R*)	100 (2)	77 (*S*)
11	**L54b**	100 (0.5)	97 (*R*)	100 (2)	85 (*R*)
12	**L55b**	100 (0.5)	96 (*R*)	100 (2)	86 (*R*)
13	**L55c**	100 (0.5)	80 (*S*)	100 (2)	84 (*S*)
14	**L55d**	100 (0.5)	28 (*R*)	100 (2)	13 (*S*)
15	**L55e**	100 (0.5)	40 (*R*)	100 (2)	11 (*S*)
16	**L56b**	100 (0.5)	96 (*R*)	100 (2)	90 (*R*)
17	**L57b**	100 (0.5)	97 (R)	100 (2)	90 (*R*)
18	**L58b**	100 (0.5)	99 (R)	100 (2)	94 (*R*)

[a] 0.5 mol% $[PdCl(\eta^3\text{-}C_3H_5)]_2$, ligand (0.011 mmol), substrate (1 mmol), CH_2Cl_2 (2 mL), BSA (3 eq), dimethyl malonate (3 eq), KOAc (pinch). [b] Conversion percentage determined by ^{1}H-NMR. [c] Enantiomeric excesses determined by HPLC for **S1** and GC for **S2**. Absolute configuration drawn in parentheses.

Comparing the results of ligands **L51a**-**g** (entries 1-7), that contain different P-donor groups, it is seen that the chiral backbone of the ligand cannot control the tropoisomerism in the biphenyl phosphite moieties **a** (entries 1-3) and the enantiopure biaryl phosphite group is therefore needed for enantioselectivities to be high (entries 2-3). We also found that the chirality at the biaryl phosphite moiety controls the sense of enantioselectivity. Accordingly, ligands **L51**-**L58b**, with (*S*)-configuration at biaryl phosphite moiety, gave (*R*)-

alkylated products, while ligands **L51**-**L58c**, with (*R*)-configuration at the biaryl phosphite group, gave (*S*)-alkylated products. For the linear substrate **S1** there is a remarkable cooperative effect between the configuration of the biaryl phosphite moiety and the ligand backbone that results in a matched combination with ligand **L1b**, containing an (*R*)-biaryl phosphite group (entry 2 vs 3). This cooperative effect is less pronounced in the allylic substitution of cyclic substrate **S2** and both enantiomers of the alkylated products are therefore easily accessible by simply setting the configuration of the biaryl phosphite moiety. Finally by comparing ligands **L51**-**L58b** (entries 2, 8, 9, 11, 12 and 16-18), we found that the electronic and steric properties of the thioether substituent influence the catalytic performance less. However, ligands with bulky aryl-thioether groups (i.e. ligand **L58b**; entry 18) lead to somewhat higher enantioselectivities, especially in the allylic substitution of the cyclic substrate **S2**.

5.4.2.2. Allylic substitution of linear substrates S1, S3-S7 using several nucleophiles

We initially considered the allylic substitution of substrate **S1** with an extensive range of C-, N- and O-nucleophiles. In general, Pd/**L51**-**L58a**-**g** catalysts followed the same trends as the allylic substitution of **S1** using dimethyl malonate. Figure 5.4.2 shows the results using ligand **L58b** as example, which had provided the best results in the allylic alkylation of **S1** with dimetyl malonate as model nucleophile. Advantageous, a variety of malonates, including the more challenging and interesting from a synthetic point of view substituted allyl-, butenyl-, pentenyl- and propargyl-malonates (see section 5.4.2.5 below), reacted cleaned with **S1** to provide products **3**-**9** in high yield and enantioselectivities (ee's up to 99). The addition of acetylacetone and benzylamine also proceed with high enantiocontrol (ee's up to 98%).

The reaction also worked well when pyrroles were used as nucleophiles. These are important results because N-containing heterocycles are present in many relevant compounds. In this respect, an important class of electron-rich N-containing heterocycles is pyrroles, which are widely present in biologically compounds and have versatile synthetic applications.[7] Despite this, only one catalytic system has previously been successfully applied in the Pd-allylic alkylation of **S1** type substrates, however it required low temperature (-20 °C) to achieved high ee.[8] We were pleased to see that we could reach ee's up to 99% and high yield working at room temperature.

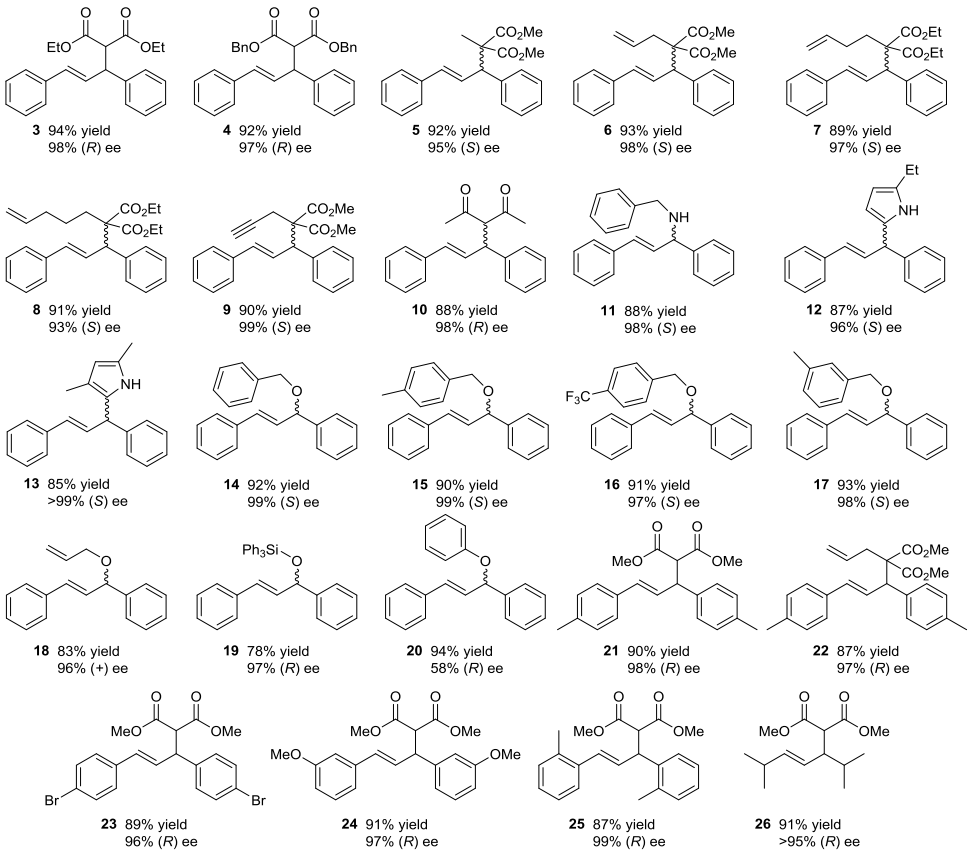


Figure 5.4.2. Allylic substitution of **S1**, **S3**-**S7** with C-, N- and O-nucleophiles using Pd-**L58b** catalytic system. Reactions were run at 23 °C with $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (0.5 mol %), CH_2Cl_2 as solvent, ligand (1.1 mol %), BSA (3 equiv), and KOAc. Full conversions were achieved after 4 h. [a] Reactions carried out using 2 mol % $[PdCl(\eta^3\text{-}C_3H_5)]_2$, 4 mol % ligand, and Cs_2CO_3 (3 equiv). Full conversions were achieved after 18 h.

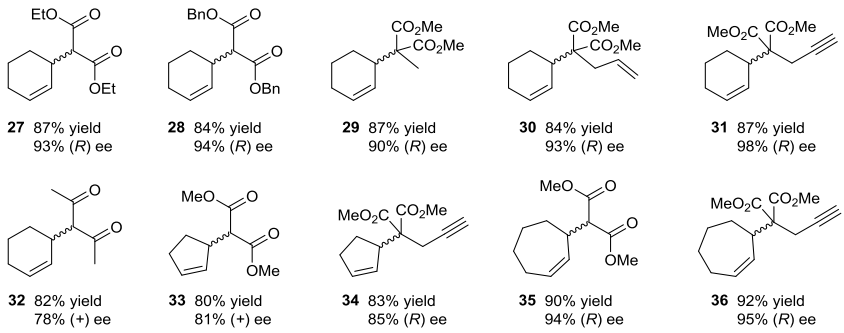
The excellent enantiocontrol also extends to the use of several aliphatic alcohols (compounds **14**-**18**, ee's up to 99%). The results show that the catalytic performance is not affected by the steric and electronic properties of the aryl group. Therefore, a variety of aliphatic alcohols reacted with **S1** in high yield, and enantioselectivities that were as high as or higher than those obtained with dimethyl malonate. The effective allylic substitution with this type of O-nucleophiles opens up a path for the construction of aliphatic chiral ethers which are important for the synthesis of biologically active targets.[9] However, although the Pd-allylic etherification is currently studied by relevant research groups, few successful examples have been reported and most of them are phenols,[10] while aliphatic alchohols have been less studied.[11] Even more remarkable are the almost perfect enantioselectivities (ee's up to 99%) and high yields achieved in the etherification of **S1** with the triphenylsilanol (compound **19**). The Pd-catalyzed allylic etherification of allylic substrates with silanols is an elegant route for obtaining chiral silyl ethers than can further

be transformed into high-value compounds such as chiral aromatic allylic alcohols. Nonetheless, silanols have been less studied than other type of nucleophile and only the Pd/CycloN_2P_2-Phos catalytic type system has reach high enantioselectivities (up to 94%).[11d]

We then move on to study the allylic alkylation of other 6 linear substrates (Figure 5.4.2) with different electronic and steric requirements (*rac*-1,3-di(4-tolyl)-3-acetoxyprop-1-ene **S3**, *rac*-1,3-di(4-bromophenyl)-3-acetoxyprop-1-ene **S4** and *rac*-1,3-di(3-methoxyphenyl)-3-acetoxyprop-1-ene **S5,** *rac*-1,3-di(2-tolyl)-3-acetoxyprop-1-ene **S6** and *rac*-(*E*)-ethyl-2,5-dimethyl-3-hex-4-enylcarbonate **S7**). Advantageously, we found that the catalytic performance is unaffected by the introduction of *ortho*- and *metha*-substituents at the phenyl groups of the substrate, as well as by the introduction of electron withdrawing and electron donating groups. Also, the Pd-allylic alkylation of substrate **S7**, which is more sterically demanding and is usually substituted much less enantioselectively than **S1**,[1] also proceeded with high enantioselectivity (>95% ee).

5.4.2.3. Allylic substitution of cyclic substrates S2, S8-S9 using other C-nucleophiles

Finally, we wanted to see if the high enantioselectivities achieved in the allylic substitution of linear substrates (see section 5.4.2.2) were retained for the even more challenging cyclic analogues. A number of cyclic substrates with different ring size were tested (Figure 5.4.3). For substrate **S2**, yields and enantioselectivities as high or ever higher than with the dimethyl malonates were obtained with a range of C-nucleophiles (ee's up to 98%, products **27**-**32**) except when acetylacetone was used as nucleophile, which led to somewhat lower enantioselectivity. Even more interesting is that the good performance (high yields and enantioselectivities) also extended to the allylic substitution of other cyclic substrates such as *rac*-3-acetoxycyclopentene **S8** (compounds **33** and **34**), which is often substituted with lower enantioselectivity than the 6-membered cyclic substrate **S2**, and *rac*-3-acetoxycycloheptene **S9** (compounds **35** and **36**).



27 87% yield, 93% (*R*) ee
28 84% yield, 94% (*R*) ee
29 87% yield, 90% (*R*) ee
30 84% yield, 93% (*R*) ee
31 87% yield, 98% (*R*) ee
32 82% yield, 78% (+) ee
33 80% yield, 81% (+) ee
34 83% yield, 85% (*R*) ee
35 90% yield, 94% (*R*) ee
36 92% yield, 95% (*R*) ee

Figure 5.4.3. Allylic substitution of **S2**, **S8**-**S9** with C-nucleophiles using Pd-**L58b** catalytic system. Reactions were run at 23 °C with $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (0.5 mol %), CH_2Cl_2 as solvent, ligand (1.1 mol %), BSA (3 equiv), and KOAc. Full conversions were achieved after 6 h.

5.4.2.4. Allylic substitution using propylene carbonate

Propylene carbonate (PC) has emerged as a sustainable "green" alternative to standard organic solvents because of its high boiling point, low toxicity and environmentally friendly synthesis.[12] To study whether the new Pd-phosphite/phosphinite-thioether catalytic systems developed in this study can be used efficiently with PC, we performed the allylic substitution of substrates **S1**-**S9** using the ligand **L58b** that provided the best enantioselectivities. Several C- and N-nucleophiles were also used. The results can be found in Table 5.4.2. We were pleased to see that when the new catalyst library was used in PC, the enantioselectivities remained as high as those observed when dichloromethane was used for a wide range of nucleophiles. Unfortunately, the catalysts could not be efficiently recycled because of the high polarity of the alkylation and amination products considered.[13]

Table 5.4.2. Selected results for the Pd-catalyzed allylic substitution of **S1-S9** with Pd-**L58b** catalytic system in PC as a solvent.[a]

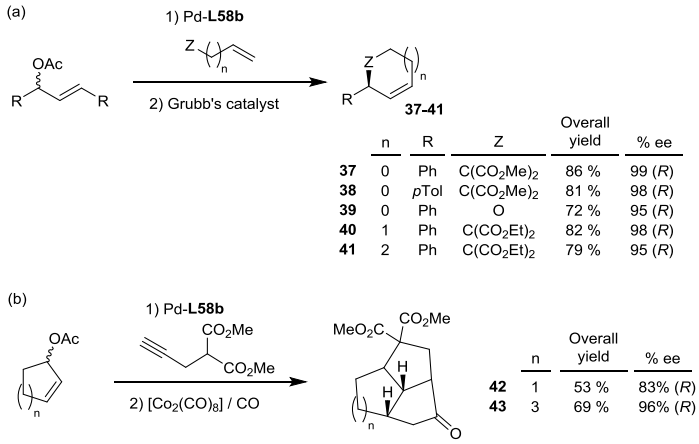
Entry	Substrate	H-Nu	Product	% Conv (h)[b]	% Yield	% ee[c]
1	**S1**	H-CH(COOMe)$_2$	**1**	100 (0.5)	89	97 (*R*)
2	**S1**	H-CMe(COOMe)$_2$	**5**	100 (0.5)	90	96 (*S*)
3	**S1**	H-CAllyl(COOMe)$_2$	**6**	100 (0.5)	92	96 (*S*)
4	**S1**	H-CButenyl(COOMe)$_2$	**7**	100 (0.5)	88	97 (*S*)
5	**S1**	H-CPentenyl(COOMe)$_2$	**8**	100 (0.5)	87	93 (*S*)
6	**S1**	H-CPropargyl(COOMe)$_2$	**9**	100 (0.5)	86	99 (*S*)
7	**S1**	H-CH(COMe)$_2$	**10**	100 (0.5)	84	96 (*R*)
8	**S1**	H-NHCH$_2$Ph	**11**	100 (2)	86	96 (*S*)
9	**S2**	H-CH(COOMe)$_2$	**2**	100 (6)	91	90 (*R*)
10	**S3**	H-CH(COOMe)$_2$	**21**	98 (1)	88	97 (*R*)
11	**S4**	H-CH(COOMe)$_2$	**23**	100 (1)	93	96 (*R*)
12	**S5**	H-CH(COOMe)$_2$	**24**	99 (1)	87	96 (*R*)
13	**S6**	H-CH(COOMe)$_2$	**25**	100 (1)	88	98 (*R*)
14	**S7**	H-CH(COOMe)$_2$	**26**	100 (24)	90	>95 (*R*)
15	**S8**	H-CH(COOMe)$_2$	**33**	100 (6)	83	82 (+)
16	**S9**	H-CH(COOMe)$_2$	**35**	100 (6)	88	92 (*R*)

[a] All reactions were run at 40 °C. 0.5 mol% [PdCl(η^3-C_3H_5)]$_2$. 1 mol% ligand. [b] Conversion measured by GC or ^{1}H-NMR. Reaction time shown in parentheses. [c] Enantiomeric excesses. Absolute configuration shown in parentheses.

5.4.2.5. Synthetic applications of the allylic substitution compounds. Preparation of chiral functionalized (poli)cyclic compounds 37-44

To illustrate the synthetic applications of the compounds obtained from the enantioselective Pd-catalyzed allylic substitution using other nucleophiles than dimethyl malonate, we have prepared a range of chiral functionalized (poli)carbocycles and heterocycles (compounds **37**-**44**; Scheme 5.4.1). These compounds have been prepared by simple tandem reactions involving allylic substitution of the substrate and ring-closing metathesis reactions (Scheme 5.4.1a) or the sequential allylic substitution and Pauson-Khand (Scheme 5.4.1b) reactions. Allylic alkylated compounds **6**-**8** and **22** (see Figure 5.4.2) can undergo a clean ring-closing metathesis with no loss of enantiopurity. Therefore a

number of 5, 6 and 7-membered carbocycles, containing substituents with different electronic and steric proprieties, can be prepared in high yields and enantioselectivities (compounds **37**-**38** and **40**-**41**). Similarly, the heterocycle (*R*)-**39** is achieved by sequential allylic etherification of **S1** with allyl alcohol and a ring-closing metathesis reaction (Scheme 5.4.1b). Other examples of sequential reactions is the [2+2+1] cycloaddition of the 1,6-enynes **34** and **36**, formed from the allylic alkylation of **S8** and **S9** with dimethyl propargylmalonate, with CO to yield tricyclic ketones **42** and **43** (Scheme 5.4.1b).



	n	R	Z	Overall yield	% ee
37	0	Ph	$C(CO_2Me)_2$	86 %	99 (*R*)
38	0	*p*Tol	$C(CO_2Me)_2$	81 %	98 (*R*)
39	0	Ph	O	72 %	95 (*R*)
40	1	Ph	$C(CO_2Et)_2$	82 %	98 (*R*)
41	2	Ph	$C(CO_2Et)_2$	79 %	95 (*R*)

	n	Overall yield	% ee
42	1	53 %	83% (*R*)
43	3	69 %	96% (*R*)

Scheme 5.4.1. Preparation of chiral functionalized (poli)cyclic compounds **37**-**43**.

5.4.3. Conclusions

A library of phosphite/phosphinite-thioether ligands **L51**-**L58a**-**g** has been successfully applied in the Pd-catalyzed allylic substitution reactions of a range of substrates, with different steric demands, using a wide range of C-, N- and O-nucleophiles, among which are the little studied α-substituted malonates, β-diketones, pyrroles, alkyl alcohols and silanols. We found that the extent to which the chiral information was transferred to the product can be tuned by correctly choosing the ligand components. The combination of a bulky thioether group and an enantiopure (*R*)-biaryl phosphite moiety played an essential role in increasing the versatility of the Pd-catalytic systems. Enantioselectivities were therefore high in a wide range of substrates using several C-, N- and O-nucleophiles. Of particular note were the high enantioselectivities (up to >99% ee) and high activities obtained for both linear and cyclic substrates, which are comparable with the best ones reported in the literature. The potential application of allylic substitution using functionalized malonates has been demonstrated by the practical synthesis of the chiral (poli)carbocyclic using simple sequential allylic alkylation/ring-closing metathesis and allylic alkylation/Pauson-Khand reactions. The new phosphite-thioether ligands not only perform well in traditional organic solvents but also in propylene carbonate which is an alternative environmentally friendly solvent.

5.4.4. Experimental section

5.4.4.1. General considerations

All reactions were carried out using standard Schlenk techniques under an argon atmosphere. Commercial chemicals were used as received. Solvents were dried by means of standard procedures and stored under argon. ^{1}H, ^{13}C{^{1}H} and ^{31}P{^{1}H} NMR spectra were recorded using a Varian Mercury-400 MHz spectrometer. Chemical shifts are relative to that of $SiMe_4$ (^{1}H and ^{13}C{^{1}H}) as an internal standard. Racemic substrates **S1**-**S9** were prepared as previously reported.[14] The synthesis of ligands **L51**-**L57a**-**e** is described in section 3.5 (Chapter 3).

5.4.4.2. Preparation of (1*S*,2*S*)-1-(anthracen-9-ylthio)-2,3-dihydro-1H-inden-2-ol

A solution of indene oxide (2 mmol, 264 mg) in dioxane (4.5 mL/mmol of indene oxide) is treated with anthracene-9-thiol (3 mmol, 631 mg). Then, a solution of NaOH (3 mmol, 120 mg) in water (0.45 mL/mmol of indene oxide) is added dropwise. The reaction mixture is capped and stirred at 55 °C until the epoxide is consumed according to TLC analysis (*ca*. 45-60 min). After this, the mixture is cooled to RT, diluted with water and extracted with CH_2Cl_2 (×3). The combined organic layers are dried over Na_2SO_4 and concentrated to give a residue that is purified by flash chromatography on silica gel (gradient from cyclohexane/EtOAc = 100:0 to cyclohexane/EtOAc = 80:20) to give the desired hydroxysulfide as a yellow solid. Yield: 308 mg (45%). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.33 (d, 1H, OH, $^{3}J_{H-H}$ =5.1 Hz), 2.80 (dd, 1H, CH_2, $^{2}J_{H-H}$ =16.4, $^{3}J_{H-H}$ =2.6 Hz), 3.58 (dd, 1H, CH_2, $^{2}J_{H-H}$ =16.4, $^{3}J_{H-H}$ =5.6 Hz), 4.40 (m, 1H, CH-O), 4.55 (d, 1H, CH-S, $^{3}J_{H-H}$ =2.2 Hz), 7.16 (t, 1H, CH=, $^{3}J_{H-H}$ =7.5 Hz), 7.24 (t, 1H, CH=, $^{3}J_{H-H}$ =7.5 Hz), 7.25-7.30 (m , 2H, CH=), 7.52 (ddd, 2H, CH=, $^{3}J_{H-H}$ =8.0 Hz, $^{3}J_{H-H}$ =6.5 Hz, $^{4}J_{H-H}$ =1.1 Hz), 7.61 (ddd, 2H, CH=, $^{3}J_{H-H}$ =8.9 Hz, $^{3}J_{H-H}$ =6.5 Hz, $^{4}J_{H-H}$ =1.0 Hz), 8.05 (d, 2H, CH=, $^{3}J_{H-H}$ =8.4 Hz), 8.54 (s, 1H, CH=), 8.98 (dq, 2H, CH=, $^{3}J_{H-H}$ =8.9, $^{4}J_{H-H}$ =1.0 Hz).^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 40.1 (CH_2), 61.2 (CH-S), 78.7 (CH-O), 125.3 (CH=), 125.4 (CH=), 125.7 (CH=), 126.6 (CH=), 126.9 (CH=), 127.0 (CH=), 127.7 (CH=), 128.4 (CH=), 129.1 (CH=), 129.6 (C=), 131.8 (C=), 134.9 (C=), 140.2 (C=), 140.8 (C=).

5.4.4.3. Preparation of phosphite-thioether ligand L58b

The corresponding phosphorochloridite (1.1 mmol) produced in situ was dissolved in toluene (5 mL), and pyridine (0.3 mL, 3.9 mmol) was added. The corresponding thioether-hydroxyl compound (1 mmol) was azeotropically dried with toluene (3 x 2 mL) and then dissolved in toluene (5 mL) to which pyridine (0.3 mL, 3.9 mmol) was added. The alcohol solution was transferred slowly to a solution of phosphorochloridite. The reaction mixture was stirred at 80°C for 90 min, after which the pyridine salts were removed by filtration. Evaporation of the solvent gave a white foam, which was purified by flash chromatography in silica (Hexane/Toluene/NEt_3 = 7/3/1) to produce the corresponding ligand as a white solid. Yield: 94.3 mg (27%). ^{31}P NMR (161.9 MHz, C_6D_6): δ=136.1 (s). ^{1}H NMR (400 MHz, C_6D_6): δ=1.28 (s, 9H, CH_3, ^{t}Bu), 1.39 (s, 9H, CH_3, ^{t}Bu), 1.65 (s, 3H, CH_3), 1.79 (s, 3H, CH_3), 2.02 (s, 3H, CH_3), 2.03 (s, 3H, CH_3), 2.91 (d, 1H, CH_2, $^{2}J_{H-H}$ =16.8 Hz), 3.45 (dd, 1H, CH_2, $^{2}J_{H-H}$ =16.8 Hz, $^{3}J_{H-H}$ =5.2 Hz), 4.92-4.95 (m, 1H, CH-OP), 5.22 (b, 1H, CH-S), 6.55-6.63 (m, 2H, CH=), 6.90

(s, 2H, CH=), 7.11-7.28 (m, 6H, CH=), 7.73 (d, 2 H, CH=, $^{3}J_{H-H}$ =8,0 Hz), 8.16 (s, 1, CH=), 8.96 (d, 2 H, CH=, $^{3}J_{H-H}$ =8,4 Hz). ^{13}C NMR (100.6 MHz, C_6D_6): δ=16.2 (CH_3), 16.6 (CH_3), 20.0 (CH_3), 20.1 (CH_3), 31.1 (CH_3, ^{t}Bu), 31.3 (d, CH_3, ^{t}Bu, J_{C-P} =5.4 Hz), 34.4 (C, ^{t}Bu), 39.7 (CH_2), 60.1 (CH-S), 81.4 (CH-OP), 124.8-145.7 (aromatic carbons). MS HR-ESI [found 747.3048, $C_{47}H_{49}O_3PS$ $(M\text{-}Na)^+$ requires 747.3028].

5.4.4.4. General procedure for the preparation of the phosphinite-thioether ligands L51f-g

The corresponding thioether-hydroxyl compound (0.5 mmol, 104.2 mg) and DMAP (6.7 mg, 0.055 mmol) were dissolved in toluene (1 ml), and triethylamine was added (0.09 ml, 0.65 mmol) at r.t, followed by the addition of the corresponding chlorophosphine (0.55 mmol) via syringe. The reaction was stirred for 20 min at r.t. The solvent was removed *in vacuo*, and the product was purified by flash chromatography on alumina (toluene/NEt_3 = 100/1) to produce the corresponding ligand as an oil.

L51f. Yield: 128.9 mg (61%). ^{31}P NMR (161.9 MHz, C_6D_6): δ=140.4 (s). ^{1}H NMR (400 MHz, C_6D_6): δ=1.08-1.20 (m, 6H, CH_2, Cy), 1.22 (d, 3H, CH_3, ^{i}Pr, $^{3}J_{H-H}$ =6.4 Hz), 1.25-1.35 (m, 5H, CH_2, Cy), 1.38 (d, 3H, CH_3, ^{i}Pr, $^{3}J_{H-H}$ =6.4 Hz), 1.48-1.61 (m, 5H, CH_2, Cy), 1.69 (b, 5H, CH, CH_2, Cy), 1.86 (m, 2H, CH_2, Cy), 2.98 (d, 1H, CH_2, $^{2}J_{H-H}$ =16.0 Hz), 3.10-3.17 (m, 1H, CH ^{i}Pr), 3.41 (dd, 1H, CH_2, $^{2}J_{H-H}$ =16.4 Hz, $^{3}J_{H-H}$ =5.6 Hz), 4.51-4.54 (m, 2H, CH-S, CH-OP), 6.99-7.15 (m, 3H, CH=), 7.40 (d, 1H, CH=, $^{3}J_{H-H}$ =8.0 Hz), 7.52 (m, 2H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ=23.3 (CH_3, ^{i}Pr), 24.0 (CH_3, ^{i}Pr), 26.5-27.1 (CH_2, Cy), 28.1 (CH_2, Cy), 28.3 (CH_2, Cy), 28.5 (CH_2, Cy), 35.2 (CH, ^{i}Pr), 37.6 (d, CH, $^{1}J_{C-P}$ =8.5 Hz), 37.8 (d, CH, $^{1}J_{C-P}$ =9.9 Hz), 39.3 (d, CH_2, $^{3}J_{C-P}$ =6.1 Hz), 54.8 (d, CH-S, $^{3}J_{C-P}$ =6.1 Hz), 87.7 (d, CH-OP, $^{2}J_{C-P}$ =18.4 Hz), 124.8-141.5 (aromatic carbons).

L51g. Yield: 129.9 mg (54%). ^{31}P NMR (161.9 MHz, C_6D_6): δ=114.5 (s). ^{1}H NMR (400 MHz, C_6D_6): δ=1.11 (d, 3H, CH_3, ^{i}Pr, $^{3}J_{H-H}$ =6.8 Hz), 1.22 (d, 3H, CH_3, ^{i}Pr, $^{3}J_{H-H}$ =6.4 Hz), 2.04 (s, 3H, *p*-CH_3, Mes), 2.06 (s, 3H, *p*-CH_3, Mes), 2.39 (s, 12H, *o*-CH_3, Mes), 2.85-2.99 (m, 2H, CH ^{i}Pr, CH_2), 3.33 (dd, 1H, CH_2, $^{2}J_{H-H}$ =16.4 Hz, $^{3}J_{H-H}$ =5.6 Hz), 4.46 (b, 1H, CH-S), 4.66 (m, 1H, CH-OP), 6.63 (s, 1H, CH=), 6.64 (s, 1H, CH=), 6.65 (s, 1H, CH=), 6.66 (s, 1H, CH=), 6.94-7.05 (m, 2H, CH=), 7.12 (m, 1H, CH=), 7.31 (m, 1H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ=20.6 (*p*-CH_3, Mes), 22.1 (d, *o*-CH_3, Mes, $^{3}J_{C-P}$ =3.0 Hz), 22.2 (d, *o*-CH_3, Mes, $^{3}J_{C-P}$ =3.1 Hz), 23.2 (CH_3, ^{i}Pr), 23.9 (CH_3, ^{i}Pr), 35.2 (CH, ^{i}Pr), 38.9 (d, CH_2, $^{3}J_{C-P}$ =6.8 Hz), 54.6 (d, CH-S, $^{3}J_{C-P}$ =7.6 Hz), 87.6 (d, CH-OP, $^{2}J_{C-P}$ =22,1 Hz), 124.7-141.6 (aromatic carbons).

5.4.4.5. Typical procedure for the allylic alkylation of disubstituted linear (S1, S3-S7) and cyclic (S2, S8-S9) substrates

A degassed solution of $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (0.9 mg, 0.0025 mmol) and the corresponding phosphite/phosphinite-thioether ligand (0.0055 mmol) in dichloromethane (0.5 mL) was stirred for 30 min. Subsequently, a solution of the corresponding substrate (0.5 mmol) in dichloromethane (1.5 mL), nucleophile (1.5 mmol), *N*,*O*-bis(trimethylsilyl)-acetamide (370 μL, 1.5 mmol) and KOAc (3mg, 003 mmol) was added. The reaction mixture was stirred at room temperature. After the desired reaction time the reaction mixture was diluted with Et_2O (5 mL) and saturated NH_4Cl (aq) (25 mL) was added. The mixture was extracted with Et_2O (3 x 10 mL) and the extract dried over $MgSO_4$. For compounds **1**, **2**-**10**, **14**-**25** and **27**-**28**, the solvent was removed, conversions were measured by ^{1}H NMR and enantiomeric

excesses were determined by HPLC.[3g] For compounds **2**, **31**-**32** and **34**-**26**, conversion and enantiomeric excesses were determined by GC.[3g] For compounds **26** and **33**, conversion were measured by ^{1}H NMR and ee's were determined by ^{1}H NMR using [Eu(hfc)$_3$].[3g]

5.4.4.6. Typical procedure for the allylic amination of disubstituted linear substrate S1

A degassed solution of [PdCl(η^3-C_3H_5)]$_2$ (0.9 mg, 0.0025 mmol) and the corresponding phosphite/phosphinite-thioether (0.0055 mmol) in dichloromethane (0.5 mL) was stirred for 30 min. Subsequently, a solution of the corresponding substrate (0.5 mmol) in dichloromethane (1.5 mL) and benzylamine (131 μL, 1.5 mmol) were added. The reaction mixture was stirred at room temperature. After the desired reaction time, the reaction mixture was diluted with Et_2O (5 mL) and saturated NH_4Cl (aq) (25 mL) was added. The mixture was extracted with Et_2O (3 x 10 mL) and the extract dried over $MgSO_4$. The solvent was removed, conversions were measured by ^{1}H NMR and enantiomeric excesses were determined by HPLC.[3b]

5.4.4.7. Typical procedure for the allylic substitution of disubstituted linear substrate S1 using pyrroles

A degassed solution of [PdCl(η^3-C_3H_5)]$_2$ (1.8 mg, 0.005 mmol) and the corresponding phosphite/phosphinite-thioether (0.011 mmol) in dichloromethane (0.5 mL) was stirred for 30 min. Subsequently, a solution of the corresponding substrate (0.5 mmol) in dichloromethane (1.5 mL), the corresponding pyrrole (0.4 mmol) and K_2CO_3 (110 mg, 0.8 mmol) were added. The reaction mixture was stirred at room temperature. After the desired reaction time, the reaction mixture was diluted with Et_2O (5 mL) and saturated NH_4Cl (aq) (25 mL) was added. The mixture was extracted with Et_2O (3 x 10 mL) and the extract dried over $MgSO_4$. The solvent was removed, conversions were measured by ^{1}H NMR and enantiomeric excesses were determined by HPLC.[8]

5.4.4.8. Typical procedure for the allylic etherification and sylilation of disubstituted linear substrate S1

A degassed solution of [PdCl(η^3-C_3H_5)]$_2$ (0.9 mg, 0.0025 mmol) and the corresponding phosphite/phosphinite-thioether (0.0055 mmol) in dichloromethane (0.5 mL) was stirred for 30 min. Subsequently, a solution of the corresponding substrate (31.5 mg, 0.125 mmol) in dichloromethane (1.5 mL) was added. After 10 minutes, Cs_2CO_3 (122 mg, 0.375 mmol) and nucleophile (0.375 mmol) were added. The reaction mixture was stirred at room temperature. After the desired reaction time, the reaction mixture was diluted with Et_2O (5 mL) and saturated NH_4Cl (aq) (25 mL) was added. The mixture was extracted with Et_2O (3 x 10 mL) and the extract dried over $MgSO_4$. The solvent was removed, conversions were measured by ^{1}H NMR and enantiomeric excesses were determined by HPLC.[3g]

5.4.4.9. Typical procedure for the preparation of carbocycles 37-41

A solution of Grubbs II catalyst (5 mg, 0.006 mmol) and the corresponding alkylated product (0.12 mmol) in CH_2Cl_2 (3 mL) was stirred for 16 h. The solution was purified directly

by flash chromatography (Hex/EtOAc = 95/5) to obtain the desired carbocycle. For characterization details and details for ee determination see ref.[3f]

5.4.4.10. Typical procedure for the preparation of carbocycles 42-44

A solution of the starting enyne (0.187 mmol) in 1 mL of *tert*-butylbenzene is added to a solution of $Co_2(CO)_8$ (83 mg, 0.243 mmmol) in 0.5 mL of *tert*-butylbenzene under air. The flask is rinsed with 0.5 mL more of the same solvent. The resulting mixture is stirred at RT for 1 h, until full consumption of the starting material is observed by TLC. After that, the system is heated at 170 °C for a further hour. Then, it is cooled to RT, filtered on Celite with CH_2Cl_2 and concentrated in vacuo. The crude mixture is purified by flash column chromatography on silica gel eluting with cyclohexane/EtOAc (gradient form 90:10 to 70:30) to furnish the desired tricyclic compound as a white solid.

Dimethyl (2a^1*R*,4a*S*)-6-oxooctahydrocyclopenta[*cd*]pentalene-2,2(1*H*)-dicarboxylate (42). Enantiomeric excess determined by SFC using Daicel Chiralpak ID-3 column (100 x 4.6 mm, 3 µm), 35 °C, CO_2/MeOH (85:15), ABPR = 1500 psi, flow rate 3.0 mL/min, λ = 227 nm. t_{major} = 1.32 min; t_{minor} = 1.15 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.92 (tdd, *J* = 12.9, 11.5, 7.0 Hz, 1H), 1.58 (dt, *J* = 12.9, 7.0 Hz, 1H), 1.79 (dd, *J* = 13.3, 7.0 Hz, 1H), 1.94 (td, *J* = 13.3, 10.1, 6.8 Hz, 1H), 2.84 (dd, *J* = 10.1, 5.3 Hz, 1H), 2.91 (ddd, *J* = 17.5, 2.0, 1.2 Hz, 1H), 3.13 (dt, *J* = 11.5, 7.4 Hz, 1H), 3.55 (t, *J* = 6.2 Hz, 1H), 3.66 (d, *J* = 17.5 Hz, 1H), 3.71 (s, 3H), 3.78 (s, 3H), 6.02 (t, *J* = 2.0 Hz, 1H). ^{13}H NMR (100 MHz, $CDCl_3$): δ=25.4, 31.0, 35.7, 46.1, 51.4, 52.6, 53.1, 57.4, 62.5, 129.2, 169.8, 172.2, 183.8, 212.2.

Dimethyl (2a1R,4aS)-6-oxodecahydrocyclopenta[cd]azulene-2,2(1H)-dicarboxylate (43). Enantiomeric excess determined by SFC using Daicel Chiralpak IB-3 column (100 x 4.6 mm, 3 µm), 35 °C, CO_2/^{i}PrOH (90:10), ABPR = 1500 psi, flow rate 3.0 mL/min, λ = 225 nm: t_{major} = 1.55 min; t_{minor} = 1.66 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.30-1.10 (m, 3H), 1.45-1.30 (m, 1H), 2.00-1.90 (m, 1H), 2.18-2.00 (m, 3H), 2.25-2.20 (m, 1H), 2.55 (ddd, *J* = 12.9, 7.7, 5.7 Hz, 1H), 3.00 (dt, *J* = 18.5, 1.1 Hz, 1H), 3.16 (dddt, *J* = 13.3, 7.1, 2.2, 1.4 Hz, 1H), 3.58 (ddt, *J* = 18.5, 2.2, 1.1 Hz, 1H), 3.77 (s, 3H), 3.78 (s, 3H), 5.86 (td, *J* = 2.1, 1.1 Hz, 1H). ^{1}H NMR (100 MHz, $CDCl_3$): δ=27.2, 28.2, 30.2, 30.4, 36.4, 48.8, 49.5, 52.7, 52.8, 54.1, 62.3, 124.8, 171.2, 171.3, 182.8, 211.4.

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5.4.6. References

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5.5. Application of pyranoside phosphite-pyridine ligands to enantioselective Pd-catalyzed allylic substitutions

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***Abstract**: A series of glucopyranoside phosphite-pyridine ligands have been applied in the Pd-catalyzed allylic substitution reactions of several substrate types. We have been able to identify ligands that provided promising enantioselectivities in the Pd-catalyzed intermolecular allylic substitution of cyclic substrates (ee's up to 86%) and desymmetrization (ee's up to 94%).*

5.5.1. Introduction

Nowadays the preparation of enantiomerically pure compounds plays a vital role in important areas such as pharmaceuticals, agrochemicals, fine chemicals, and natural product chemistry. Asymmetric catalysis has emerged as a powerful tool for producing enantiopure compounds. In this respect the metal-catalyzed allylic substitution[1] is one of the most powerful carbon-carbon bond forming reactions for the construction of enantioenriched synthons for both biologically active and natural compounds. The significant advantage of these processes is their high compatibility with many functional groups. In order to achieve the highest levels of reactivity and selectivity in metal-catalyzed asymmetric reactions, several reaction parameters must be optimized, the most crucial of which is perhaps the design of the chiral ligand.

Over the last few years, a variety of sugar-derived ligands have been successfully employed in several asymmetric metal-catalyzed processes.[2] Interest toward this class of building blocks is justified by numerous advantages: the availability of stereogenic centers at low cost, access to different epimers, abundance of groups that can be straightforwardly functionalized in order to modulate the coordinating and the steric and electronic properties of the ligands. On this basis, modular libraries of ligands are approachable by the suitable choice of a sugar backbone and the coordinating motifs. In this context, however, bidentate P,N-ligands based on a glucopyranose backbone have been poorly explored,[3] and mostly when the coordinating functions are provided by phosphite and pyridine moieties. This is in contrast with the importance of heterodonor P,N-ligands, which have been successfully applied in many useful processes.[4] Their versatility is mainly due to the contemporaneous presence of a soft and a hard coordinating function.[5] The hard end weakly coordinates to soft metal centers, and easily dissociates in solution. This provides a vacant site whenever demanded, but also has a chance of stabilizing the metal by chelation in the absence of competing donors.

For these reasons, we recently decided to prepare and investigate the performance of pseudo-enantiomeric classes of glucosebased P,N-ligands (Figure 5.5.1) in asymmetric reactions where phosphite-pyridine systems are known to be effective,[6] such as the asymmetric allylic alkylations and alkene hydrogenations.[7] In a previous paper,[8] we

described the synthesis and the behavior of part of ligands **L59** and **L60** (Figure 5.5.1) in the Ir-catalyzed hydrogenation of poorly functionalized alkenes (see Chapter 3, section 3.6). Satisfactory results were attained, which also allowed a reasonable rationalization of the factors which affect the enantioselectivity of the reaction.

Herein we report an extension of the type **1** family, and use of the two classes of ligands in asymmetric Pd-catalyzed allylic substitution. These ligands contemplate systematic variations of the position of the phosphite group at both C-2 (ligands **L59**) and C-3 (ligands **L60**) of the pyranoside backbone, as well as different substituents and configurations in the biaryl phosphite moiety **a**-**f** with the aim of maximizing the catalyst performance.

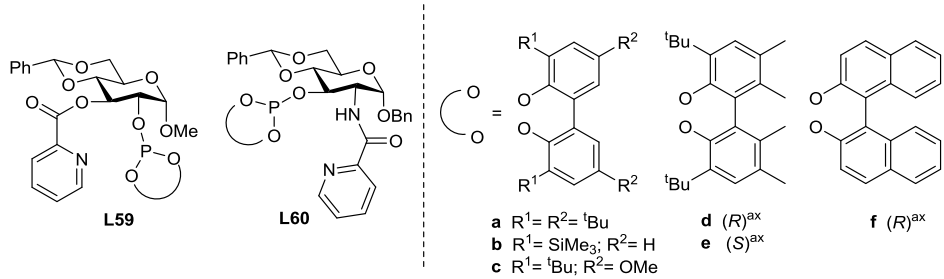


Figure 5.5.1. Carbohydrate-based phosphite-pyridine ligands **L59a-f** and **L60a,c,d**.

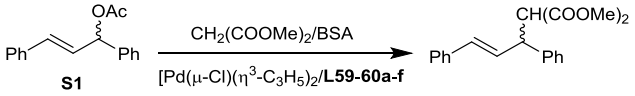
5.5.2. Results and discussion.

5.5.2.1. Synthesis of the ligands

The structure of the two libraries was developed by immediate functionalization of the easily available D-glucose and D-glucosamine as described in Chapter 3.2 (section 3.6, Scheme 3.6.1).[8] The new phosphite-pyridine ligands **L59c** and **L59f** were synthesized using the procedure previously described for ligands **L59a**-**b**,**d**-**e**. They were stable during purification on neutral alumina under an atmosphere of argon and isolated as white solids. They were stable at room temperature and very stable to hydrolysis. The elemental analyses were in agreement with the assigned structure. The ^{1}H, ^{13}C and ^{31}P NMR spectra were as expected for these C_1 ligands. Thus, rapid ring inversions (tropoisomerization) in the biphenyl-phosphorus moiety **c** occurred on the NMR timescale, since the expected diastereoisomers were not detected by low-temperature phosphorus NMR.[9]

5.5.2.2. Asymmetric Pd-catalyzed allylic alkylation reactions

For the initial evaluation of phosphite–pyridine ligands **L59**-**69a**-**f**, we chose the Pd-catalyzed allylic substitution of *rac*-1,3-diphenyl-3-acetoxyprop-1-ene **S1**, which is widely used as a model substrate, with dimethyl malonate (Scheme 5.5.1). The catalysts were generated in situ from the π-allyl-palladium chloride dimer $[PdCl(\eta^3\text{-}C_3H_5)]_2$, the corresponding ligand and a catalytic amount of the corresponding base. The nucleophile was generated from dimethyl malonate in the presence of N,O-bis(trimethylsilyl)-acetamide (BSA).



Scheme 5.5.1. Asymmetric Pd-catalyzed allylic alkylation of the model substrate *rac*-**S1**.

The effects of the solvent and ligand-to-palladium ratio were investigated using the catalyst precursor containing ligand **L59a** (Table 5.5.1). Our results show that both solvent and ligand-to-palladium ratio affected the catalytic performance. The optimum trade-off between enantioselectivities and activities was obtained when dichloromethane (DCM) was used as a solvent and without excess of ligand (Table 5.5.1, entry 6). Toluene and THF provided the lowest activities and enantioselectivities (Table 5.5.1, entries 2 and 3). On the other hand, the activity obtained with DMF was higher than in dichloromethane, but the enantioselectivity was lower (Table 5.5.1, entries 4 vs 1). It should be noted that the sense of enantioselectivity achieved in DMF is opposite to that of DCM, which suggests that the coordination of DMF plays a role in the active species, probably replacing the pyridine moiety and therefore forcing the ligand to coordinate in a monodentate manner.[10]

Table 5.5.1. Asymmetric allylic alkylation of *rac*-**S1** with dimethylmalonate using ligand **L59a**. Effect of the solvent and ligand-to-palladium ratio.[a]

Entry	Solvent	Ratio L/Pd	% Conv[b] (h)	%ee[c]
1	DCM	1.1/1	100 (8)	41 (*R*)
2	Toluene	1.1/1	18 (20)	0 (*S*)
3	THF	1.1/1	16 (8)	6 (*R*)
4	DMF	1.1/1	100 (2)	26 (*S*)
5	DCM	2/1	100 (8)	34 (*R*)
6	DCM	0.75/1	100 (8)	42 (*R*)

[a] Reaction conditions: 2 mL of solvent, 0.005 mmol of $[Pd(\mu\text{-}Cl)(\eta^3\text{-}C_3H_5)]_2$, 0.5 mmol of substrate, 0.2 mL of dimethylmalonate, 0.4 mL of BSA, a small amount of KOAc at rt. [b] Evaluated by NMR spectroscopy of the crude reaction mixture. Reaction time in hours shown in parentheses. [c] Determined by HPLC on a Chiralcel-OJ column.

Varying the ligand-to-palladium ratio showed that an excess of ligand was not needed (Table 5.5.1, entries 1 vs 6). The enantioselectivity diminished upon increasing the amount of ligand (Table 5.5.1, entry 5), probably due to the formation of a less selective PdL_2 species.[10]

Under the optimized reaction conditions (i.e., dichloromethane as the solvent and an L/Pd ratio of 0.75) we tested the remaining ligands. The results, which are summarized in Table 5.5.2, indicate that enantioselectivities are affected by the position of the phosphite moiety at either C-2 (ligands **L59**) or C-3 (ligands **L60**) of the pyranoside backbone as well as the substituents/configuration of the biaryl phosphite moiety.

The use of ligands **L60** with the phosphite group attached to the C-3 of the pyranoside backbone showed much lower activities and enantioselectivities than those obtained with the catalytic system Pd/**L59** (i.e., Table 5.5.2, entries 1 and 7).

The effect of the substituents and configuration at the biaryl phosphite moiety was studied using ligands **L59-f**. With regard to the effect of the substituents at the biphenyl phosphite moiety, we found that the presence of bulky trimethylsilyl groups at the *ortho*

position had a positive effect on the enantioselectivity (Table 5.5.2, entries 2 vs 1 and 3), while the presence of methoxy groups at the *para*-positions had a negative effect (Table 5.5.2, entry 3). With ligands **L59d** and **L59e**, which contain different, and enantiomerically pure biphenyl moieties, we found that there was a cooperative effect between the configuration of the biaryl moiety and the ligand backbone on the enantioselectivity. This led to a matched combination for ligand **L59d**, which contains an (*R*)-biphenyl moiety (Table 5.5.2, entry 4). In addition, if we compare the results of using ligands **L59a**-**e**, we can also conclude that although the fluxional biphenyl phosphite moieties in ligands **L59a**-**c** adopt mainly the (*R*)-configuration, the tropoisomerism of the fluxional biphenyl moieties in ligands **L59a**-**c** is controlled by substituents at the *ortho*- and *para*-positions of the biphenyl phosphite moiety. Thus, for example while the presence of bulky trimethyl silyl groups at the *ortho*-positions controls the tropoisomerization almost completely, the presence of methoxy groups at the *para*-positions led to poor tropoisomerism control.

Table 5.5.2. Asymmetric allylic alkylation of *rac*-**S1** with dimethylmalonate using ligands **L59**-**60a**-**f**.[a]

Entry	Ligand	% Conv[b] (h)	% ee[c]
1	**L59a**	100 (8)	42 (*R*)
2	**L59b**	86 (8)	50 (*R*)
3	**L59c**	100 (8)	35 (*R*)
4	**L59d**	100 (8)	52 (*R*)
5	**L59e**	100 (8)	21 (*S*)
6	**L59f**	100 (8)	26 (*S*)
7	**L60a**	6 (8)	0
8	**L60d**	11 (8)	2 (*S*)
9	**L60e**	19 (8)	0

[a] Reaction conditions: 2 mL of CH_2Cl_2, 0.005 mmol of $[Pd(\mu\text{-}Cl)(\eta^3\text{-}C_3H_5)]_2$,0.0075 mmol of ligand, 0.5 mmol of substrate, 0.2 mL of dimethylmalonate, 0.4 mL of BSA, a small amount of KOAc at rt. [b] Evaluated by NMR spectroscopy of the crude reaction mixture. Reaction time in hours shown in parentheses. [c] Determined by HPLC on a Chiralcel-OJ column.

We next applied ligands **L59**-**60a**-**f** in the allylic alkylation of the less sterically demanding linear substrate *rac*-1,3-dimethyl-3-acetoxyprop-1-ene **S2** and cyclic substrates *rac*-3-acetoxycyclohexene **S3** (widely used as a model substrate), *rac*-3-acetoxycyclopentene **S4**, and *rac*-3-acetoxycycloheptene **S5** (Figure 5.5.2). For these substrates, it is usually more difficult to control the enantioselectivity, mainly because of the presence of less sterically hindering substituents, which are thought to play a crucial role in the enantioselection observed in the corresponding Pd-allyl intermediate.

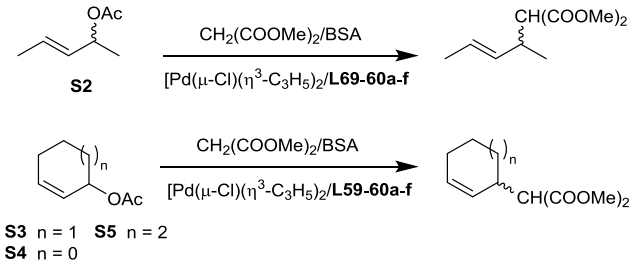


Figure 5.5.2. Asymmetric Pd-catalyzed allylic alkylation of unhindered linear substrate *rac*-**S2** and cyclcic *rac*-**S3**-**S5**.

Our preliminary investigations into the solvent effect using ligand **L59a** provided a different trend to that observed in the previously tested hindered substrate **S1** (Table 5.5.3). The optimum compromise between enantioselectivities and reaction rates was therefore obtained when DMF was used as a solvent (entry 4).

Table 5.5.3. Asymmetric allylic alkylation of unhindered linear *rac*-**S2** and cyclic *rac*-**S3** substrates with dimethylmalonate using ligand **L59a**. Effect of the solvent.[a]

Entry	Solvent	**S2**		**S3**	
		% Conv[b] (h)	% ee[c]	% Conv[b] (h)	% ee[c]
1	DCM	56 (8)	4 (*S*)	5 (18)	19 (*R*)
2	Toluene	10 (8)	0	<5 (18)	nd
3	THF	24 (8)	9 (*S*)	15 (18)	16 (*R*)
4	DMF	100 (8)	10 (*R*)	25 (18)	14 (*R*)

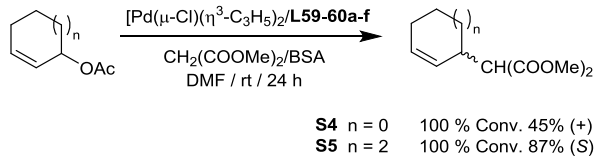
[a] Reaction conditions: 2 mL of solvent, 0.005 mmol of $[Pd(\mu\text{-}Cl)(\eta^3\text{-}C_3H_5)]_2$, 0.0075 mmol of ligand, 0.5 mmol of substrate, 0.2 mL of dimethylmalonate, 0.4 mL of BSA, a small amount of KOAc at rt. [b] Evaluated by GC. Reaction time in hours shown in parentheses. [c] Determined by GC on a Chiralsil-Dex CB column.

Under the optimized conditions, the results in Table 5.5.4 again showed that ligands **L59** provided better enantioselectivities than ligands **L60** (entries 1, 4 and 5 vs 7-9). However, the effect of the substituents and the configuration at the biaryl phosphite moiety depends on the substrate type and it is different from substrate **S1**. Thus, for linear substrate **S2** the best results were achieved using ligand **L59e** (ee's up to 33%; Table 5.5.4, entry 5), for cyclic substrates, the highest enantioselectivities were obtained when using the Pd/**L59f** catalytic system (ee's up to 86%; Table 5.5.4, entries 6 and 10). For the linear substrate **S2**, enantioselectivities were poor, while for the unhindered cyclic substrate **S3**, enantioselectivities increased up to 86% (Table 5.5.4, entry 10). This latter result encouraged us to test other cyclic substrates (Scheme 5.5.2). For the seven-membered cyclic substrate **S5**, enantioselectivities of up to 87% were obtained.

Table 5.5.4. Asymmetric allylic alkylation of unhindered linear *rac*-**S2** and cyclic *rac*-**S3** substrates with dimethylmalonate using ligands **L59**-**69a**-**f**.[a]

Entry	Ligand	S2		S3	
		% Conv[b] (h)	% ee[c]	% Conv[b] (h)	% ee[c]
1	**L59a**	100 (8)	10 (*R*)	25 (18)	14 (*R*)
2	**L59b**	100 (6)	16 (*R*)	32 (20)	50 (*S*)
3	**L59c**	100 (6)	9 (*R*)	25 (20)	21 (*S*)
4	**L59d**	100 (6)	2 (*R*)	52 (20)	30 (*R*)
5	**L59e**	100 (6)	33 (*R*)	1 (20)	59 (*S*)
6	**L59f**	100 (6)	12 (*R*)	83 (20)	72 (*S*)[d]
7	**L60a**	100 (6)	0	6 (20)	30 (*R*)
8	**L60d**	100 (6)	2 (*R*)	11 (20)	16 (*R*)
9	**L60e**	100 (6)	2 (*R*)	9 (20)	22 (*S*)
10	**L60f**	-	-	21 (120)	86 (*S*)

[a] Reaction conditions: 2 mL of DMF, 0.005 mmol of $[Pd(\mu\text{-}Cl)(\eta^3\text{-}C_3H_5)]_2$, 0.0075 mmol of ligand, 0.5 mmol of substrate, 0.2 mL of dimethylmalonate, 0.4 mL of BSA, a small amount of KOAc at rt. [b] Evaluated by GC. Reaction time in hours shown in parentheses. [c] Determined by GC on a Chiralsil-Dex CB column. [d] The same reaction carried out in dichloromethane afforded 6% conversion in 64% ee (*S*). [e] Reaction carried out at 0 °C.

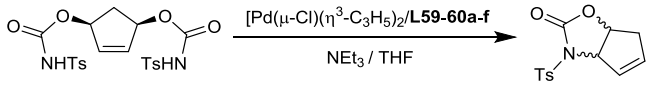


Scheme 5.5.2. Pd-catalyzed allylic alkylation of cyclic substrates **S4** and **S5**.

Finally, the ligands were examined in an intramolecular allylic substitution (Table 5.5.5); namely the desymmetrisation of mesocyclopent-2-ene-1,4-diol **S6**, which affords a key precursor of the mannostatines.[11] In contrast to the intermolecular allylic alkylation of **S1**-**S5**, the catalysts were generated in situ from $[Pd_2(dba)_3(CHCl_3)]$, the corresponding ligand and using triethylamine as a base, which are used as the standard conditions.[11]

The results shown in Table 5.5.5 indicate that enantioselectivities were affected by the position of the phosphite moiety at either C-2 (ligands **L59**) or C-3 (ligands **L60**) of the pyranoside backbone as well as the substituents of the biaryl phosphite moiety, while there was no effect on the configuration of the biaryl phosphite moiety. In contrast to previously used substrates **S1**-**S5**, although the activities achieved with ligands **L60** were much lower than with ligands **L59**, the enantioselectivities were higher with ligands **L60** (Table 5.5.5, entries 4-5 vs 8-9). In general, the enantioselectivity seemed to be enhanced by the significant overall steric hindrance of the phosphite moiety, as found in **L59f**, which allowed us to obtain the chiral product in high ee (94%, entry 6).

Table 5.5.5. Intramolecular asymmetric allylic substitution of *meso*-**S6** using ligands **L59**-**60a**-**f**.[a]



Entry	Ligand	% Conv[b] (h)	% ee[c]
1	**L59a**	100 (0.5)	76 (+)-(*S*,*R*)
2	**L59b**	67 (0.5)	80 (+)-(*S*,*R*)
3	**L59c**	100 (0.5)	62 (+)-(*S*,*R*)
4	**L59d**	93 (0.5)	19 (+)-(*S*,*R*)
5	**L59e**	100 (0.5)	17 (+)-(*S*,*R*)
6	**L59f**	92 (0.5)	94 (+)-(*S*,*R*)
7	**L60a**	<10 (0.5)	nd
8	**L60d**	26 (0.5)	61 (+)-(*S*,*R*)
9	**L60e**	55 (0.5)	54 (+)-(*S*,*R*)

[a] Reaction conditions: 1 mL of THF, 0.005 mmol of $[Pd_2(dba)_3(CHCl_3]$, 0.015 mmol of ligand, 0.2 mmol of substrate, 0.3 mL of triethylamine at rt. [b] Evaluated by NMR spectroscopy of the crude reaction mixture. Reaction time in hours shown in parentheses. [c] Determined by HPLC on a Chiralcel-ODH column.

5.5.3. Conclusion

A series of phosphite-pyridine ligands with the readily available glucopyranoside backbone have been applied in the Pd-catalyzed allylic substitution of several substrate types. By varying the position of the phosphite moiety and the substituents/configuration at the biaryl phosphite moiety we have been able to identify ligands that provide high enantioselectivities in the Pd-catalyzed intermolecular allylic substitution of cyclic substrates **S3**-**S5** (ee's up to 86%) and desymmetrization of *meso*-cyclopent-2-ene-1,4-diol **S6** (ee's up to 94%).

5.5.4. Experimental

5.5.4.1. General

All reactions were carried out using standard Schlenk techniques under an atmosphere of argon or nitrogen. Solvents were purified and dried by standard procedures. ^{1}H, $^{13}C\{^{1}H\}$ NMR and $^{31}P\{^{1}H\}$ NMR spectra were recorded on a Varian Gemini 400 MHz spectrometer. Chemical shifts are relative to TMS (^{1}H and ^{13}C) as internal standard or H_3PO_4 (^{31}P) as external standard. Ligands **L59a**-**b**,**d**-**e** and **L60a**-**f** were prepared as described in Chapter 3 (section 3.6).

5.5.4.2. Typical procedure for the preparation of phosphite–pyridine ligands L59c,f

The corresponding phosphorochloridite (0.55 mmol) produced in situ[12] was dissolved in toluene (2.5 mL) and pyridine (0.15 mL, 1.95 mmol) was added. The corresponding pyridine-hydroxyl compound 3 (0.5 mmol) was azeotropically dried with toluene (3x2 mL) and then dissolved in toluene (2.5 mL) to which pyridine (0.15 mL, 1.95 mmol) was added. The alcohol solution was then transferred slowly to a solution of phosphorochloridite. The reaction mixture was stirred at 80 °C for 90 min, and the pyridine salts were removed by filtration. Evaporation of the solvent gave a white foam, which was purified by flash

chromatography in alumina (toluene/NEt_3 = 100/1) to produce the corresponding ligand as a white solid.

L59c. Yield: 131 mg (34%). ^{31}P NMR (C_6D_6), δ: 145.4. 1H NMR (C_6D_6), δ: 1.53 (s, 9H, CH_3, ^tBu), 1.56 (s, 9H, CH_3, ^tBu), 2.92 (s, 3H, CH_3–O), 3.29 (s, 3H, CH_3–O), 3.32 (s, 3H, CH_3–O), 3.38 (m, 1H, H-6), 3.64 (m, 1H, H-4), 3.93 (m, 1H, H-5), 4.04 (dd, 1H, H-6', $^3J_{6'-6}$ = 10.4 Hz, $^3J_{6'-5}$ = 5.2 Hz), 4.53 (d, 1H, H-1, $^3J_{1-2}$ = 3.6 Hz), 4.94 (m, 1H, H-2), 5.10 (s, 1H, H-7), 6.38 (m, 1H, H-3), 6.5–8.4 (m, 13H, CH=). ^{13}C NMR (C_6D_6), d: 30.8 (CH_3, ^tBu), 30.9 (CH_3, ^tBu), 35.2 (C, ^tBu), 54.6 (CH_3-O), 54.7 (CH_3-O), 54.8 (CH_3-O), 62.5 (C-5), 68.5 (C-6), 71.4 (d, C-3, $^3J_{C-P}$ = 3.8 Hz), 72.8 (C-2), 79.6 (C-4), 99.6 (C-1), 101.2 (C-7), 128-165 (aromatic carbons). Anal. Calcd (%) for $C_{42}H_{48}NO_{11}P$: C, 65.19; H, 6.25; N, 1.81. Found: C, 65.16; H, 6.27; N, 1.80.

L59f. Yield: 144 mg (41%). ^{31}P NMR (C_6D_6), δ: 150.6. ^1H NMR (C_6D_6), δ: 2.82 (s, 3H, CH_3, CH_3–O), 3.40 (m, 1H, H-6), 3.62 (m, 1H, H-4), 3.97 (m, 1H, CH, H-5), 4.03 (dd, 1H, H-6' , $^3J_{6'-6}$ = 10.0 Hz, $^3J_{6'-5}$ = 5.2 Hz), 4.38 (d, 1H, H-1, $^3J_{1-2}$ = 4.0 Hz), 4.72 (m, 1H, H-2), 5.24 (s, 1H, H-7), 6.45 (m, 1H, CH=), 6.50 (m, 1H, H-3), 6.8–8.4 (m, 20H, CH=). ^{13}C NMR (C_6D_6), δ: 54.8 (CH_3-O), 62.4 (C-5), 68.6 (C-6), 71.9 (C-3), 74.1 (d, C-2, $^3J_{C-P}$ = 13.7 Hz), 79.4 (C-4), 99.5 (d, C-1, $^3J_{C-P}$ = 4.6 Hz), 101.4 (C-7), 121–165 (aromatic carbons). Anal. Calcd.(%) for $C_{40}H_{32}NO_9P$: C, 68.47; H, 4.60; N, 2.00. Found: C, 68.38; H, 4.57; N, 1.97.

5.5.4.3. Typical procedure for the allylic alkylation of substrates S1–S5

A solution of $[Pd(\mu\text{-}Cl)(\eta^3\text{-}C_3H_5)]_2$ (0.005 mmol) and ligand in the desired solvent (1.0 mL) was stirred for 30 min. Next, a solution of the corresponding substrate (0.5 mmol) in the same solvent (1.0 mL), dimethylmalonate (0.200 mL), N,O-bis(trimethylsilyl) acetamide (0.400 mL, 1.5 mmol), and a small amount of KOAc were added. The reaction mixture was then stirred at room temperature. After the desired reaction time, the reaction mixture was diluted with Et_2O (5 mL) and a saturated aqueous NH_4Cl solution (25 mL) was added. The organic phase was extracted and dried over $MgSO_4$. For substrate **S1**, the solvent was removed and the conversion was measured by ^1H NMR. To determine the ee by HPLC (Chiralcel OJ-H, 13% 2-propanol/hexane, flow 0.5 mL/min), a sample was filtered through basic alumina using dichloromethane as the eluent.[13] For substrates **S2**, **S3**, and **S5**, the conversion and enantiomeric excess were determined by GC (Chiralsil-Dex CB column).[14] For substrate **S4**, the conversion was measured by ^1H NMR and the ee was determined by ^1H NMR using $[Eu(hfc)_3]$.[15]

5.5.4.4. Typical procedure for the desymmetrisation of S6

meso-2-Cyclopenten-1,4-diol-isocyanate (0.10 g, 0.20 mmol), $[Pd_2(dba)_3]\cdot CHCl_3$ (0.005 g, 0.005 mmol), and the ligand (0.015 mmol) were dissolved in dry THF (1 mL) containing triethylamine (0.030 g, 0.30 mmol). The mixture was then stirred at room temperature, and, after the required reaction time, the solvent was removed under vacuum. Column chromatography on silica gel (1:2 ethyl acetate/hexane) gave the desired product as a white solid in 80–85% yield. The conversion was measured by ^1H NMR and the ee was determined by HPLC on a Chiralcel OD-H column.

5.5.5. References

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5.6. Screening a new readily available phosphite-triazole ligand library in asymmetric Pd-catalyzed allylic alkylation reactions

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***Abstract**: The preliminary results from the application of the new readily available phosphite-triazole ligand library **L61**-**67a**-**c** in the asymmetric Pd-catalyzed allylic alkylation of different model substrates with dimethyl malonate is herein presented. Moderate to high enantioselectivities were achieved in the alkylation of diphenylated linear susbtrate **S1** (ee's up to 91%). Moreover, in the alkylation of the more challenging substrate **S2**, both product enantiomers could be obtained in up to 76% ee by simply changing the configuration of the axially chiral biphenyl moiety. Finally, ligands **L61**-**67a**-**c** were also applied in the alkylation of the difficult unsymmetrical linear substrate **S3** but unfortunatelly, low regio- and enantioselectivities were achieved.*

5.6.1. Introduction

Asymmetric Pd-catallyzed allylic substitution is nowadays an important tool for organic synthesis. It allows the formation of different kind of bonds (carbon-carbon and carbon-heteroatom) under mild conditions with high regio- and stereoselectivity.[1] Consequently it has been widely used as a key step for the preparation of many bioactive compounds.[1d]

The first example of an enantioselective Pd-catallyzed allylic substitution reaction with a stabilized nucleophile came in 1977.[2] Since then, a huge improvement on the enantioselectivity has been seen in this field. Many efforts have been done in the search of catalytic systems able to induce high levels of enantioselectivity. Hence, a large number of chiral ligands has been developed for this purpose. Most of the successful ligands applied in this field are heterodonor bidentate P,N-ligands (mainly phosphine/phosphinite-oxazoline) because of their ability of electronically differenciate the two carbon allylic termini due to the different *trans* influences of both donor groups.[1]

However, the catalytic systems developed to date still have some drawbacks. There are few catalysts able to provide high enantioselectivities in the allylation of several substrate types.[1] Our group discovered that the introduction of a phosphite moiety in the ligand scaffold was advantageous in terms of activity and enantioselectivity. This is because its larger π-acceptor character increases reactions rates and its flexibility enables the catalyst chiral pocket to adapt to both hindered and unhindered susbstrates. In addition, in the allylic substitution of monosubstitited linear substrates, regioselectivity towards the desired branched isomer increased because of the π-acceptor ability of the phosphite moiety (which makes the most substituted allylic terminal carbon atom more electrophilic through the *trans* influence) that together with the steric effect of the ligand favors the nucleophilic attack at this carbon atom.[3] Therefore, our group has developed several successful phosphite-oxazoline ligands for Pd-catalyzed allylic substitutions.[4]

On the other hand, only few successful heterodonor ligands that incorporate more robust groups than oxazolines (e.g amine,[5] pyridine,[6] thioether[7]) have been effective in this transformation and most of them are limited in terms of substrate scope. To address this point, our group has recently reported the application of phosphite-pyridine/thioether/amine ligands in the Pd-catalyzed substitution of several substrate types with different nucleophiles.[8]

In chapter 3 (section 3.7) we have reported the synthesis of a new readily available P,N-ligand library (**L61**-**67a**-**c**, Figure 5.6.1) that incoroporates a robust triazole ring in the ligand structure and we have applied them in the Ir-catalyzed hydrogenation of minimally functionalized olefins. Having in mind that ligands able to catalyze several processes are of interest, we wanted to see if these new phosphite-triazole ligands were effective in Pd-catalyzed allylic alkylation reactions. Hence, we present in this chapter the application of new phosphite-triazole ligand library **L61**-**67a**-**c** in the Pd-alkylation of the benchmark substrates (*rac*)-1,3-diphenyl-3-acetoxyprop-1-ene (**S1**), (*rac*)-3-acetoxycyclohexene (**S2**) and (*rac*)-1-(naphthalen-1-yl)allyl acetate (**S3**) with dimethyl malonate.

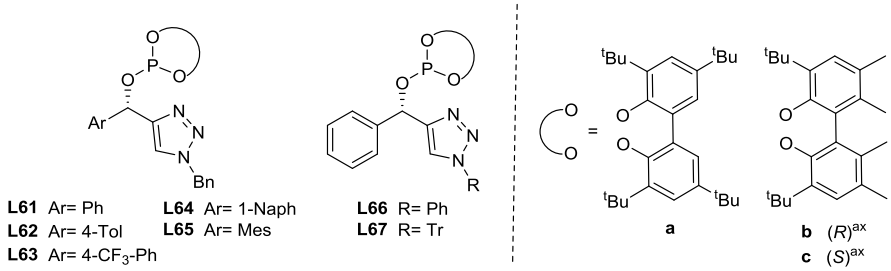


Figure 5.6.1. Phosphite-triazole ligand library **L61**-**L67a**-**c**.

5.6.2. Results and discussion

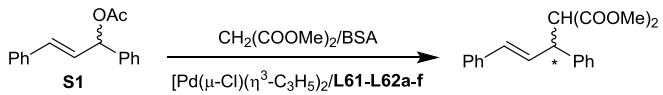
5.6.2.1. Allylic alkylation of the symmetrical linear disubstitued substrate (*rac*)-1,3-diphenyl-3-acetoxyprop-1-ene (S1)

Ligands **L61**-**67a**-**c** were initially screened in the Pd-allylic alkylation of the linear disubstituted substrate (*rac*)-1,3-diphenyl-3-acetoxyprop-1-ene (**S1**) using dimethyl malonate as nucleophile. Table 5.6.1 shows the catalytic results. All ligands led to full conversions after only 2h. We can see that an enantiomerically pure biphenyl phosphite moiety is needed in order to achieve high enantioselectivities. Therefore, whereas the use of ligand **L61a**, which contains a tropoisomeric phosphite biphenyl group, afforded the racemic alkylated product (Table 5.6.1, entry 1), ligands **L61**-**67b**-**c** provided moderate to high enantioselectivities (ee's up to 91%, Table 5.6.1, entry 2-13). In addition, both product enantiomers were achieved in most of the cases by simply changing the configuration of the biphenyl phosphite group (**b** or **c**).

Apart from the biaryl phosphite moiety, the synthetic strategy used for synthesizing ligands **L61**-**67a**-**c** allows the fine tuning of the ligand backbone (see Chapter 3, section 3.7. Scheme 3.7.1). Therefore, both the aryl group and the *N*-substituent of the triazole ring can

be easily modified. We therefore studied the effect of *para*-substitutents in the aryl group with ligands **L62**-**L63b**-**c**, the effect of having bulky aryl groups with ligands **L64**-**65b**-**c**, and the effect of modifying the *N*-substituent of the triazole ring with ligands **L66**-**67a**-**c**. In general, no significantly changes were observed on the enantioselectivity when using modified ligands **L62**-**67a**-**c**. However, the introduction of a donor *p*-CH_3 in the aryl group (**L63b**) led to an improved enantioselectivity. Hence, ee values up to 91% could be achieved in the alkylation of model substrate **S1** (Table 5.6.1).

Table 5.6.1. Pd-catalyzed allylic alkylation of model substrate **S1** with dimethyl malonate using ligands **L61**-**67**.[a]



Entry	Ligand	% Conv (h)[b]	ee%[c]
1	**L61a**	100 (2)	0
2	**L61b**	100 (2)	82 (*R*)
3	**L61c**	100 (2)	75 (*S*)
4	**L62b**	100 (2)	78 (*R*)
5	**L63b**	100 (2)	91 (*R*)
6	**L63c**	100 (2)	70 (*S*)
7	**L64b**	100 (2)	85 (*R*)
8	**L65b**	100 (2)	84 (*R*)
9	**L65c**	100 (2)	81 (*S*)
10	**L66b**	100 (2)	85 (*R*)
11	**L66c**	100 (2)	74 (*S*)
12	**L67b**	100 (2)	83 (*R*)
13	**L67c**	100 (2)	53 (*S*)

[a] All reactions were run at 23 °C, 1 mol% $[Pd(\mu\text{-}Cl)(\eta^3\text{-}C_3H_5)]_2$, CH_2Cl_2 as solvent, 2 mol% of ligand, 0.25M substrate. [b] Evaluated by NMR spectroscopy of the crude reaction mixture. Reaction time in hours shown in parentheses. [c] Determined by HPLC on a Chiralcel-OJ column.

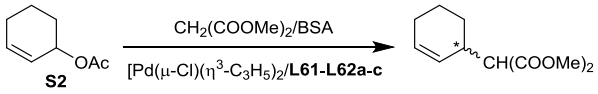
5.6.2.2. Allylic alkylation of the undemanding cyclic disubstituted substrate (*rac*)-3-acetoxycyclohexene (S2)

The allylic substitution of cyclic substrates is more difficult to control due to the presence of sterically demanding *anti* substituents in this substrate class. These *anti* substituents are thought to to play a crucial role in the enantioselection observed in the corresponding Pd-allyl intermediates.[1]

New phosphite-triazole ligands **L61**-**67a**-**c** were also tested in the Pd-allylic alkylation of this challenging substrate (**S2**) with dimethyl malonate Table 5.6.2. The results showed again that an enantiomerically pure biphenyl moiety has to be present in the ligand structure to maximize enantioselectivities. Therefore, promising enantioselectivities in the alkylation of this challenging substrate type could be achieved with ligands **L61b** and **L61c**. In addition, both enantiomers of the alkylated product were achieved in good enantioselectivities (76 % (*R*) and 75 % (*S*), respectively). In contrast to the allylic alkylation of **S1**, in which any of the possible modifications of the chiral backbone had not a

significantly effect on the enantioselectivity, the use of either of modified ligands **L62**-**67** resulted in poorer enantioselectivities. (Table 5.6.2, entries 2-13).

Table 5.6.2. Pd-catalyzed allylic alkylation of model cyclic substrate **S2** with dimethyl malonate using ligands **L61**-**67**.[a]



Entry	Ligand	% Conv (h)[b]	ee%[c]
1	**L61a**	100 (4)	9 (*S*)
2	**L61b**	100 (4)	76 (*R*)
3	**L61c**	100 (4)	75 (*S*)
4	**L62b**	100 (4)	44 (*R*)
5	**L63b**	100 (4)	61 (*R*)
6	**L63c**	100 (4)	62 (*S*)
7	**L64b**	100 (4)	52 (*R*)
8	**L65b**	100 (4)	60 (*R*)
9	**L65c**	100 (4)	66 (*S*)
10	**L66b**	100 (4)	66 (*R*)
11	**L66c**	100 (4)	64 (*S*)
12	**L67b**	100 (4)	50 (*R*)
13	**L67c**	100 (4)	44 (*S*)

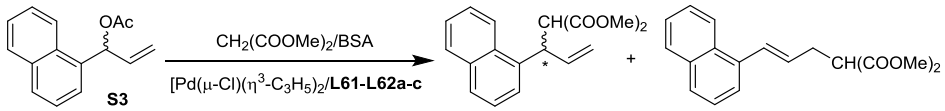
[a] All reactions were run at 23 °C, 1 mol% $[Pd(\mu\text{-}Cl)(\eta^3\text{-}C_3H_5)]_2$, CH_2Cl_2 as solvent, 2 mol% of ligand, 0.25M substrate. [b] Evaluated by NMR spectroscopy of the crude reaction mixture. Reaction time in hours shown in parentheses. [c] Determined by GC.

5.6.2.3. Allylic alkylation of the unsymmetrical linear substrate (*rac*)-1-(naphthalen-1-yl)allyl acetate (S3)

Finally, ligands **L61**-**67a**-**c** were screened in the more challenging monosubstituted linear substrate (*rac*)-1-(naphthalen-1-yl)allyl acetate (**S3**). For this kind of unsymmetrical substrates not only does the enantioselectivity need to be controlled but also the regioselectivity is a problem because a mixture of isomers can be obtained. The achiral linear product is often obtained rather than the desired chiral branched isomer.[1]

Catalytic results are summarized in Table 5.6.3. Alkylated products were afforded in full conversions after 2h in all cases. Unfortunately, mixtures of both regioisomers were obtained in low selectivities towards the branched product (up to 60/40 (b/l)). Furthermore, although ligands containing enantiopure biphenyl moieties (**b** and **c**) were able to induce some enantiocontrol, the chiral branched product was obtained in moderate-to-low enantioselectivities (ee's up to 52%; entry 6).

Table 5.6.3. Pd-catalyzed allylic alkylation of model unsymmetrical linear substrate **S3** with dimethyl malonate using ligands **L61**-**67**.[a]



Entry	Ligand	% Conv (h)[b]	b/l	ee%[c]
1	**L61a**	100 (2)	60/40	2 (*S*)
2	**L61b**	100 (2)	50/50	23 (*R*)
3	**L61c**	100 (2)	50/50	30 (*S*)
4	**L62b**	100 (2)	45/55	21 (*R*)
5	**L63b**	100 (2)	40/60	20 (*S*)
6	**L63c**	100 (2)	45/55	52 (*S*)
7	**L64b**	100 (2)	45/55	15 (*R*)
8	**L65b**	100 (2)	60/40	30 (*R*)
9	**L65c**	100 (2)	60/40	29 (*S*)
10	**L66b**	100 (2)	40/60	6 (*R*)
11	**L66c**	100 (2)	50/50	28 (*S*)
12	**L67b**	100 (2)	30/70	6 (*R*)
13	**L67c**	100 (2)	35/65	25 (*S*)

[a] All reactions were run at 23 °C, 1 mol% $[Pd(\mu\text{-}Cl)(\eta^3\text{-}C_3H_5)]_2$, CH_2Cl_2 as solvent, 2 mol% of ligand, 0.25M substrate. [b] Evaluated by NMR spectroscopy of the crude reaction mixture. Reaction time in hours shown in parentheses. [c] Determined by HPLC on a Chiralcel-OJ column.

5.6.3. Conclusions

The new readily available phosphite-triazole ligand library **L61**-**67a**-**c** was tested in the asymmetric Pd-catalyzed allylic alkylation of three different model substrates (**S1**, **S2** and **S3**) with dimethyl malonate. In all cases an enantiomerically pure biphenyl moiety was needed in order to achieve high enantioselectivities. Furthermore, the configuration of the chiral biphenyl moieties dictates the sense on the enantioselectivity. On the contrary, the enantioselectivity was only slightly dependent on the aryl group and the *N*-substituent of the triazole ring. Moderate to high enantioselectivities were achieved in the alkylation of diphenylated linear susbtrate **S1** (ee's up to 91%). Promising enantioselectivities were obtained in the alkylation of the more challenging unhindered cyclic substrate **S2**. Hence, both alkylated enantiomers of the alkylated product were obtained in up to 76% ee. However, the application of ligands **L61**-**67a**-**c** in allylic alkylation of the unsymmetrical substrate **S3** resulted in low regio- and enantioselectivities.

5.6.4. Experimental part

5.6.5. General considerations

All reactions were carried out using standard Schlenk techniques under an atmosphere of argon. Solvents were purified and dried by standard procedures. The synthesis of phosphite-triazole ligands has been previously described in Chapter 3 (section 3.2). All other reagents were used as commercially available. Substrate **S1**-**S3** were synthesized as previously descrived.[9]

5.6.4.1. Typical procedure for the allylic alkylation of substrates S1–S3

A solution of $[Pd(\mu\text{-}Cl)(\eta_3\text{-}C_3H_5)]_2$ (1.8 mg, 0.005 mmol) and ligand (0.011 mmol) in CH_2Cl_2 (1 mL) was stirred for 30 min. Next, a solution of the corresponding substrate (0.5 mmol) in the same solvent (1.0 mL), dimethylmalonate (171 µL), N,O-bis(trimethylsilyl) acetamide (370 µL, 1.5 mmol), and a small amount of KOAc were added. The reaction mixture was then stirred at room temperature. After the desired reaction time, the reaction mixture was diluted with Et_2O (5 mL) and a saturated aqueous NH_4Cl solution (25 mL) was added. The organic phase was extracted and dried over $MgSO_4$. For substrate **S1** and **S3**, the solvent was removed and the conversion was measured by ^1H NMR spectroscopy. To determine the ee by HPLC (Chiralcel OJ-H, 13% 2-propanol/hexane, flow 0.5 mL/min), a sample was filtered through basic alumina using dichloromethane as the eluent.[10] For substrate **S2** the conversion and enantiomeric excess were determined by GC (Chiralsil-Dex CB column).[11]

5.6.6. Acknowledgements

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5.6.7. References

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[5] See, for instance: a) Kubota, H.; Koga, K. *Heterocycles* **1996**, *42*, 543 (up to>95% ee for **S1**); b) Jin, M.-J.; Jung, J.-A.; Kim, S.-H. *Tetrahedron Lett*. **1999**, *40*, 5197 (up to 98% ee at 0 °C for **S1**); c) Okuyama, Y.; Nakano, H.; Hongo, H. *Tetrahedron: Asymmetry* **2000**, *11*, 1193 (up to 96% ee for **S1**); d) Widhalm, M.; Nettekoven, U.; Kalchhauser, H.; Mereiter, K.; Calhorda, M. J.; Félix, V. *Organometallics* **2002**, *21*, 315 (up to 97% ee for **S1** and 49% ee for **S2**); e) Vasse, J.-L.; Stranne, R.; Zalubovskis, R.; Gayet, C.; Moberg, C. *J. Org. Chem.* **2003**, *68*, 3258 (up to 98% ee for **S1** and 27% ee for **S2**); f) Chen, G.; Li, X.; Zhang, H.; Gong, L.; Mi, A.; Cui, X.; Jiang, Y.; Choi, M. C. K.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2002**, *13*, 809 (up to 95% ee at -20 °C for **S1**); g) Jin, M.-J.; Kim, S.-H.; Lee, S.-J.; Kim, Y.-M. *Tetrahedron Lett.* **2002**, *43*, 7409 (up to 99% ee at 10 °C for **S1**); h) Mino, T.; Hata, S.; Ohtaka, K.; Sakamoto, M. Fujita, T. *Tetrahedron Lett*. **2001**, *42*, 4837 (up to 95% ee at -20 °C for **S1**); i) Lee, E.-K.; Kim, S.-H.; Jung, B.-H.; Ahn, W.-S.; Kim, G.-J.

Tetrahedron Lett. **2003**, *44*, 1971 (up to 98% ee at 0 °C for **S1**); j) Tanaka, Y.; Mino, T.; Akita, K.; Sakamoto, M.; Fujita, T. *J. Org. Chem*. **2004**, *69*, 6679 (up to 98% ee at 20 °C for **S1**); k) Sun, X.-M.; Koizumi, M.; Manabe, K.; Kobayashi, S. *Adv. Synth. Catal.* **2005**, *347*, 1893 (up to 96% ee at -20 °C for **S1**).

[6] See, for instance: a) Bunlaksananusorn, T.; Luna, A. P.; Bonin, M.; Micouin, L.; Knochel, P. *Synlett* **2003**, 2240 (up to 96% ee for **S1**); b) Ito, K.; Kashiwagi, R.; Iwsaki, K.; Katsuki, T. *Synlett* **1999**, 1563 (up to 96% ee for **S1**); c) Goldfuss, B.; Lçschmann, T.; Rominger, F. *Chem. Eur. J.* **2004**, *10*, 5422 (up to 83% ee for **S1**); d) Liu, Q.-B.; Zhou, Y.-G. *Tetrahedron Lett.* **2007**, *48*, 2101 (up to 95% ee for **S1**); e) Meng, X.; Gao, Y.; Li, X.; Xu, D. *Catal. Commun.* **2009**, *10*, 950 (up to 97% ee for **S1** and 80% ee for **S2**); f) Leca, F.; Fernández, F.; Muller, G.; Lescop, Réau, C. R.; Gómez, M. *Eur. J. Inorg. Chem.* **2009**, 5583 (up to 12 and 31% ee for **S1** and **S2**, respectively).

[7] See: a) Evans, D. A.; Campos, K. R.; Tedrow, J. S.; Michael, F. E.; Gagné, M. R. *J. Am. Chem. Soc.* **2000**, *122*, 7905 (up to 98%, 90%, and 65% ee at -20 °C for **S1**, **S2** and **S4**, respectively); b) Nakano, H.; Okuyama, Y.; Hongo, H. *Tetrahedron Lett.* **2000**, *41*, 4615 (up to 94% ee at -30 °C for **S1**); c) García Mancheño, O.; Priego, J.; Cabrera, S.; Gómez Arrayás, R.; Llamas, T.; Carretero, J. C.; *J. Org. Chem.* **2003**, *68*, 3679 (up to 97% ee at -20 °C for **S1**); d) Enders, D.; Peters, R.; Runsink, J.; Bats, J. W. *Org. Lett*. **1999**, *1*, 1863 (up to 97% ee at -20 °C for **S1**); e) Guimet, E.; Diéguez, M.; Ruiz, A.; Claver, C. *Tetrahedron: Asymmetry* **2005**, *16*, 959 (up to 93% ee at 0 °C for **S1**); f) Caldentey, X.; Pericàs, M. A.; *J. Org. Chem.* **2010**, *75*, 2628 (up to 96% ee at RT for **S1**).

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SCREENING OF MODULAR AND READILY AVAILABLE LIGAND LIBRARIES FOR C-X (X=H, C, N AND O) BOND FORMING REACTIONS. THE USE OF DFT STUDIES FOR CATALYSTS OPTIMIZATION
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Chapter 6

Asymmetric Ni-catalyzed 1,2-addition of trialkylaluminum to aldehydes

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6. Asymmetric Ni-catalyzed 1,2-addition of trialkylaluminum to aldehydes

6.1. Background

The addition of organometallic compounds to aldehydes is an interesting method for obtaining optically active secondary alcohols, which are interesting compounds for the preparation of fine chemicals and pharmaceuticals.

As it has been discussed in the introduction, the catalytic addition of dialkylzinc reagents is most often the route of choice for obtaining chiral alcohols. However, the use of trialkylaluminum compounds as alkylating reagents is more interesting since they are economically available in industrial scale from aluminum hydride and olefins. Furthermore they have a high functional group tolerance due to their moderate reactivity. Despite these advantages there are not many examples in the literature. Two methods exist for the enantioselective addition of trialkylaluminum reagents to aldehydes. The first one is the titanium-mediated process in presence of chiral diols or *N*-sulfonylated amino alcohols. These catalysts usually afford high enantioselectivities but high catalysts loadings are needed (10-20 mol%). The second one, developed by Woodward and coworkers, is the Ni-catalyzed addition of organoaluminum compounds to aldehydes. For this latter method, only lower catalyst loadings are needed for achieving high activities (0.05-1 mol%). However, few successful ligands have been developed for this process. Most of them use chiral monodentated phosphoroamidite and phosphine ligands. Nevertheless, our group has demonstrated that bidentated phosphite-phosphoroamidite ligands are also able to induce high enantioselectivities.

With the aim to expand the range of successful ligands for this process, in this chapter, we report the first application of a phosphite-thioether ligand library (**L1**-**L19a**-**g**) in the asymmetric Ni-catalyzed 1,2-addition of trialkylaluminum reagents to aldehydes. These ligands, which have been described in Chapter 3 (section 3.2), are derived from inexpensive L-(+)-tartaric acid or D-mannitol, are highly modular and present high resistance towards oxygen and other oxidizing agents. In addition, they have been found to be high versatile ligands since we have successfully applied them in the asymmetric Rh- and Ir-catalyzed hydrogenation of functionalized and minimally functionalized olefins, and in Pd-catalyzed allylic substitution reactions (sections 3.2, 3.3 and 5.2). By carefully selecting the ligand parameters, high enantioselectivities (ee's up to 82%) were obtained in the Ni-catalyzed 1,2-addition of different alkylaluminum agents to several aryl aldehydes.

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Jèssica Margalef Pallarès

6.2. The first application of phosphite-thioether ligand family in the asymmetric Ni-catalyzed 1,2-addition of trialkylaluminum to aldehydes

Jèssica Margalef, Carlota Borràs, Oscar Pàmies and Montserrat Diéguez (preliminary results)

***Abstract**: We have shown for the first time that a chiral bidentate P,S-ligand family is able to induce enantioselectivity in the Ni-catalyzed 1,2-addition of organoaluminum reagents to aldehydes. The phosphite-thioeter ligands used in this work are prepared from inexpensive L-(+)-tartaric acid or D-mannitol and combine the advantages of a sugar core and the presence of both thioether and phosphite moieties (i.e. modular design at a low price and high stability towards oxygen and other oxidizing reagents). Excellent activities and high enantioselectivities have been obtained in the addition of different alkylaluminum reagents to several aldehydes (ee's up to 82%) by using only 1 mol% of catalyst precursor.*

6.2.1. Introduction

Chiral alcohols are highly valuable intermediates for preparing chiral pharmaceutical and agricultural products. A useful and efficient procedure for synthesizing such compounds is the asymmetric metal-catalyzed 1,2-addition of organometallic reagents to aldehydes.[1] The addition of dialkylzinc to aldehydes is the most studied 1,2-addition process.[1,2] However, trialkylaluminum compounds are more interesting than other organometallic reagents because they are economically obtained in industrial scale from aluminum hydride and olefins, and they present a high functional group tolerance.[3] Despite these advantages, their use is rare.[4,5]

Regarding the metal source, the few most successful catalysts for the enantioselective addition of trialkylaluminum reagents to aldehydes have been titanium complexes bearing chiral diols or *N*-sulfonylated amino alcohols as ligands.[4] However, the high catalyst loadings needed (10-20 mol%) and the slow turnover rates hamper the potential utility of these catalytic systems. In 2005 Woodward and coworkers overcame these limitations by using Ni-catalyst modified with chiral monodentated phosphoroamidite and phosphine ligands.[5a-b] Chiral secondary alcohols were obtained in asymmetric inductions of up to 95% ee by using low catalysts loadings. Later on, our group explored these reactions with different type of chelate ligands such as monophosphite,[5c,g] monophosphoramidite,[5e] phosphite-oxazoline,[5d] and phosphite-phosphoramidite[5d,f] carbohydrate-based ligands.

To further expand the range of ligands and performance of the asymmetric nickel-catalyzed addition of organoaluminum reagents to aldehydes, we report in this chapter the application of bidentate thioether-phosphite ligands (Figure 6.2.1). These ligands, which are derived from natural L-(+)-tartaric acid (**L1**-**L10**) or D-mannitol (**L11**-**L19**) have the advantages of sugar and phosphite cores, such as availability at low price from readily available alcohols, high resistance to oxidation, and facile modular construction. Moreover, the introduction of a thioether moiety in the ligand design may be beneficial, because the S

atom becomes a stereogenic center when coordinated to the metal, which moves the chirality closer to the metal.[6] To the best of our knowledge this is the first application of phosphite-thioether ligands in this catalytic process.

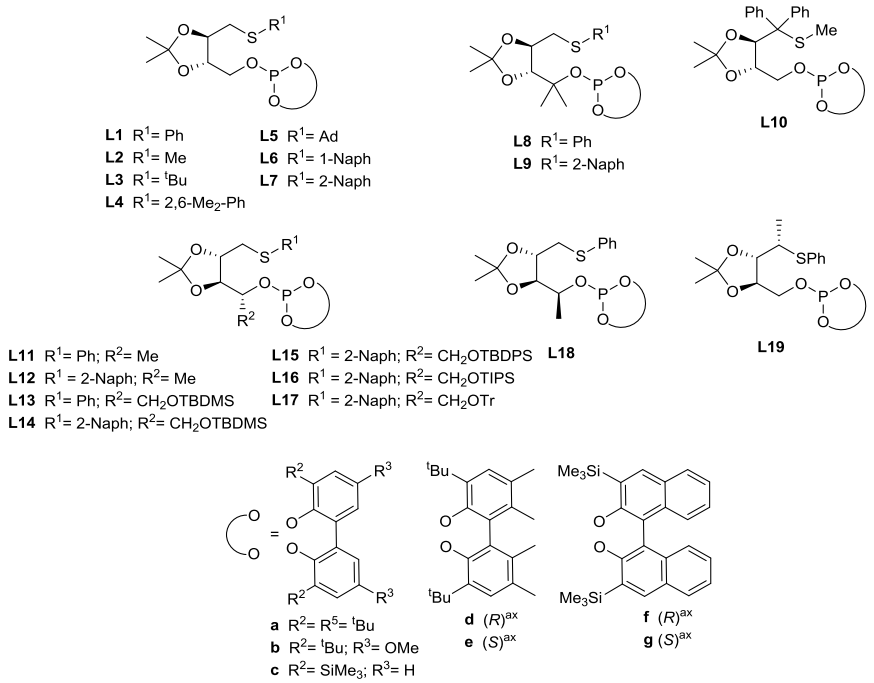


Figure 6.2.1. Carbohydrate-derived phosphite-thioether ligands **L1**-**L19a**-**g** applied in the Ni-catalyzed trialkylaluminum 1,2-addition to aldehydes.

6.2.2. Results and discussion

6.2.2.1. Asymmetric Ni-catalyzed addition of trimethylaluminum to benzaldehyde (S1)

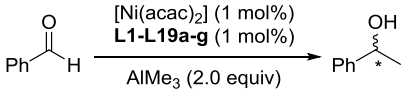
To make an initial evaluation of this new type of ligands (**L1**-**L19a**-**g**), we chose the nickel-catalyzed asymmetric addition of trimethylaluminum to benzaldehyde (**S1**), which was used as the model substrate (Table 6.2.1).[4,5] The catalytic system was generated *in situ* by adding the corresponding ligand to a suspension of the catalyst precursor [Ni(acac)$_2$] (acac = acetylacetonate). In all cases excellent isolated yields (>86%) of the desired 2-phenylethanol were obtained.

In a first set of experiments we studied the ligand-to-nickel ratio in the product outcome (entries 1-3). Our results indicated that no excess of ligand is needed for high yields and good enantioselectivities.

First, we studied the effect of the thioether substituent with ligands **L1**-**L7a** (Table 6.2.1, entries 1, 8, 9, 12, 15, 18 and 21). Enantioselectivity was mainly affected by the steric properties of these substituents. Enantioselectivities were therefore higher when more sterically demanding alkyl substituents were present (i.e., Ad > ^{t}Bu > Ph > Me). The use of

aryl thioether substituents, with different steric demands, all gave similar enantioselectivities (around 40% ee; entries 1, 12, 18 and 21).

Table 6.2.1. Selected Ni-catalyzed asymmetric addition of $AlMe_3$ to benzaldehyde using thioether-phosphite ligand library **L1**-**L19a**-**g**.[a]



Entry	Ligand	L/Ni	% Conv[b]	% ee[d]	Entry	Ligand	L/Ni	% Conv[b]	% ee[d]
1	**L1a**	1	100 (96)	42 (*R*)	23	**L7e**	1	100 (95)	29 (*R*)
2	**L1a**	0.5	98 (95)	41 (*R*)	24	**L8a**	1	100 (92)	5 (*R*)
3	**L1a**	2	100 (94)	42 (*R*)	25	**L8d**	1	100 (88)	28 (*R*)
4	**L1b**	1	100 (93)	41 (*R*)	26	**L8e**	1	100 (89)	20 (*S*)
5	**L1c**	1	100 (91)	40 (*R*)	27	**L9a**	1	100 (90)	7 (*R*)
6	**L1d**	1	100 (96)	12 (*R*)	28	**L10a**	1	100 (89)	5 (*R*)
7	**L1e**	1	100 (97)	31 (*R*)	29	**L11a**	1	100 (92)	45 (*R*)
8	**L2a**	1	100 (92)	28 (*R*)	30	**L11f**	1	100 (90)	24 (*S*)
9	**L3a**	1	100 (96)	52 (*R*)	31	**L11g**	1	100 (89)	30 (*R*)
10	**L3d**	1	100 (95)	12 (*R*)	32	**L12g**	1	100 (85)	29 (*R*)
11	**L3e**	1	100 (97)	17 (*R*)	33	**L13g**	1	100 (88)	32 (*R*)
12	**L4a**	1	100 (96)	45 (*R*)	34	**L14g**	1	100 (90)	30 (*R*)
13	**L4d**	1	100 (96)	20 (*R*)	35	**L15g**	1	100 (92)	31 (*R*)
14	**L4e**	1	100 (96)	31 (*R*)	36	**L16g**	1	100 (91)	28 (*R*)
15	**L5a**	1	100 (91)	61 (*R*)	37	**L17g**	1	100 (90)	29 (*R*)
16	**L5d**	1	100 (96)	29 (*R*)	38	**L18a**	1	100 (91)	27 (*R*)
17	**L5e**	1	100 (96)	39 (*R*)	39	**L18f**	1	100 (93)	30 (*S*)
18	**L6a**	1	100 (89)	41 (*R*)	40	**L18g**	1	100 (90)	50 (*R*)
19	**L6d**	1	100 (91)	11 (*R*)	41	**L19a**	1	100 (90)	40 (*S*)
20	**L6e**	1	100 (93)	29 (*R*)	42	**L19f**	1	100 (93)	70 (*S*)
21	**L7a**	1	100 (90)	41 (*R*)	43	**L19g**	1	100 (89)	64 (*R*)
22	**L7d**	1	100 (89)	10 (*R*)					

[a] Reaction conditions: T= -20 °C, $[Ni(acac)_2]$ (1 mol%), $AlMe_3$ (2 equiv.), substrate (1 mmol), THF (8 mL). [b] % Conversion determined by GC after 3 hours. In brackets are shown the isolated yields. [d] Enantiomeric excess measured by GC using Cyclodex-B column.

With ligands **L1**-**L7a**-**e**, we next studied the effect of the biaryl phosphite moiety on the product outcome. The results using **L1a**-**c** indicated that the substituents at both *ortho*- and *para*-positions of the biphenyl moiety had no effect on the enantioselectivity (i.e. Table 5.2.1, entries 1 vs 4 and 5). However, the results using ligands **L1**-**L7d**-**e**, which contain enantiopure biphenyl moieties, showed a clear cooperative effect between the configuration of the biaryl phosphite moiety and the ligand backbone. This resulted in a matched combination for ligands **L1**-**L7e**, which contains an enantiopure (*S*)-biphenyl phosphite moiety (Table 6.2.1, i.e. entry 7 vs 6). Nevertheless, it should be pointed out that the highest enantioselectivities were achieved using ligands containing tropoisomeric biphenyl moieties (Table 6.2.1, i.e. entries 1 vs 6 and 7).

The results using ligands **L8**-**L10** indicated that the presence of two substituents attached either to the carbon close to the phosphite moiety or to the carbon close to the

thioether group had a negative effect on enantioselectivity (entries 24-28). Similarly, the use of ligands **L11**-**L18**, with several substituents attached to the stereogenic carbon next to the phosphite group, also had a negative effect on enantioselectivity regardless the configuration of the stereogenic carbon atom.

Nevertheless, the use of ligands **L19**, with a stereogenic carbon atom adjacent to the thioether group, had a positive effect on enantioselectivity. Moreover, we observed a cooperative effect between the configuration of the biaryl phosphite group and the ligand backbone, that results in a matched combination for ligand **L19f**, containing an (*R*)-biaryl phosphite group. In summary, the best enantioselectivity (up to 70% ee) was achieved with **L19f**, which has the appropriate combination of ligand parameters.

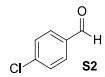
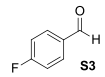
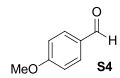
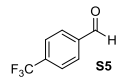
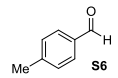
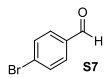
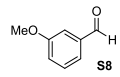
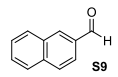
6.2.2.2. Asymmetric Ni-catalyzed of several organoaluminum reagents to a range of aldehydes

To further assess the catalytic efficiency of the Ni/**L19f** catalytic system, we next tested it in the nickel-catalyzed addition of several trialkylaluminum sources (AlR_3, R = Me or Et; and DABAL-Me_3) to other benchmark aldehydes with different steric and electronic properties. The results are summarized in Table 6.2.2.

The results using trimethylaluminum as alkylating reagent indicated that catalytic performance (activity and enantioselectivity) were hardly affected by the presence of either electron-donating or electron-withdrawing groups at the *para*- or *meta*-position of the phenyl group of the substrate (Table 6.2.2, entries 1-9). Hence, while the presence of a methoxy group at the *para*-position had a slightly negative effect on the enantioselectivity (Table 6.2.2, entry 1 vs 4), the highest enantioselectivity (82% ee) was achieved using 2-naphthaldehyde as substrate (Table 6.2.2, entry 9). In contrast to the most successful sugar-based phosphite ligands,[5c,f] conversions and enantiomeric excesses did not decreased when 2-substituted benzaldehydes were used (Table 6.2.2, entries 10 and 11).

The results of using triethylaluminum and air-stable methylating reagent DABAL-Me_3 indicated that the catalytic performance follows the same trend as for the trimethylaluminum addition. However, yields and enantioselectivities were somewhat lower using DABAL-Me_3, probably because of the higher temperature required to achieve full conversions.

Table 6.2.2. Ni-catalyzed asymmetric addition of organoaluminum reagents to aldehyde using thioether-phosphite ligand **L19f**.[a]

Entry	Substrate	$AlMe_3$		$AlEt_3$		DABAL-Me_3[b]	
		% Conv[c]	% ee[d]	% Conv[c]	% ee[d]	% Conv[c]	% ee[d]
1	 **S1**	100 (93)	70 (*S*)	100 (89)	69 (*S*)	92 (78)	61 (*S*)
2	 **S2**	100 (91)	69 (*S*)	100 (87)	70 (*S*)	90 (81)	63 (*S*)
3	 **S3**	100 (90)	72 (*S*)	100 (91)	75 (*S*)	89 (80)	69 (*S*)
4	 **S4**	100 (92)	58 (*S*)	100 (90)	61 (*S*)	84 (77)	53 (*S*)
5	 **S5**	100 (88)	76 (*S*)	100 (88)	75 (*S*)	80 (72)	68 (*S*)
6	 **S6**	100 (89)	71 (*S*)	100 (87)	72 (*S*)	90 (79)	63 (*S*)
7	 **S7**	100 (91)	67 (*S*)	100 (89)	68 (*S*)	85 (74)	62 (*S*)
8	 **S8**	100 (86)	69 (*S*)	100 (84)	72 (*S*)	89 (80)	61 (*S*)
9	 **S9**	100 (92)	82 (*S*)	100 (90)	79 (*S*)	86 (73)	73 (*S*)
10	 **S10**	100 (83)	75 (*S*)	100 (87)	76 (*S*)	91 (84)	70 (*S*)
11	 **S11**	100 (91)	66 (*R*)	100 (92)	64 (*R*)	79 (68)	60 (*R*)

[a] Reaction conditions: T= -20 °C, [Ni(acac)$_2$] (1 mol%), AlR'$_3$ (2 equiv.), substrate (1 mmol), THF (8 mL). [b] Reaction conditions: T= 5 °C, [Ni(acac)$_2$] (1 mol%), DABAL-Me_3 (1.2 equiv.), substrate (1 mmol), THF (8 mL). [c] % Conversion determined by GC after 3 hour. In brackets are shown the yields determined by GC using dodecane as internal standard. [d] Enantiomeric excess measured by GC using Cyclodex-CB column.

6.2.3. Conclusions

Phosphite-thioether ligands **L1**-**L19** have been applied for the first time in the Ni-catalyzed 1,2-addition of different organoaluminum reagents to several aldehydes. Only 1 mol% of catalyst was used to achieve full conversions. We were able to systematically investigate the effect of varying the thioether substituent, the substituents/configurations in the biaryl phosphite moiety and the substituents in the alkyl backbone chain next to the both phosphite and thioether moieties. Therefore, by carefully selecting the ligand parameters we could achieve an enantioselectivity of up to 70% ee in the addition of trimethylaluminum to benzaldehyde (with **L19f**). The use of aldehydes containing electonwithdrawing aryl groups provided higher enantioselectivities (up to 82% ee).

6.2.4. Experimental part

6.2.4.1. General considerations

All syntheses were performed by using standard Schlenk techniques under an argon atmosphere. Solvents were purified by standard procedures. The synthesis of ligands **L1**-**19a**-**g** has been previously described in section 3.2 (Chapter 3). All other reagents were used as commercially available.

6.2.4.2. Typical procedure for the Ni-catalyzed enantioselective 1,2- addition of trialkylaluminum reagents to aldehydes

[$Ni(acac)_2$] (2.4 mg, 9.32 μmol, 1 mol %) and the corresponding ligand (9.32 μmol, 1 mol %) were stirred in dry THF (8 mL) under an argon atmosphere at -20 ^oC for 10 min. Neat aldehyde (1 mmol) was then added and trialkylaluminum (2 mmol) was added dropwise over 10 min. After the desired reaction time, the reaction was quenched with 2 M HCl (8 mL). Then, dodecane (80 μL) was added and the mixture was extracted with Et_2O (10 mL). The organic layer was dried over $MgSO_4$ and analyzed by GC.[5a]

6.2.4.3. Typical procedure for the Ni-catalyzed enantioselective 1,2-addition of DABAL-Me_3 to aldehydes

[$Ni(acac)_2$] (2.4 mg, 9.32 μmol, 1 mol %) and the corresponding ligand (9.32 μmol, 1 mol %) were stirred in dry THF (8 mL) under an argon atmosphere at 5 ^oC for 10 min. Neat aldehyde (1 mmol) was then added and DABAL-Me_3 (336 mg, 1.3 mmol) was added over 10 min. After the desired reaction time, the reaction was quenched with 2 M HCl (8 mL). Then, dodecane (80 μL) was added and the mixture was extracted with Et_2O (10 mL). The organic layer was dried over $MgSO_4$ and analyzed by GC.[5a]

6.2.5. Acknowledgements

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6.2.6. References

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UNIVERSITAT ROVIRA I VIRGILI
SCREENING OF MODULAR AND READILY AVAILABLE LIGAND LIBRARIES FOR C-X (X=H, C, N AND O) BOND FORMING REACTIONS. THE USE OF DFT STUDIES FOR CATALYSTS OPTIMIZATION
Jèssica Margalef Pallarès

Chapter 7

Conclusions

UNIVERSITAT ROVIRA I VIRGILI
SCREENING OF MODULAR AND READILY AVAILABLE LIGAND LIBRARIES FOR C-X (X=H, C, N AND O) BOND FORMING REACTIONS. THE USE OF DFT STUDIES FOR CATALYSTS OPTIMIZATION
Jèssica Margalef Pallarès

7. Conclusions

1. Chapter 3. *Aymmetric hydrogenation reactions*. The conclusions of this chapter can be summarized as follows:

- Five different phosphorus-containing ligand families have been successfully synthesized from readily available starting materials for their application in Rh- and Ir-catalyzed hydrogenation of functionalized and minimally functionalized olefins.

- A large modular phosphite-thioether/selenoether ligand library has been successfully synthesized from L-tartaric acid and D-mannitol. These ligands have been successfully applied in both the Rh- and Ir-catalyzed asymmetric hydrogenation of a wide variety of functionalized and unfunctionalized olefins. We found that in both processes enantioselectivity is mainly affected by the ligand parameters as well as the substrate class. By carefully selecting the ligand components, full conversions and high enantioselectivities have been achieved in the reduction of several α,β-unsaturated carboxylic acid derivatives, substrates containing poorly coordinative groups (i.e. alkenylboronic esters, α,β-unsaturated amides and esters, …), and also for the more challenging disubstituted olefins. It should be noted that excellent enantioselectivities were achieved in the Ir-catalyzed hydrogenation of β-aryl enamides, which gave access to 2-aminotetralines and 3-aminochromanes in enantioselectivities up to 99%.

- A new library of modularly constructed phosphite/phosphinite-thioether ligands derived from the ring opening of enantiopure epoxides has been evaluated in the asymmetric iridium-catalyzed hydrogenation of a wide range of olefins. DFT studies gave an understanding of the enantiocontrol in the reaction allowing rationalization of the modifications required for improving selectivity. Hence, excellent enantioselectivities (ee's up to 99%) have been obtained for a range of substrates, including (*E*)- and (*Z*)-trisubstituted and 1,1-disubstituted olefins, α,β-unsaturated enones, tri- and disubstituted alkenylboronic esters and olefins with trifluoromethyl substitutents. Furthermore, asymmetric hydrogenations also performed well in propylene carbonate, which allowed the Ir-catalysts to be reused.

- A new indene-based phosphite/phosphinite-thioether ligand family has been successfully synthesized in only three simple steps. Preliminary results on their application in the Ir-catalyzed hydrogenation of minimally functionalized olefins showed that enantioselectivity is mainly affected by the phosphorus and thioether substituents. However, the observed trend on enantioselectivity was different depending on the substrate type. By carefully selecting the ligand components high enantioselectivities could be achieved in the hydrogenation of a model 1,1-disubstituted olefin (97% ee).

- A new carbohydrate-based phosphite-pyridine ligand family has been successfully synthesized and applied in the Ir-catalyzed hydrogenation of poorly functionalized olefins. Enantioslelectivities depended on the relative position of the coordinating groups and the geometric properties of the biaryl phosphite moieties. By carefully selecting this ligand parameter ee's up to 90% were obtained in the reduction of the model (*E*)-substrate.

- We have been able to successfully develop a new chiral phosphite-triazole ligand library in a few simple steps procedure. It was found that in general, enantioselectivities were highly affected by the configuration of the phosphite biphenyl moiety. Promising results were obtained in the hydrogenation of the more challenging disubstituted substrate 3,3-dimethyl-2-phenyl-1-butene (ee's up to 87%).

2. Chapter 4. *Asymmetric transfer hydrogenation of olefins*. The conclusions of this chapter can be summarized as follows:

- A large library of furanoside-based hydroxyamide and thioamide ligands **L68**-**L73a**-**j** has been synthesized from inexpensive natural chiral feedstocks. They have been successfully applied in the Ru- and Rh-asymmetric transfer hydrogenation of ketones. Their modular nature made easy to identify two catalytic systems that provided excellent enantioselectivities (ee's typically ranging between 95% and >99%) in a broad range of ketones. Moreover both enantiomers of the reduction products can be obtained with excellent enantioselectivities by simply changing either the Ru-hydroxyamide catalyst precursor to Rh-thioamide or the absolute configuration of the thioamide substituent. We have been able to discover a new type of ligand for the highly enantioselective reduction of industrially relevant substrates as well as their use in tandem reactions involving ATH.

3. Chapter 5. *Asymmetric allylic substitution reactions*. The conclusions of this chapter can be summarized as follows:

- In the application of the carbohydrate-based phosphite-thioether/selenoether ligand library in Pd-catalyzed allylic substitutions we found that the flexibility conferred by the biaryl phosphite group together with the possibility of changing the ligand parameters helped us to identify ligands able to accommodate substrates with different steric demands. Enantioselectivities were therefore high in a wide range of disubstituted substrates using several C-, N- and O-nucleophiles (ee's up to 99%).

- A large library of furanoside phosphite/phosphinite/phosphine-thioether ligands have been applied in the Pd-catalyzed allylic substitution reactions of several substrate types using a wide range of nucleophiles (ee's up to >99%). Again we have shown that the modular nature of the ligands allowed us to identify highly enantioselective catalytic systems. Moreover the use of DFT in combination with NMR studies of the Pd-π-allyl intermediates helped us to better understand the origin of the enantioselectivity. Of particular note are the excellent enantioselectivities obtained in the etherification of linear and cyclic substrates, which represent the first example of successful etherification of both substrate types.

- In the application of the library of indene-based phosphite/phosphinite-thioether ligands in Pd-catalyzed allylic substitution reactions we found that the extent to which the chiral information was transferred to the product can be tuned by correctly choosing the ligand components. The combination of a bulky thioether group and an enantiopure (*R*)-biaryl phosphite moiety played an essential role in increasing the versatility of the Pd-catalytic systems of a range of substrates, with different steric demands, using several C-, N- and O-nucleophiles, among which are the little studied α-substituted malonates, β-diketones, pyrroles, alkyl alcohols and silanols (enantioselectivities up to >99%).

- In the application of glucopyranoside-based phosphite-pyridine ligand library in the Pd-catalyzed allylic substitution we were able to identify ligands that provided high enantioselectivities in the Pd-catalyzed intermolecular allylic substitution of cyclic substrates (ee's up to 86%) and desymmetrization of *meso*-cyclopent-2-ene-1,4-diol (ee's up to 94%).

- In the application of the phosphite-triazole ligand family in Pd-allylic alkylation reactions we found that an enantiomerically pure biphenyl moiety was needed in order to achieve high enantioselectivities. Furthermore, the configuration of the chiral biphenyl moieties dictates the sense on the enantioselectivity. Promising enantioselectivities were obtained in the alkylation of the more challenging unhindered cyclic substrate (up to 76% ee).

4. Chapter 6. *Asymmetric Ni-catalyzed 1,2-addition of trialkylaluminum to aldehydes.* The conclusions of this chapter can be summarized as follows:

- In the application of carbohydrate-based phosphite-thioether ligands in the Ni-catalyzed 1,2-addition of organoaluminum reagents to aldehydes we have shown for the first time that bidentate P,S-ligands are able to induce enantioselectivity in this transformation. By carefully selecting the ligand components we achieved enantioselectivities up to 82%.

UNIVERSITAT ROVIRA I VIRGILI
SCREENING OF MODULAR AND READILY AVAILABLE LIGAND LIBRARIES FOR C-X (X=H, C, N AND O) BOND FORMING REACTIONS. THE USE OF DFT STUDIES FOR CATALYSTS OPTIMIZATION
Jèssica Margalef Pallarès

Chapter 8

Summary

UNIVERSITAT ROVIRA I VIRGILI
SCREENING OF MODULAR AND READILY AVAILABLE LIGAND LIBRARIES FOR C-X (X=H, C, N AND O) BOND FORMING REACTIONS. THE USE OF DFT STUDIES FOR CATALYSTS OPTIMIZATION
Jèssica Margalef Pallarès

8. Resum (Summary)

La necessitat de desenvolupar processos per a l'obtenció de compostos enantiomèricament purs, ha conduït a un important desenvolupament de la catàlisi asimètrica, sobretot utilitzant compostos organometàl·lics quirals. La modificació de les propietats dels lligands quirals és l'estratègia més utilitzada en l'optimització dels catalitzadors per tal d'aconseguir altes selectivitats i activitats per cada reacció en particular. Altres requisits perquè un lligand sigui d'interès industrial és que sigui fàcil de sintetitzar a partir de productes de partida fàcilment accessibles i que a més a més sigui estable i fàcil de manipular.

En aquest context, aquesta tesis és centra en la síntesis de vàries famílies de lligands quirals que compleixin els requisits esmentats i en la seva aplicació a diferents reaccions asimètriques d'alt interès industrial: hidrogenació d'olefines funcionalitzades i no funcionalitzades catalitzada per Rh i Ir, reducció de cetones mitjançant transferència d'hidrogen catalitzada per Rh i Ru, reaccions de substitució al·lílica catalitzada per Pd i addició de reactius organoalumini a aldehids catalitzada per Ni. En concret s'han sintetitzat diferents famílies fosfit/fosfinit-tioèter/selenoèter, fosfit-piridina, fosfit-triazol i lligands hidroxiamida i tioamida. A més a més s'han realitzat en alguns casos estudis DFT per tal de facilitar el procés d'optimització del lligand.

Després de la introducció (**capítol 1**) i els objectius (**capítol 2**), al **capítol 3** es presenten sis apartats on es discuteix la síntesi de varies llibreries de lligands quirals i l'aplicació en reaccions d'hidrogenació d'olefines. La primera part inclou el manuscrit *Rh-Catalyzed asymmetric hydrogenation of functionalized olefins using phosphite-thioether/selenoether ligands*, on es descriu la síntesis i l'aplicació de lligands fosfit-tioèter/selenoèter, derivats de L-àcid tartàric o del D-manitol, en la reacció d'hidrogenació asimètrica, catalitzada per Rh, de diverses olefines funcionalitzades. L'alta modularitat d'aquests lligands ha permès obtenir altes enantioselectivitats, com per exemple en la hidrogenació d'enamides (enantioselectivitats de fins al 98%).

En la segona part es descriu el treball titulat *Ir-Catalyzed asymmetric hydrogenation of olefins using phosphite-thioether/selenoether ligands.* Aquest treball consisteix en la aplicació dels lligands fosfit-tioèter/selenoèter descrits a l'apartat anterior, en la reacció d'hidrogenació catalitzada per Ir. Gràcies a l'alta modularitat d'aquesta família de lligands s'han pogut identificar sistemes catalítics capaços d'hidrogenar una gran varietat d'olefines tant mínimament funcionalitzades com funcionalitzades en bones activitats i enantioselectivitiats (fins a un excés enantiomèric del 99%)

La tercera part composta per l'article, *A theoretically-guided optimization of a new family of modular P,S-ligands for iridium-catalyzed hydrogenation of minimally functionalized olefins*, descriu l'obtenció i l'ús dels compostos fosfit-tioèter i fosfinit-tioèter com a lligands en la hidrogenació asimètrica d'olefines no funcionalitzades catalitzada per iridi. A més a més s'ha realitzat un estudi DFT del estats de transició donats en aquesta reacció catalítica, per tal d'agilitzar el procés d'optimització de l'esquelet del lligand. Així doncs, s'han pogut obtenir excel·lents enantioselectivitats en la reducció d'una gran varietat d'olefines d'alt interès sintètic (excessos enantiomèrics fins a 99%). Finalment

també s'han realitzat les reaccions en carbonat de polipropilè, el qual ha permès la recuperació del catalitzador.

La quarta part inclou el treball titulat *Screening of an indene-based phosphite/phosphinite-thioether ligands in the asymmetric Ir-hydrogenation of minimally functionalized olefins*. Els lligands presentats en aquesta secció han estat sintetitzats en només tres passos a partir de productes químics de fàcil disponibilitat. Es presenten també els resultats preliminars obtinguts de la seva aplicació a la hidrogenació catalitzada per Ir de tres tipus de substrats model.

La cinquena part inclou l'article titulat *The application of pyranoside phosphite-pyridine ligands to enantioselective Ir-catalyzed hydrogenations of highly unfunctionalized olefins*. En aquest article es discuteix la síntesis d'una família de lligands derivada de sucres i la seva aplicació en la hidrogenació de diferents substrats, en la qual es van obtenir excessos enantiomèrics de fins al 90%.

En la sisena part es discuteix el treball *The development of readily accessible phoshite-triazole ligands and their application in the Ir-catalyzed hydrogenation of minimally functionalized olefins*. En aquest treball es presenta la síntesis d'una nova familia de lligands fosfit-triazol, la qual s'ha dut a terme en pocs passos que a més a més comporten el fàcil aïllament del producte. S'ha fet una primera avaluació d'aquests lligands en la hidrogenació catalitzada per Ir de tres substrats model.

En el **capítol 4** es presenta un sol treball titulat *Highly versatile Ru- and Rh-catalysts for the asymmetric transfer hydrogenation of ketones. Application to tandem reactions*. En aquest capítol es detalla la síntesis de dues famílies altament modulars de lligands hidroxiamida i tioamida derivats de D-manosa i aminoàcids. Aquests lligands han estat evaluats en la transferència d'hidrogen a cetones catalitzada per Ru i Rh. S'han pogut identificar dos sistemes catalítics capaços de reduir cetones d'una gran diversitat en excel·lents excessos enantiomèrics (95->99%). A més a més aquests catalitzadors privilegiats s'han utilitzat en reaccions tàndem que han permès l'obtenció estereoselectiva d'alcohols quirals a partir d'altres productes de partida d'alta disponibilitat (per exemple alcohols vinílics).

En el **capítol 5** es presenten 5 apartats on s'apliquen vàries famílies de lligands P-S i P-N, la majoria d'elles sintetitzades al capítol 3, en reaccions de substitució al·lílica catalitzada per Pd. En el primer apartat s'inclou el treball titulat *Asymmetric Pd-catalyzed allylic substitution reactions using phosphite-thioether/selenoether ligands*, on s'ha aplicat la família dels lligands fosfit-tioèter/selenoèter en reaccions de substitució al·lílica catalitzades per Pd. Seleccionant els paràmetres estructurals adequats, s'han pogut identificar lligands capaços de proveir altes enantioselectivitats en l'alquilació de substrats amb diferents requeriments estèrics utilitzant una gran varietat de nucleòfils (C, N i O).

En el segon apartat titulat *Asymmetric catalyzed allylic substitution using a Pd/P-S catalyst library with exceptional high substrate and nucleophile versatility. DFT and Pd-π-allyl key intermediates studies*, es presenta l'extensió d'una família de lligands P-S derivats de carbohidrats, la qual va ser desenvolupada al nostre grup a l'any 2014 i va donar grans resultats en la reacció de substitució al·lílica. Així doncs s'ha ampliat aquest treball incloent-hi exemples de substitucions amb més substrats i nucleòfils de diferent natura, obtenint

excessos enantiomèrics molt elevats (>99%). A més a més s'han realitzat estudis DFT i s'han sintetitzat i caracteritzat els intermedis al·lílics de Pd per tal d'entendre millor l'origen de l'enantioselectivitat d'aquests lligands privilegiats.

En el tercer apartat anomenat *Asymmetric Pd-catalyzed allylic substitution reactions using indene-based phosphite/phosphinite-thioether ligands*, s'han aplicat la família de lligands P-S derivats de l'indè a la substitució al·lílica de diferents substrats utilitzant varis nucleòfils (C, N i O). A més a més s'ha demostrat el valor sintètic d'aquest procés catalítics transformant seqüencialment els productes obtinguts en carbocicles biològicament actius. Una altre punt a destacar és que s'han pogut realitzar les reaccions catalítiques en un medi més benigne pel medi ambient (utilitzant carbonat de polipropilè) mantenint les altes enantioselectivitats.

En el quart apartat es presenta el treball titulat *Application of pyranoside phosphite-pyridine ligands to enantioselective Pd-catalyzed allylic substitutions*, en el qual es presenta l'aplicació de la lligandoteca de fosfits-piridina en l'alquilació al·lílica de diferents tipus de substrats. És interessant destacar que s'ha obtingut fins a un excés enantiomèric del 94% en la dessimetrització d'un *meso*-compost, mitjançant una substitució al·lílica intramolecular.

En el cinquè i últim apartat d'aquest capítol es presenta el treball tituat *Screening a new readily available phosphite-triazole ligand library in asymmetric Pd-catalyzed allylic alkylation reactions*. En aquest treball es mostren els resultats preliminars de l'aplicació dels lligands fosfit-triazola en l'alquilació al·lílica de tres substrats model amb diferents requeriments estèrics. Els excessos enantiomèrics obtinguts han estat de fins a un 91%.

Finalment, al **capítol 6** es presenta un sol apartat titulat *The first application of phosphite-thioether ligand family in the asymmetric Ni-catalyzed 1,2-addition of trialkylaluminum to aldehydes*. En aquest treball es detallen els resultats preliminars de l'aplicació dels lligands fòsfit-tioèter basats en L-tartrat i D-manitol en l'adició de reactius alquilalumini a aldehids catalitzada per Ni. S'ha demostrat per primer cop que els lligands P-S poden induir enantioselectivitat en aquesta reacció, ja que s'ha obtingut un excés enantiomèric de fins al 82%.

UNIVERSITAT ROVIRA I VIRGILI
SCREENING OF MODULAR AND READILY AVAILABLE LIGAND LIBRARIES FOR C-X (X=H, C, N AND O) BOND FORMING REACTIONS. THE USE OF DFT STUDIES FOR CATALYSTS OPTIMIZATION
Jèssica Margalef Pallarès

Chapter 9

Appendix

UNIVERSITAT ROVIRA I VIRGILI
SCREENING OF MODULAR AND READILY AVAILABLE LIGAND LIBRARIES FOR C-X (X=H, C, N AND O) BOND FORMING REACTIONS. THE USE OF DFT STUDIES FOR CATALYSTS OPTIMIZATION
Jèssica Margalef Pallarès

9. List of papers and meeting contributions

9.1. List of papers

1. Margalef, Jèssica; Lega, Matteo; Ruffo, Francesco; Pamies, Oscar; Dieguez, Montserrat, "The application of pyranoside phosphite-pyridine ligands to enantioselective Ir-catalyzed hydrogenations of highly unfunctionalized olefins", *Tetrahedron: Asymmetry*, **2012**, *23*, 945-951.

2. Lega, Matteo; Margalef, Jèssica; Ruffo, Francesco; Pamies, Oscar; Dieguez, Montserrat, "Application of pyranoside phosphite-pyridine ligands to enantioselective metal-catalyzed allylic substitutions and conjugate 1,4-additions", *Tetrahedron: Asymmetry*, **2013**, *24*, 995-1000.

3. Margalef, Jèssica; Caldentey, Xisco; Karlsson, Erik A.; Coll, Merce; Mazuela, Javier; Pamies, Oscar; Dieguez, Montserrat; Pericas, Miquel A., "A theoretically-guided optimization of a new family of modular P,S-ligands for iridium-catalyzed hydrogenation of minimally functionalized olefins", *Chemistry - A European Journal*, **2014**, *20*, 12201-12214.

4. Margalef, Jèssica; Pamies, Oscar; Dieguez, Montserrat, "Designing new readily available sugar-based ligands for asymmetric transfer hydrogenation of ketones. In the guest to expand the substrate scope", *Tetrahedron Letters*, **2016**, *57*, 1301-1308.

5. Margalef, Jèssica; Borràs, Carlota; Alegre, Sabina; Alberico, Elisabeta; Pàmies, Oscar; Diéguez, Montserrat, "Rh-Catalyzed asymmetric hydrogenation of functionalized olefins using phosphite-thioether/selenoether ligands", manuscript to be submitted

6. Margalef, Jèssica; Borràs, Carlota; Alegre, Sabina; Pàmies, Oscar; Diéguez, Montserrat, Ir-Catalyzed asymmetric hydrogenation of olefins using phosphite-thioether/selenoether ligands", manuscript to be submitted

7. Margalef, Jèssica; Slagbrand, Tove; Tinnis, Fredrik; Adolfsson, Hans; Diéguez, Montserrat; Pàmies, Oscar, "Highly versatile Ru- and Rh-catalysts for the asymmetric transfer hydrogenation of ketones. Application to tandem reactions", manuscript to be submitted

8. Margalef, Jèssica; Coll, Mercè; Norrby, Per-Ola; Pàmies, Oscar; Diéguez, Montserrat, "Asymmetric catalyzed allylic substitution using an Pd/P-S catalyst library with exceptional high substrate and nucleophile versatility. DFT and Pd-π-allyl key intermediates studies", manuscript to be submitted

9. Margalef, Jèssica; Borràs, Carlota; Alegre, Sabina; Pàmies, Oscar; Diéguez, Montserrat, "Asymmetric Pd-catalyzed allylic substitution reactions using phosphite-thioether/selenoether ligands" manuscript to be submitted

10. Biosca, Maria; Margalef, Jèssica; Caldentey, Xisco; Karlsson, Erik A.; Rodriguez, Carlos; Pericas, Miquel A.; Pamies, Oscar; Dieguez, Montserrat, "Asymmetric Pd-catalyzed allylic substitution reactions using indene-based phosphite/phosphinite-thioether ligands", manuscript to be submitted

9.2. Meeting contributions

1. **Authors**: Margalef, Jessica; Lega, Matteo; Ruffo, Francesco; Pamies, Oscar; Dieguez, Montserrat
Title: Sugar-based P-N ligands for Ir-catalyzed hydrogenation of minimally functionalized olefins
Type of presentation: Poster
Meeting: CEICS Nobel Campus, Chemistry for life
Place: Tarragona, Spain
Year: July 2012

2. **Authors**: Margalef, Jessica; Caldentey, Xisco; Karlsson, Erik A.; Coll, Merce; Mazuela, Javier; Pamies, Oscar; Dieguez, Montserrat; Pericas, Miquel A.
Title: A combined theoretical and experimental study in the iridium-catalyzed hydrogenation of minimally functionalized olefins using new modular P,S-ligands
Type of presentation: Poster
Meeting: CHIRALITY 2014 Symposium
Place: Prague, Czech Republic
Year: July 2014

3. **Authors**: Margalef, Jessica; Lega, Matteo; Ruffo, Francesco; Pamies, Oscar; Dieguez, Montserrat
Title: Application of pyranoside phosphite-pyridine ligands to enantioselective metal-catalyzed allylic substitutions and conjugate 1,4-additions
Type of presentation: Organization and poster
Meeting: GEQO XXXII meeting
Place: Tarragona, Spain
Year: September 2014

4. **Type of presentation**: Organization and attendance
Meeting: CARISMA meeting
Place: Tarragona, Spain
Year: March 2015

5. **Authors**: Margalef, Jessica; Pamies, Oscar; Dieguez, Montserrat
Title: Asymmetric Pd-catalyzed allylic substitutions using P-S ligands
Type of presentation: Poster
Meeting: OMCOS 18 IUPAC International Symposium
Place: Sitges, Spain
Year: June-July 2015

UNIVERSITAT ROVIRA I VIRGILI
SCREENING OF MODULAR AND READILY AVAILABLE LIGAND LIBRARIES FOR C-X (X=H, C, N AND O) BOND FORMING REACTIONS. THE USE OF DFT STUDIES FOR CATALYSTS OPTIMIZATION
Jèssica Margalef Pallarès