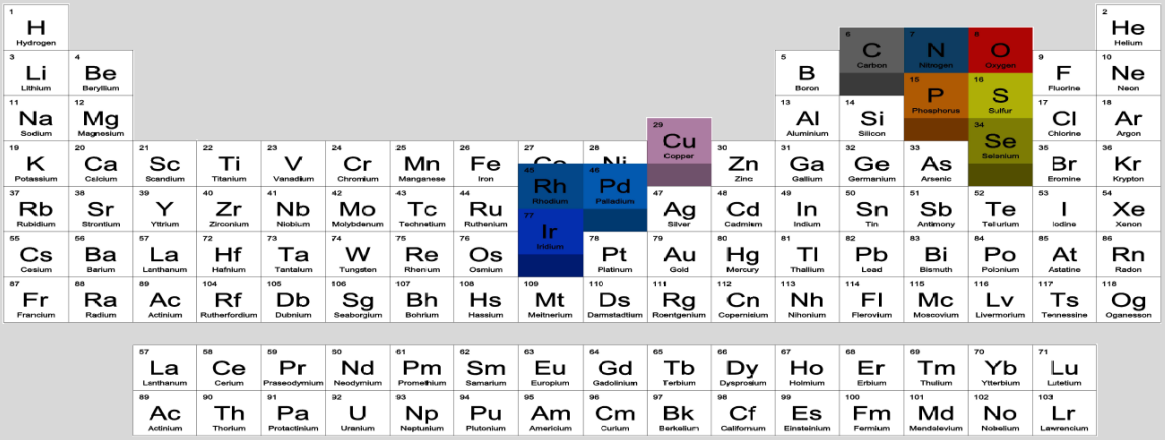
SUSTAINABLE AND COST-EFFECTIVE DEVELOPMENT OF CHIRAL METAL-CATALYSTS FOR C-H AND C-X BOND FORMING REACTIONS

Carlota Borràs Noguera

UNIVERSITAT ROVIRA i VIRGILI

Sustainable and cost-effective development of chiral metal-catalysts for C-H and C-X bond forming reactions

CARLOTA BORRÀS NOGUERA



DOCTORAL THESIS
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Sustainable and cost-effective development of chiral metal-catalysts for C-H and C-X bond forming reactions

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

UNIVERSITAT ROVIRA I VIRGILI
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PROF. MONTSERRAT DIÉGUEZ FERNÁNDEZ i DR. OSCAR PÀMIES OLLÉ, catedràtica i cap del departament de Química Física i Inorgànica de la Facultat de Química de la Universitat Rovira i Virgili

FEM CONSTAR:

Que aquest treball, titulat "**Sustainable and cost-effective development of chiral metal-catalysts for C-H and C-X bond forming reactions**", que presenta CARLOTA BORRÀS NOGUERA 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, Juliol de 2018

Prof. Montserrat Diéguez Fernández Dr. Oscar Pàmies Ollé

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Table of contents

Chapter 1

INTRODUCTION

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1. INTRODUCTION

A wide range of relevant fields, such as agrochemicals, pharmaceuticals, fine chemicals and natural products chemistry, require the preparation of enantiomerically pure compounds. This is due that in many cases only one enantiomer has the desired properties while the other enantiomer is inactive or might give undesirable side-effects.[1] Enormous efforts are being made to discover enantioselective routes for their preparation. Of these routes the asymmetric catalysis, using the appropriate metal catalyst, has emerged as one of the most efficient, sustainable and straightforward. 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 maximize activity and enantioselectivity in metal-catalyzed asymmetric reactions several parameters must be taken into account. The most crucial parameter is probably the selection and design of the chiral ligand.[1] In this field, the use of cheap and readily available natural chiral products is a clever strategy because it avoids the use of tedious optical-resolution. The use of highly modular ligand scaffolds is also desirable because it facilitates the synthesis and screening of series of chiral ligands (ligand library) in the search to maximize activity and selectivity for each particular asymmetric catalytic reaction.[1]

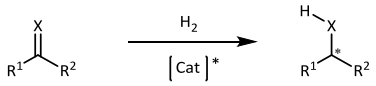
The most investigated chiral ligands contain P-donor groups.[1e,2] Phosphine and to a less extent phosphinite-containing ligands have had a predominant role.[2] In the last decades, phosphite-containing compounds have also emerged as an extremely efficient type of ligands, due to their easy preparation from alcohols and their higher stability towards air and other oxidizing agents than the commonly used phosphines and phosphinites.[3] Heterodonor bidentated P,X-ligands have several advantages over homodonors. They can provide different electronic background because of the different *trans* influence of the P and X atoms. Among the heterodonor ligands P,N-ligands have been the most studied. Transition-metal complexes with chiral sulfur-containing ligands have been less investigated,[4] although in recent decades the number of studies on thioether-containing catalytic systems has increased.[4] Compared to phosphorous, sulfur has a less donor and acceptor character. In addition, to these electronic considerations sulfur atom has two substituents, which can create a less hindered environment than the trivalent phosphorus atom. When the thioether group is coordinated to the metal center it becomes a stereogenic center and a mixture of diasteromeric thioether complexes can be formed. The difficulty to control their interconversion has been regarded as a problem for asymmetric induction in catalysis. Despite this, thioether-containing ligands have proven to be as useful as other classical asymmetric ligands, especially in heterodonor ligands.[4] Recently, our group has shown their potential with the successful application of the P-thioether ligands in the Ir-catalyzed hydrogenation of minimally functionalized olefins, Rh-

catalyzed hydrogenation of cyclic β-enamides substrates and Pd-allylic substitution reactions.[5] Another group of heterodonor based ligands that have been little used in asymmetric catalysis are the P,O-donor compounds although some of them have reported enantioselectivities as high as the most studied and successful P,N-ligands.[6] In the last two decades, N-heterocyclic carbenes (NHCs) have emerged as a class of powerful ligands for promoting catalytic activity. Owing to their strong σ-donor ability, air stability, and low toxicity, NHCs have been considered as practical alternatives to the more commonly used phosphines.[7] Because of these unique features, exploring new classes of NHCs has been an attractive target of organometallic chemistry. Several groups have demonstrated the great potential of this ligand class in catalysis, which has spurred further development.[7] Despite these prospects, the development of heterodonor-carbene ligands has predominantly focused on pyridyl units, while other heteroatom donor groups have not been explored extensively.

In this context, this thesis has been focused in the design of eight new chiral heterodonor ligand libraries from readily available materials and their application in several enantioselective metal-catalyzed transformations. In this respect, three phosphorus-thioether ligand libraries have been developed for application in the Ir- and Rh-catalyzed asymmetric hydrogenation of minimally functionalized and functionalized olefins, and in the enantioselective Pd-catalyzed allylic substitution reactions. A new carbene-thioether ligand family has been prepared for application in Ir-catalyzed asymmetric hydrogenation. One new heterodonor sugar-based P,O ligand library have been successfully applied in the Ir-catalyzed hydrogenation of minimally functionalized olefins. One sugar-based P,N-ligand library has been developed for Pd-catalyzed allylic substitutions. Finally, two tridentated P,N,N-ligand libraries have been synthesized for the hydrogenation of ketones and for the asymmetric propargylic substitution. The background of each of these catalytic reactions is described in the following sections.

1.1. Asymmetric hydrogenation reactions

Because of its high efficiency, atom economy and operational simplicity, the metal-catalyzed asymmetric hydrogenation using molecular hydrogen of properly selected prochiral olefins, ketones and imines can be a sustainable and direct synthetic tool for preparing enantiopure compounds (Scheme 1.1).[1,8] 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.[1,8]



Scheme 1.1. Asymmetric Hydrogenation of prochiral substrates.

1.1.1. Asymmetric Rh-catalyzed hydrogenation of functionalized olefins

The hydrogenation of functionalized carbon-carbon double bonds is widely used to prepare high value compounds that can be used as building blocks in asymmetric synthesis. 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 catalyst for the asymmetric hydrogenation of this type of substrate. Excellent activities and enantioselectivities have been achieved lasting recent decades for the asymmetric hydrogenation of dehydroamino acids and other functionalized substrates.[1, 6]

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 catalyst intermediates are unstable under catalytic conditions. Homogeneous catalysts 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 catalysts for imines. 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 catalysts in the reduction of enamides.

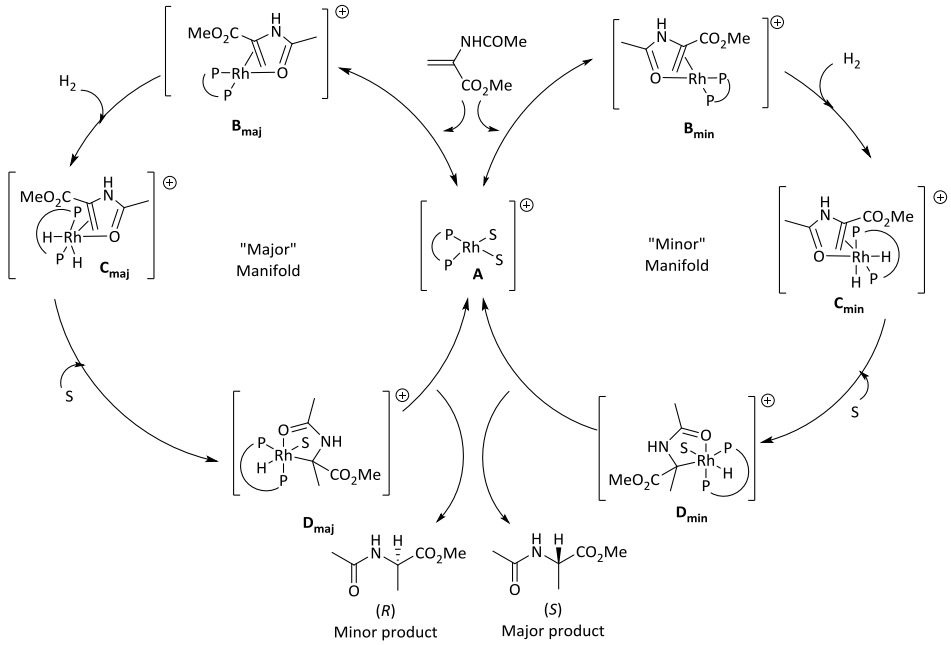
1.1.1.1. Mechanism

Scheme 1.2 shows the mechanism for the asymmetric hydrogenation of dehydroamino acids and their esters with cationic precursors with diphosphines as ligands.[9] In the last decade, this mechanism has proved to be valid for other phosphorus-based ligands (i.e. diphosphinites, diphosphites, etc.).[10] The catalytic cycle consists of two coupled diastereomeric manifolds. The specie starting the catalytic cycle is a square planar Rh(I) complex containing the chelating diphosphine

and two molecules of solvent (**A**). This specie reacts with the substrate e.g. methyl (*Z*)-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*-dihydridorhodium 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 product and regenerate the catalytically active square planar species (**A**).[9]

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.[8-9,11]



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

1.1.1.2. Ligands

The development of homogeneous asymmetric hydrogenation was initiated by Knowles[12] and Horner[13] in the late 1960s after the discovery of Wilkinson's hydrogenation catalyst [$RhCl(PPh_3)_3$].[14] 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 1.1).[15] Knowles made his significant discovery of the *C*2-symmetric chelating diphosphine ligand, **DIPAMP** (Figure 1.1).[16] Because of its high catalytic efficiency, **DIPAMP** was used in the industrial production of L-Dopa, a drug used to treat Parkinson's disease.[17] For this work Knowles was awarded the Nobel Prize in 2001.[18]

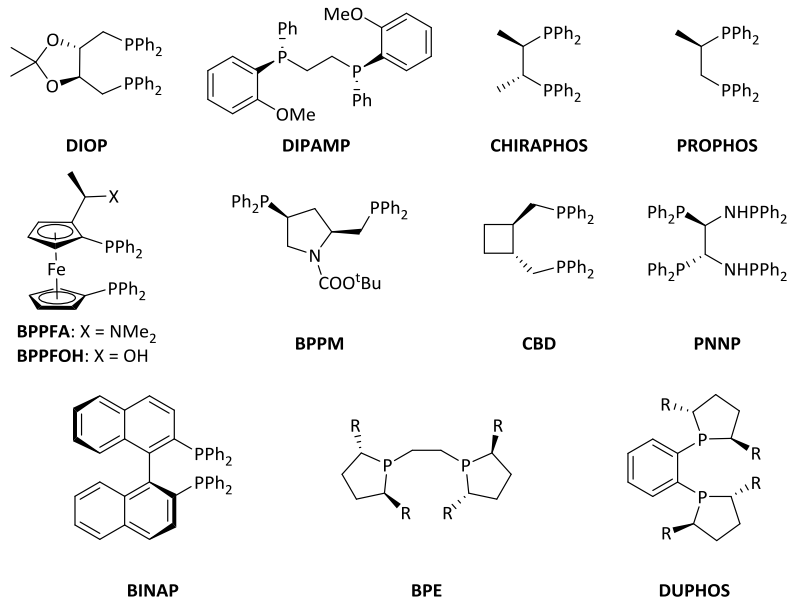


Figure 1.1. Representative diphosphine ligands in asymmetric hydrogenation.

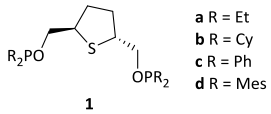
Following the significant contributions by Kagan and Knowles came the development of hundreds of successful chiral diphosphorus ligands for asymmetric hydrogenation. These include Bonisch's **CHIRAPHOS** and **PROPHOS**, Kumada's ferrocene ligands **BPPFA** and **BPPFOH**, Achiwa's **BPPM**, Rhode Poulenc's **CBD** and Giongo's bis(aminophosphine) ligand **PNNP** (Figure 1.1).[19] 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 1.1). Several prochiral olefins and ketones were hydrogenated with excellent enantioselectivity.[20] 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 1.1) for the hydrogenation of various functionalized olefins, significantly expanded the scope of asymmetric hydrogenation.[21]

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.[1,8,19] 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,3,8,19,22] 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% ee).[4] Mixed P,P'-ligands[3,23] (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.[24] 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.[2c,4] In the next section, we collect the most relevant catalytic data published for Rh-catalyzed asymmetric hydrogenation with P-thioether ligands, with the aim to compare the results obtained with the phosphite-thioether ligand library developed in this thesis (see section 3.3 below) with the state of the art.

1.1.1.2.1 Phosphorus-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 **1** (Figure 1.2) were tested in the asymmetric hydrogenation of methyl α-acetomidocinnamate, providing only moderate enantioselectivities (up to 55% ee).[25]



1

a R = Et
b R = Cy
c R = Ph
d R = Mes

Figure 1.2. 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 1.3).[26] 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 1.3). 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.

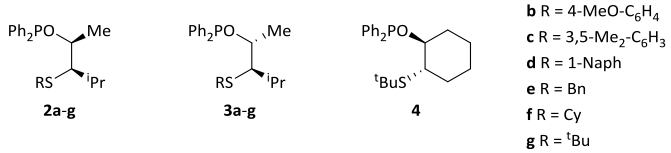


Figure 1.3. Phosphinite-thioether ligands **2**-**4** developed by Evans and coworkers.

Furanoside phosphinite-thioether ligands **5a**-**c** (Figure 1.4) were succesfully applied in the Rh- and Ir-catalyzed asymmetric hydrogenation of α-acylaminoacrilates and itaconic acid derivatives (ee's up to 96%).[27] 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.

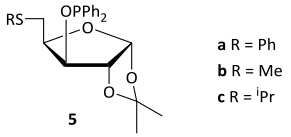


Figure 1.4. Furanoside phosphinite-thioether ligands **5a**-**c**.

Figure 1.5 shows another family of phosphinite-thioether ligands derived from carbohydrates. Cationic 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**).[28]

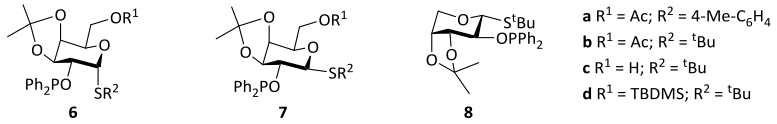


Figure 1.5. Phosphinite thioglycoside ligands **6**-**8**.

More recently, a highly modular family of phosphinite-thioether ligands derived from readily accessible enantipure epoxides, was systematically studied in the Rh-catlyzed hydrogenation of dehydroamino esters (Figure 1.6).[29] 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}).

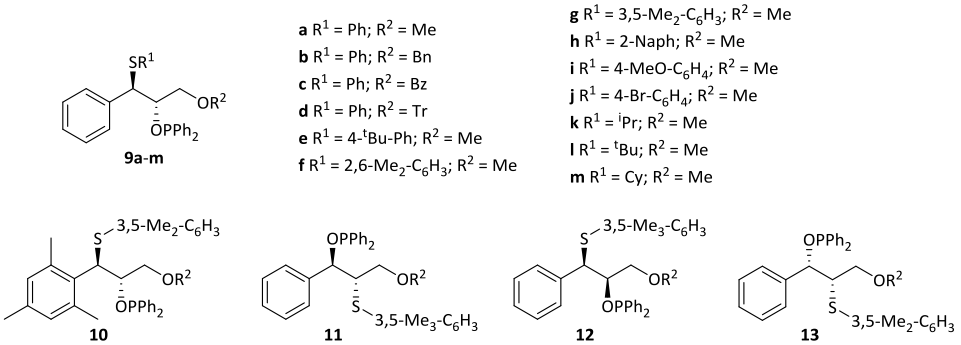


Figure 1.6. Highly modular phosphinite-thioether ligands **9**-**13.**

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 1.7).[30] All ligands showed high activities (up to 100% conv.) but enantiomeric excesses never exceeded 50% (ligand **14b**).

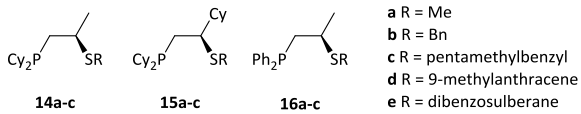


Figure 1.7. Episulfide based phosphine-thioether ligands **14**-**16**.

Another family of phosphine-thioether ligands has been used in the asymmetric Rh-hydrogenation of prochiral olefins (Figure 1.8). The enantioselectivities obtained with ligands **17**-**19** were low-to-moderate, ranging from 5 to 47% ee. [31]

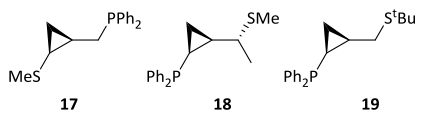


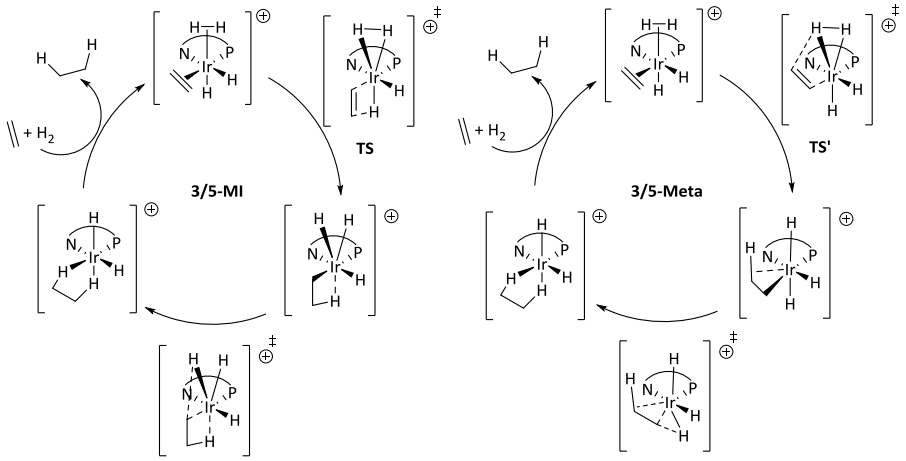
Figure 1.8. Phosphine-thioether ligands **17**-**19** based on cyclopropane backbone.

1.1.2. Asymmetric Ir-catalyzed hydrogenation of minimally functionalized olefins.

Whereas the reduction of olefins containing an adjacent polar group (i.e. dehydroamino acids) by Rh- and Ru- catalyst precursors modified with phosphorus ligands has a long history,[1,8] the asymmetric hydrogenation of minimally functionalized olefins is less developed because they have no adjacent polar group to direct the reaction. Iridium complexes with chiral P,N-ligands have become established as one of the most efficient catalyst for the hydrogenation of minimally functionalized olefins, and their scope is complementary to those of Rh- and Ru-diphosphine complexes.[32]

1.1.2.1. Mechanism

Computational and experimental research showed that the Ir-hydrogenation of minimally functionalized olefins can proceeds via two mechanism that evolved Ir^{III}/Ir^{V}, in contrast to the mechanism for the hydrogenation with Rh-catalyst which evolved Rh^{I}/Rh^{III} species.[9-10] One of the proposed routes involves an Ir^{III}/Ir^{V} migratory-insertion/reductive-elimination pathway (labeled as 3/5-MI in Scheme 1.3)[33] whereas the second mechanism uses an Ir^{III}/Ir^{V} σ-methatesis/reductive-elimination pathway (labeled as 3/5-Meta in Scheme 1.3)[34]. In both cycles, π-olefin complex and the 3/5-MI transition state (3/5-TS) or 3/5-Meta transition state (3/5-TS') are the responsible of the enantiocontrol in Ir-hydrogenation. Very recently, Pfaltz's group, based on mechanistic studies under hydrogenation conditions, was able to detect the Ir(III) dihydride alkene intermediates responsible for the catalytic performance for the first time.ref They found that, similarly to the classical Halpern-mechanism for asymmetric hydrogenation with Rh-catalysts, the minor intermediate, which is less stable, is converted to the major product enantiomer.



Scheme 1.3. 3/5-MI and 3/5-Meta catalytic cycles for the Ir-hydrogenation of minimally functionalized olefins.

1.1.2.2. Ligands

A breakthrough in the hydrogenation of unfunctionalyzed olefins came in 1997 when Pfaltz and coworkers used phosphine-oxazoline ligands PHOX[35] (Figure 1.9) to design [Ir(PHOX)(cod)]PF_6 (cod= 1,5-cyclooctadiene), a chiral analogue of Crabtree's catalyst ([Ir(py)(PCy_3)(cod)]PF_6)[36] that hydrogenated unfunctionalyzed olefins. Although this catalyst also hydrogenated prochiral olefins highly enantioselectivity, it was unstable under the reaction conditions. Pfaltz and co-workers overcame this problem by changing the catalyst anion to $[(3,5\text{-}(F_3C)_2\text{-}C_6H_3)_4B]^-$ ($[BAr_F]^-$). The result was [Ir(PHOX)(cod)]BAr_F (Figure 1.9), an active, enantioselective, and stable catalyst library for olefin hydrogenation.[37] These catalysts have been successfully used for the asymmetric hydrogenation of a limited range of alkenes (mainly trisubstituted *E*-olefins, Figure 1.9).[37-38] Bolm's group have recently successfully applied Ir-PHOX catalytic systems in the hydrogenation of α,β-unsaturated ketones (ee's up to 99%, Figure 1.9).[39] Hydrogenation 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.[40]

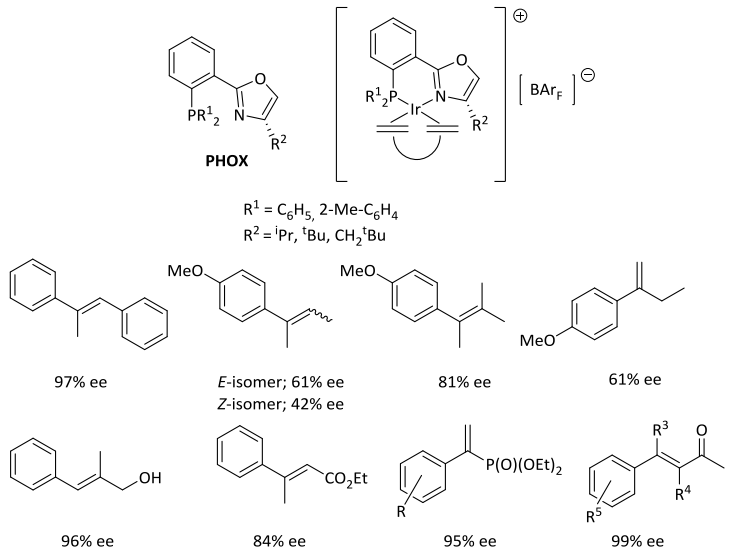


Figure 1.9. Selected Ir-hydrogenation results using PHOX ligand and similar phosphine-oxazoline ligands.

Since then, P,N-ligands library applied in the hydrogenation reaction have been extended (Figure 1.10) by initially replacing the phosphine moiety with a phosphinite or carbene group, and the oxazoline moiety with other N-donor groups (such as pyridine, thiazole and oxazole).[32] The structure of the chiral ligand's backbone has also been modified. Of them all, chiral Ir-P,N compounds have been the most studied and they have therefore become extremely useful catalytic precursors for the hydrogenation of unfunctionalized tri- and tetra-substituted olefins.[32,38a-f,39a,41] The most successful P,N-ligands contain a phosphine or phosphinite moiety as P-donor group and either an oxazoline,[38a,41a,41g] pyridine,[41d,41h,41m] oxazole,[41b] or thiazole[41i]

as N-donor group. All, these modifications have led to the discovery of new ligands that have considerably broadened the scope of Ir-catalyzed hydrogenation of trisubstituted substrates. Despite all these important contributions, the hydrogenation of unfunctionalized olefins is still highly substrate-dependent and other types of substrates still require much attention. For example, for minimally functionalized 1,1-disubstituted terminal alkenes more active and enantioselective Ir-catalysts are needed. Therefore, more research was required on the development of new ligands that can overcome these limitations.

Some years ago our group discovered that the presence of biaryl-phosphite moieties (Figure 1.10) in ligand design is highly advantageous in this process.[32e,42] Ir/phosphite-oxazoline catalytic systems provided greater substrate versatility than previous Ir/phosphinite-oxazoline systems, and high activities and enantioselectivities for several largely unfunctionalyzed *E*- and *Z*-trisubstituted and 1,1-disubstituted olefins. Several phosphite-nitrogen ligands have therefore recently emerged as extremely effective ligands for improving the activity and versatility of this process. The latest innovation in the design ligands is the use of iridium catalyst containing P,O[6] and P,S[5] heterodonor ligands have been also developed. All these modifications have led to the discovery of new ligands that have considerably broadened the scope of Ir-catalyzed hydrogenation.

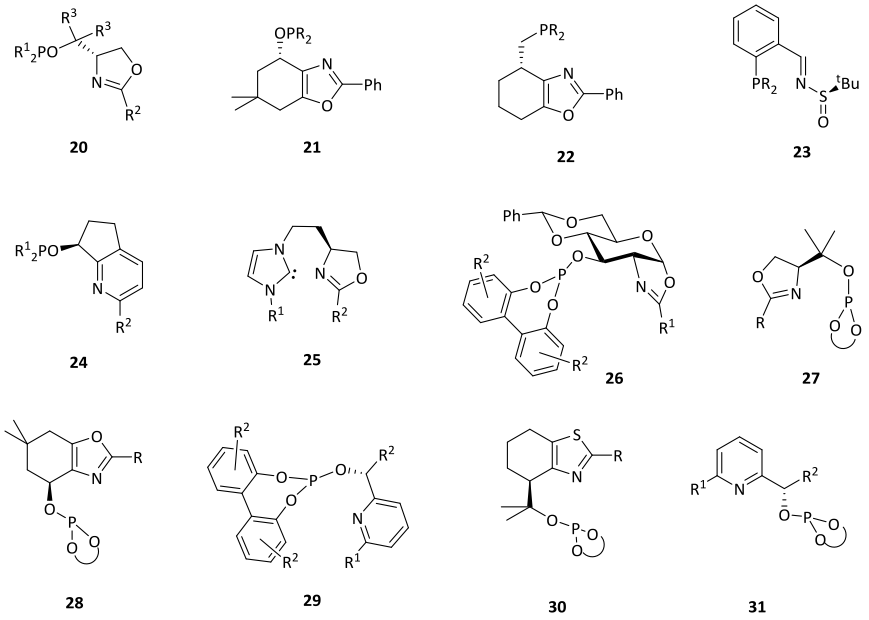


Figure 1.10. Representative P,N-ligands applied to the Ir-catalyzed asymmetric hydrogenation of minimally functionalized olefins.

As mention previously the most successful ligands are P,N-ligands bearing an oxazoline group. However, other ligands bearing more robust groups rather than oxazoline, such as thioether, amide, and urea moiety, have proved to be also efficient ligands for this catalytic process. In the next section we summarize the most relevant catalytic systems reported for asymmetric hydrogenation of minimally functionalized olefins. We only collect the results obtained with P-S and P-O ligands, in order to be able to compare with our P-thioether and P,O-ligand libraries developed in this thesis (see section 3.1-3.5 below).

1.1.2.2.1. Phosphorus-thioether ligands

A new class of non-N-donor heterodonor ligands successfully applied in the Ir-hydrogenation of minimally functionalized olefins is the thioether-phosphite ligands. Our group was first to present the application of P-thioether ligands in this process. The introduction of a thioether moiety in the ligand design was made having in mind that: (i) the S atom becomes stereogenic center when coordinated to the metal, which moves the chirality closer to the metal, and (ii) the thioether group is more stable than the oxazoline moiety. In this context our group has developed a large modular furanoside thioether-phosphite/phosphinite ligand library (Figure 1.5).[5a,b]

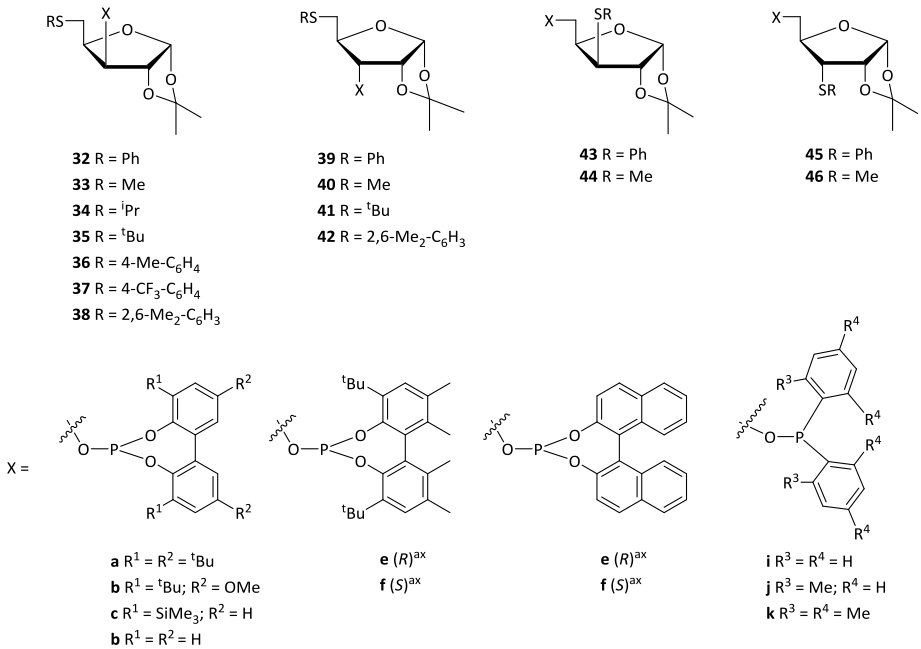


Figure 1.11. Thioether-phosphite/phosphinite/phosphine ligands **32**-**46a**-**k**.

By carefully selecting the ligand components we found that the best enantioselectivities were obtained using thioether-phosphite ligands with 5-deoxyribofuranoside backbone (**42**). Excellent enantioselectivities were therefore obtained (ee's up to 99%) in a wide range of *E*- and *Z*-trisubstituted alkenes using **42a**

and **42e**. 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 with high enantioselectivities. The good performance extends to the very challenging class of terminal disubstituted aryl/alkyl olefins. For this substrate class, the results indicated that enantioselectivity is dependent on the nature of the alkyl substrate substituent, which has been attributed to the presence of an isomerization process under hydrogenation conditions. Enantioselectivities were therefore best in the asymmetric reduction of aryl and heteroaryl/*tert*-butyl substrates (ee's up to 99%). Interestingly, for 1,1-disubstituted substrates, both enantiomers of the hydrogenated products were achieved in high enantioselectivity, simple by changing the configuration of the biaryl phosphite moiety.

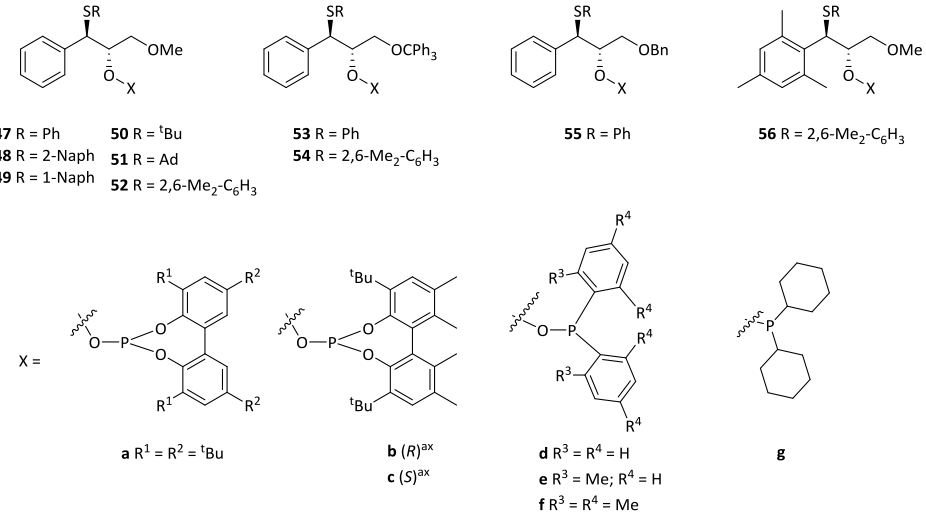
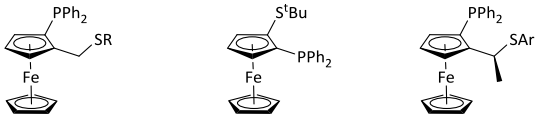


Figure 1.12. Thioether-phosphite/phosphinite ligand library **47**-**56a**-**g**.

In 2014, our group in collaboration with Pericàs group have been developed a new family of modularly constructed thioether-phosphinite/phosphite ligands (**47**-**56a**-**g**) derived from the ring opening of enantiopure epoxides (Figure 1.12).[43] In general, enantioselectivities are mainly controlled by the nature of the thioether, the aryl moieties and the type of P-donor group. Excellent enantioselectivities (ee's 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 substituents. Asymmetric hydrogenation was also performed using propylene carbonate as solvent, which allowed the Ir catalyst to be reused. Moreover, 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 stereaodefining moieties.

Recently our group, together with Manoury's research group, has reported the application of a novel ferrocenyl-based phosphine-thioether ligand family (Figure 1.13)

in the Ir-catalyzed hydrogenation of minimally functionalized olefins.[5h] The ferrocenyl moiety gives to ligands **57**-**64** planar chirality and in addition, ligands **67** and **68** 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).



57 R = Et
58 R = ^{i}Pr
59 R = Cy
60 R = ^{t}Bu
61 R = Ad
62 R = Ph
63 R = Bn
64 R = 1-Naph
65 R = 2,6-Me_2-C_6H_3

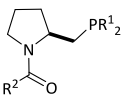
66

67 Ar = Ph
68 Ar = 2,6-Me_2-C_6H_3

Figure 1.13. Ferrocenyl-based phosphine-thioether ligands **57**-**68**.

1.1.2.2.2. Phosphorus-O ligands

In 2011, Pfaltz and coworkers reported a new L-proline-based P,O-ligands (**69**-**86**) in Ir-catalyzed hydrogenation (Figure 1.14).[6a] These ligands have been achieved from non expensive and readily available commercial products. Amido- and ureaphosphine ligands gave full conversion and excellent enantioselectivities (up to 99% ee) mainly in wide range of α,β-unsaturated esters and ketones, with similar or better results than those obtained with usual P,N-ligands.[6b] These P,O-complexes proved, however, to be less stable than proline-based P,N-catalysts and were therefore generated *in situ* prior to the hydrogenation reaction.



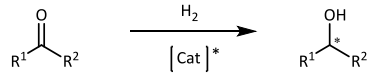
69 R^1 = Ph; R^2 = ^{t}Bu
70 R^1 = ^{t}Bu; R^2 = 1-Ad
71 R^1 = Cy; R^2 = 1-Ad
72 R^1 = Ph; R^2 = CPh_3
73 R^1 = ^{t}Bu; R^2 = CPh_3
74 R^1 = Cy; R^2 = CPh_3
75 R^1 = ^{t}Bu; R^2 = 1-AdNH
76 R^1 = Cy; R^2 = 1-AdNH
77 R^1 = ^{t}Bu; R^2 = MesNH
78 R^1 = Cy; R^2 = MesNH
79 R^1 = Ph; R^2 = Ph_3CNH
80 R^1 = ^{t}Bu; R^2 = Ph_3CNH
81 R^1 = Cy; R^2 = Ph_3CNH
82 R^1 = o-Tolyl; R^2 = $^{i}Pr_2N$
83 R^1 = ^{t}Bu; R^2 = $^{i}Pr_2N$
84 R^1 = Cy; R^2 = $^{i}Pr_2N$
85 R^1 = ^{t}Bu; R^2 = Cy_2N
86 R^1 = Cy; R^2 = Cy_2N

Figure 1.14. L-proline-based P,O-ligands **69**-**86**.

1.1.3. Asymmetric Ir-catalyzed hydrogenation of ketones.

In several numbers of pharmaceutical products, such as aprepitant, crizotinib, duloxetine and ezetimibe (Figure 1.15), the key structural block contains a chiral secondary alcohol.[19a,44] Because of their importance, special attention has been paid

to find efficient strategies to achieve chiral alcohols. The transition-metal catalyzed asymmetric hydrogenation of ketones is one of the most attractive methods for the synthesis of chiral alcohols due to its high atom economy and activity. Ru and, to a lesser extent, Rh are the most widely used metal sources.[1] Despite the good results obtained using the previous catalytic system, more recently, iridium catalytic systems emerged as an effective method for the hydrogenation of simple ketones without any other functionalized coordinative group.[45]



Scheme 1.2. Asymmetric hydrogenation of prochiral ketones

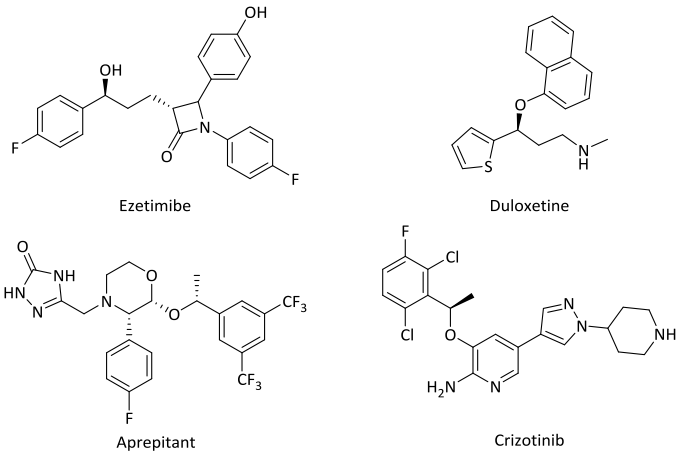


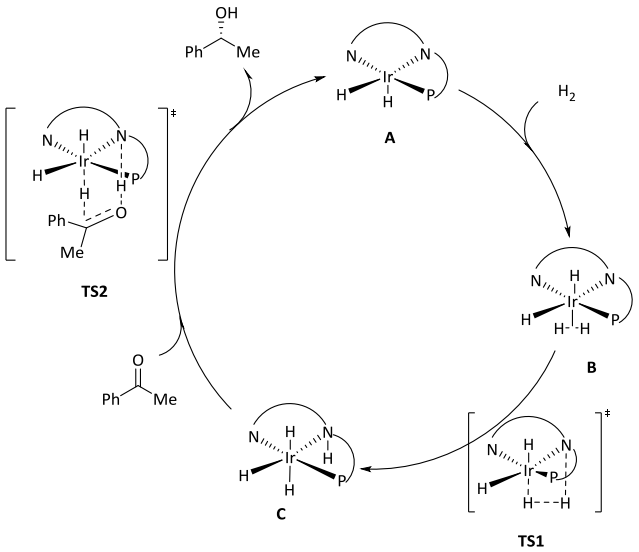
Figure 1.15. Related chiral pharmaceuticals containing key chiral structural motifs.

1.1.3.1. Mechanism

The plausible proposed mechanism for this reaction involves a "metal-catalyzed bifunctional" interaction between the catalyst and the substrate, it is shown in Scheme 1.3.[46]

Catalytic active iridium dihydride complex (**A**) have been obtained from the precursor catalyst $[Ir(\mu\text{-}Cl)(cod)_2]_2$ in presence of the corresponding tridentated P,N,N ligand, H_2 and a strong base losing one molecule of HCl. This step should explain the need to ligand containing NH moiety. The iridium complex (**A**) is further hydrogenated to octahedral intermediate (**B**). The hydrogenation on the more favorable face of the chelating N atom takes place via a concerted four-membered ring type transition state (**TS1**), which evolve to the hydride iridium intermediate (**C**). The hydrogenation of the acetophenone take place via transition state (**TS2**). Similarly, to the classical Ru-Noyori catalyst, in this step the trihydride complex (**C**) transfers a hydridic Ir-H and protic N-H unit to the carbonyl group of the ketone via six-membered cyclic transition state (**TS2**) to produce chiral alcohol and regenerated the Ir complex (**A**). The presence of a third

chelating atom, avoid the formation of inactive iridium complexes achieving better results.



Scheme 1.3. Proposed mechanism for asymmetric Ir-catalyzed hydrogenation of ketones.

1.1.3.2. Ligands

Asymmetric hydrogenation of functionalized ketones with a secondary coordination group to the metal center has been extendedly studied and several efficient catalysts have been developed for this process. [1] In contrast, the asymmetric metal-transition-catalyzed hydrogenation of simple unfunctionalyzed non-chelating ketones is less investigated and only few catalysts have been reported.

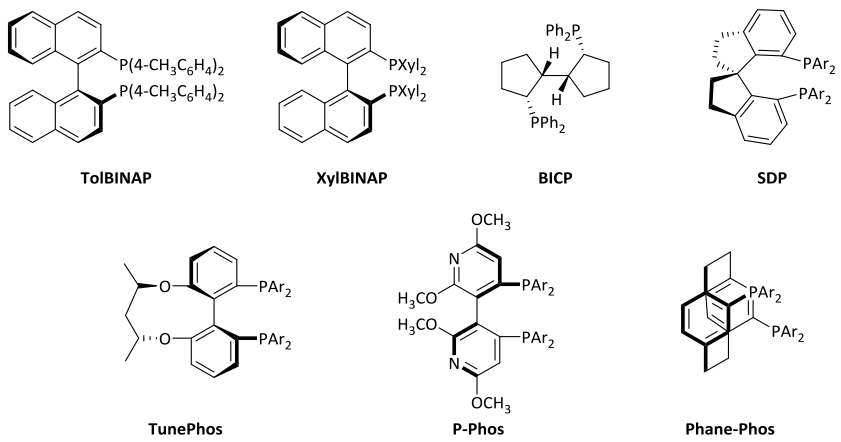


Figure 1.16. Representative chiral diphosphine ligands in hydrogenation of ketones.

A breakthrough in this field was achieved by Noyori and coworkers in 1995, which developed the highly effective **BINAP**-ruthenium-diamine catalyst system for the asymmetric hydrogenation of various simple aromatic ketones.[47] Based on this work, other chiral diphosphine ligands (**TolBINAP**,[48] **XylBINAP**,[49] **BICP**,[50] **SDP**,[51] **TunePhos**,[44e] **P-Phos**,[52] **PhanePhos**[53]) (Figure 1.16) have been developed and proved to be efficient in the Ru-catalyzed asymmetric hydrogenation of ketones.

Chiral iridium catalysts have also emerged as an effective method for the hydrogenation simple ketones. Figure 1.17 shows a selection of the most successful Ir-complexes developed.[45]

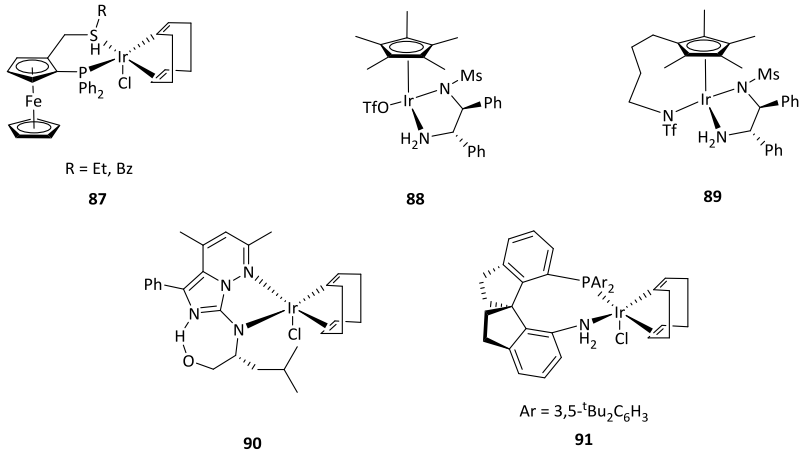


Figure 1.17. Selected chiral Ir-complex for the hydrogenation of simple ketones.

The chiral iridium complexes **87** with a planar chiral phosphine-thioether (P,S) ligand have been successfully applied in the hydrogenation of alkyl aryl ketones with moderated to high enantioselectivities (up to 99% ee) and good activities (up to 250 h^{-1} TOF).[54] A limited substrate scope was observed. Only two hydrogenated products from prochiral ketones were achieved in high enantioselectivities.

Chiral iridium complex with phosphine-free ligands also give high enantioselectivities in the asymmetric hydrogenation of ketones (Figure 1.17; **88**-**90**). Iridium-Ms-DPEN complex **88** showed high activities (up to 6000 TON) and excellent enantioselectivities (up to 99% ee) for the asymmetric hydrogenation of α-hydroxy aromatic ketones in the absence of base giving acces to chiral 1-arylethane-1,2-diols.[55]

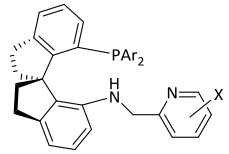
The asymmetric hydrogenation of acetophenone catalyzed by tethered chiral iridium complex **89** without using base affords chiral hydrogenated product with up to 94% ee.[56]

Iridium complex **90** under basic conditions (KO^tBu) provided excellent activities (up to 200000 TON) and enantioselectivities (up to >99% ee) for the reduction of alkyl aryl ketones.[57]

Spiro iridium catalyst **91** containing chiral spiro aminophosphine SpiroAP ligand is an effective chiral catalyst in the hydrogenation of a series of alkyl aryl ketones and α-arylmethylene cycloalkanones with high to excellent enantioselectivity (up to 97% ee). However, the turnover number using catalyst **91** only reached 10000, in spite of the TOF reached up to 37200 h^{-1}. This indicates that the iridium complex tends decompose to an inactive iridium complex with two molecules of ligand.[46a,58] In order to overcome this limitation several strategies have been developed. One of the most attractive strategies was reported by Zhou and coworkers, that consists on the addition of an extra chelating group in the ligand scaffold.[59] This open up the use of tridentated ligands. In the next section we will present the tridentated ligands applied in the hydrogenation of simple ketones.

1.1.3.2.1. Tridentated ligands

The first iridium-tridentated catalytic system for the hydrogenation of simple ketones was reported by Zhou's research group in 2011. They show the successful application of the Ir-catalytic system with a tridentated spiro P,N,N ligand **92**[59] (Figure 1.18; up to >99.9% ee) for the hydrogenation of aryl alkyl ketones[59] and of α,β-unsaturated ketones (ee's up to >99.9%)[60]. The replacing of the pyridine moiety by a sulfur group gave access to chiral spiro-P,N,S ligand **93** which have been applied in the hydrogenation of β-alkyl-β-ketoesters providing the corresponding enantiopure hydrogenated product in excellent enantioselectivities (up to 99.9% ee).[61]



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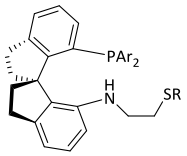
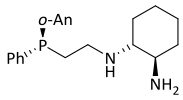


93

Figure 1.18. Chiral Spiro tridentated ligands reported by Zhou for the hydrogenation of simple ketones.

Based on the previous P,N,N-ligands, in 2013, Clarke and coworkers reported an iridium complex of a tridentate cyclohexane-based phosphine-diamine ligand **94** (Figure 1.19).[62] The application of ligand **94** in the hydrogenation of alkyl heteroaryl ketones afforded excellent enantioselectivities (up to 99% ee).



94

Figure 1.19. Chiral cyclohexane-based tridentated ligands reported by Clarke for the hydrogenation of simple ketones.

Encourage by the success of previous tridentated chiral ligands, a new family of tridentated ferrocenyl pyridine-aminophosphine ligand **95** (Figure 1.20) was developed.[63] However, only 87% ee were achieved in the hydrogenation of simple

ketones. Later, Zhang and coworkers reported a modified ferrocenyl tridentated ligand, they found that by replacing the pyridine moiety by oxazoline moiety giving an electro-donating tridentate ferrocene aminophosphoxazoline ligand **96** (f-amphox) (Figure 1.20) the enantioselectivities increased to up to 99.9%.[46b] Ligand **96** also provided excellent enantioselectivities for the hydrogenation of α-amino ketones (up to >99% ee)[64] and of α-hydroxy ketones (up to 99% ee)[65]. Finally, replacing the oxazoline substituent by a benzyl group, ligand **97** (Figure 1.20), excellent enantioselectivities were obtained for the hydrogenation of ketoamides (up to >99% ee).[66]

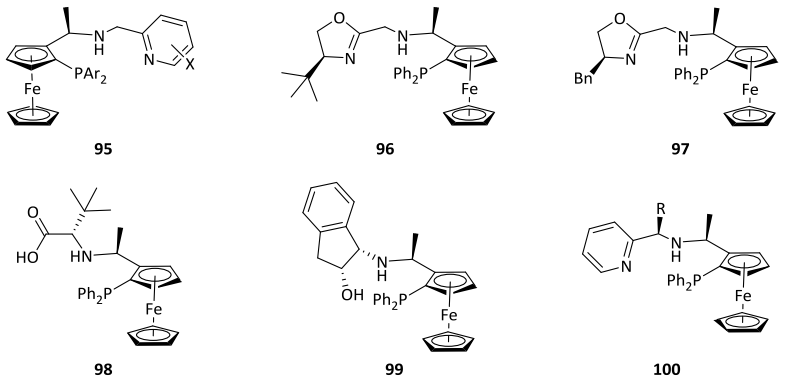


Figure 1.20. Chiral ferrocene-based tridentated ligands reported by Zhang for the hydrogenation of simple ketones.

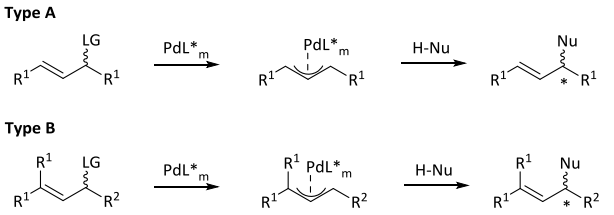
A series of tridentate ferrocene-based amino-phosphine acid ligands **98** (Figure 1.20) have been also applied in the hydrogenation of simple ketones affording chiral alcohols in excellent enantioselectivities (up to >99% ee).[67] Other type of ferrocene-based P,N,O ligands have been reported, recently by Zhang, with the use of the ferrocene-based amino-phosphine-alcohol ligand **99.** This ligand exhibited excellent catalytic performance in Ir-catalyzed asymmetric hydrogenation of simple ketones (up to 99.9% ee).[68]

Recently, Hu and coworkers reported a new ferrocene-based tridentate pyridine-aminophosphine ligand **100**[69] (Figure 1.20) adding a new stereogenic center next to pyridine moiety respect ligand **95**. These ligands provided good to excellent enantioselectivities (up to 97% ee), under mild reaction conditions, in a variety of alkyl aryl ketones.

1.2. Asymmetric Pd-catalyzed allylic substitution

Stereoselective formation of C-C, C-N and C-O bonds is one of the most important challenges in organic synthesis. In this context, palladium-catalyzed allylic substitution has proved to be an efficient synthetic method for the synthesis of natural products, due to its mild reaction conditions, the compatibility with many functional groups and the often high enantioselectivity.

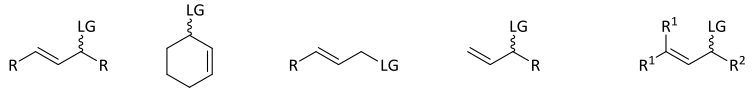
The Pd-catalyzed allylic substitution consists in the reaction between an allylic racemic substrate which contains a leaving group (such as acetate or carbonate) and a nucleophile (usually carboanion or amine). Then, a nucleophile substitution takes place and an either new carbon-carbon or carbon-nitrogen bond is generated (Scheme 1.4).[47]



Scheme 1.4. Asymmetric allylic substitution reaction with two different kind of substrates.

Two important classes of asymmetric allylic substitution depending on the kind of substrate used are evaluated. Type A reactions start from a racemic substrate (linear or cyclic) and proceed via symmetrical allyl systems (Scheme 1.4). 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.[70] Type B reactions, racemic or prochiral substrates with two identical geminal substituents at one of the allylic termini react via the π-allyl intermediate (Scheme 1.4). 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 enantioselectivity of the process need to be controlled, but the regioselectivity is also a problem because a mixture of regioisomers may be obtained.[70]

In this reaction, the range of substrates tested (linear or cyclic) is quite wide (Figure 1.21). However, 1,3-diphenylprop-2-enyl acetate **S1** (Figure 1.21) 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 catalyzed allylic substitutions. However, the most widely used catalysts are palladium complexes.[1,70] A wide range of carbon-stabilized nucleophiles bearing carbonyl, sulfone, nitrile or nitro groups 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 been only been efficiently performed in the presence of phenols. Aliphatic alcohols have found to be poor nucleophiles for such reactions.[70f]



S1 R = Ph
S2 R = Me

S3 n = 0
S4 n = 1
S5 n = 2

S6 R = 1-Naphtyl
S7 R = Ph

S8 R = 1-Naphtyl
S9 R = Ph

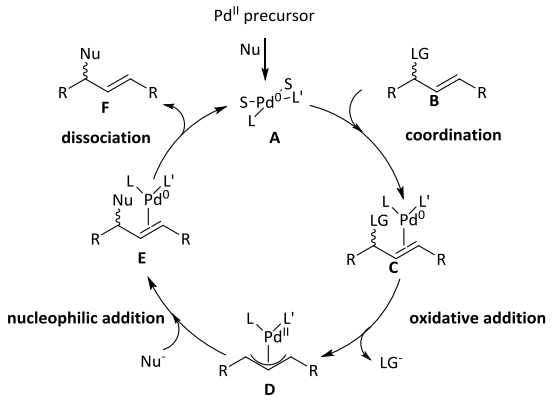
S10 R^1 = Ph; R^2 = Me
S11 R^1 = R^2 = Ph

Figure 1.21. The most common substrates used in the enantioselective allylic substitution.

1.2.1. Mechanism

The catalytic cycle for Pd-catalyzed allylic substitution reactions with stabilized nucleophiles has been widely studied during the last decades. This is partly due to the relative ease to isolate the catalytic intermediate π-allyl complexes (**D**).[70] The mechanism for palladium-catalyzed allylic substitution involves 4 steps (Scheme 1.6). The first step is the coordination of an allylic substrate (**B**) to the catalytic active specie (**A**), which is Pd specie at 0 oxidation state. Both Pd(II) and Pd(0) can be used as a catalysts precursors because Pd(II) species will be reduced in situ by the nucleophile to Pd(0) form. The most widely used catalyst precursors are $Pd_2dba_3.CHCl_3$ (dba = dibenzylidenacetone), $Pd(OAc)_2$ and $[Pd(\eta\text{-}C_3H_5)(\mu\text{-}Cl)]_2$. The next step is the oxidative addition of complex (**C**) to form the π-allyl intermediate (**D**), which is normally the rate determining step of the reaction.[70] The reason why racemic starting materials are used is because of the loss of stereochemistry once π-allyl intermediate is formed. The product of this oxidative addition has two positions that are susceptible to nucleophilic attack (two terminal carbons of the allyl system). This attack will be controlled by steric hindrance induced by chiral homodonor ligand or by electronic discrimination when heterodonor ligands are used. After the nucleophilic attack, an unstable Pd(0) olefin complex (**E**) is produced which rapidly undergoes dissociation, releasing product (**F**).

It is worth to mention that also the nucleophilic addition can be the rate determining step of the reaction, being both pathways (oxidative addition and nucleophilic attack) close in energy. Depending on the ligand used and also the substrate, those pathways can be differently favored.[47]



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

Scheme 1.6. Catalytic cycle for Pd-catalyzed allylic substitution reaction.

The enantioselectivity of the process is controlled by the external nucleophilic attack on the most allylic carbon terminus of the π-allyl intermediate (**D**). Therefore, the intermediate (**D**) plays an important role in the catalytic cycle and it is recognized as the intermediate which controls the regio- and enantioselectivity. It is stable in the absence of nucleophile and its behavior can be studied by spectroscopic techniques.

Due to dynamic behavior of this π-allyl intermediate in solution, different isomers can be present (Figure 1.22).

To achieve high enantioselectivities, the formation of only one isomer is needed, if we assume that reaction rates of all isomers are similar.

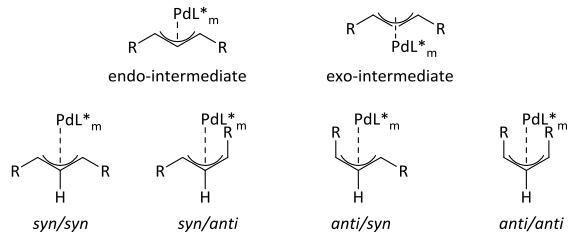


Figure 1.22. Possible isomers adopted by π-allyl palladium complex (**D**).

Both oxidative addition and nucleophilic attack take place stereoselectively with inversion of configuration. In that case, if the intermediate (**D**) does not undergo any isomeration that changes its configuration, the overall process proceeds with the retention of configuration; *i.e.* the nucleophile is introduced in the same side of the allyl plane that occupied the leaving group.

1.2.2. Ligands

Most of the successful ligands developed for this process have been designed using three main strategies. The first one was the use of a secondary interaction of the nucleophile with a side chain of the ligand to direct the approach to one of the allylic terminal atoms, by means of a secondary ligand-nucheophile interaction (Figure 1.23; **101**). The second one was to increase the ligand's bite angle in order to create a chiral cavity in which the allyl system is perfectly embedded (Figure 1.24; **102**). The third strategy consists on the use of heterodonor ligands to provide an electronic differentiation of the two allylic terminal carbons (Figure 1.25; **103**).

Concerning the secondary interaction of the nucleophile with the ligand, we can highlight the work of Hayashi and Ito *et al*. by the synthesis of **101** (Figure 1.23). By introducing a side chain into the ligand they were able to direct the approach of the nucleophile to one of the allylic terminal carbon atoms, providing high levels of enantioinduction.[71]

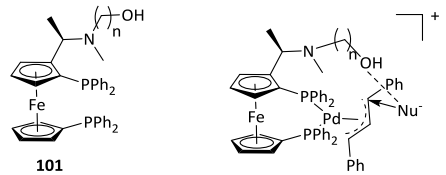
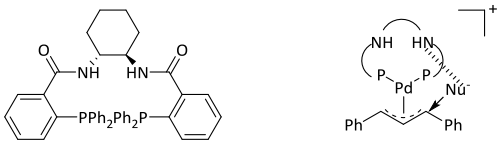


Figure 1.23. Ferrocene-based phosphine **101**. Example of a directing group ligand.

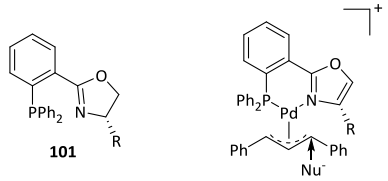
The idea of the second strategy, developed by trost and coworkers, is paved the way for the successful application of ligands with large bite angles for the allylic substitution of unhindered substrates.[72] In 2009, P.-O. Norrby in conjunction with G. C. Lloyd-Jones reported a DFT calculation analysis which determined that 13-membered chelate ring of Pd-**102** not only makes a chiral pocket where the substrate is embedded but also a secondary interaction which directs the nucleophilic attack (Figure 1.24).[73] This interaction is based on an H-bonding interaction between the nucleophile (enolate oxygen of dimethyl malonate) and the amide group of the ligand backbone. This interaction guided the enolate carbon to the proximal (pro-*S*) terminus of the η^3-carbon of the allyl with a perfect selectively. This hydrogen-bond directed delivery of the nucleophile has precedent in the elegant design of chiral ferrocene ligand **101** developed by Hayashi and Ito (Figure 1.23).



102

Figure 1.24. Secondary interactions of Trost ligand **102** reported by Norrby and Lloyd-Jones.

The other strategy consists on the use of heterodonor ligands, which create an electronic differentiation between both allylic carbons because of the different *trans* influences of the donor groups. The first ligand based on this strategy was the phosphine-oxazoline PHOX ligand **101**, developed by Pfaltz *et al*. (Figure 1.25).[74]



101

Figure 1.25. Example of electronic differentiation with. PHOX ligands.

In this context, this project will be focused in the last strategy, the application of heterodonor ligand to create electronic differentiation between both allylic carbons, more precisely in the application of P,N and P,S ligands in the Pd-allylic substitution reaction. Among heterodonor ligands, phosphorus-nitrogen ligands have been the most widely used, although other heterodonor ligands, such as phosphorus-thioether[4g,75] and phosphorus-sulfoxide[76] are emerging as alternative to P,N-based ligands. More recently, our group found that the use of biaryl phosphite-containing heterodonor ligands is highly advantageous by overcoming the most common limitations of this reaction which are low reaction rates and high substrate specificity.[77] Introducing a biaryl phosphite was crucial because its larger π-acceptor ability increases the reaction rates (lowering the energetic barrier of the nucleophilic attack, making the carbon *trans* to phosphite more electron deficient and therefore,

more reactive) and its flexibility allows the catalyst chiral pocket to adapt to both hindered and unhindered substrates.[77] In additions, the presence of biaryl phosphite moiety was also beneficial in the allylic substitution of more challenging monosubstituted 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.[74]

Following the third strategy, several mixed bidentated donor ligands (P-N[70b-f,78], P-S,[4,51] N-S[4,79] and P-P'[23c,80] 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.

1.2.2.1. Phosphorus-nitrogen ligands

The first successfully applied P,N-ligand to Pd-allyl substitution reaction was the phosphine-oxazoline PHOX ligand **101** (R= Me, Ph, ^{i}Pr, ^{t}Bu), developed simultaneously by Pfaltz, Helmchen and Williams.[74] Unfortunately, these kind of ligands only provided excellent enantioselectivities when bulky benchmark substrate **S1** was used. When less bulky dimethylated substrate **S2** or cyclic substrates **S3** were studied, enantioselectivities decreases up to 71% ee or racemic mixtures.

After this pioneering work, several modifications of those PHOX ligand **101** have been made by replacing the phosphine moiety by more electronically deficient phosphinite or phosphite, and also replacing the oxazoline moieties by other sp^2- or sp^3-nitrogen donor groups. Figure 1.26 shows the most representative successful ligands reported to date for asymmetric Pd-catalyzed allylic substitutions.

Modification on the substituent of the oxazoline ring led to ligands **102**[81] and **103**[82] (Figure 1.26). Both ligands provided similar high enantioselectivities than **PHOX** ligands in the Pd allylic substitution of model substrate **S1** (up to 98 % and up to >99% ee, respectively). However, only moderate enantioselectivities were obtained in the allylic substitution of les sterically demanding substrates such as linear substrate **S2** (ee's up to 69% with ligand **102**) or cyclic substrate **S14** (ee's up to 59% with ligand **103**).

A ferrocenyl substituent at the oxazoline ring was introduced in ligands **104**[83] and **105**[84] (Figure 1.26) instead of a phenyl ring. Both ligand families provided excellent results in the Pd-allylic alkylation of model substrate **S1** 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 **106** by introducing an enantiomerically pure binaphtyl moiety (Figure 1.26).[85] 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.

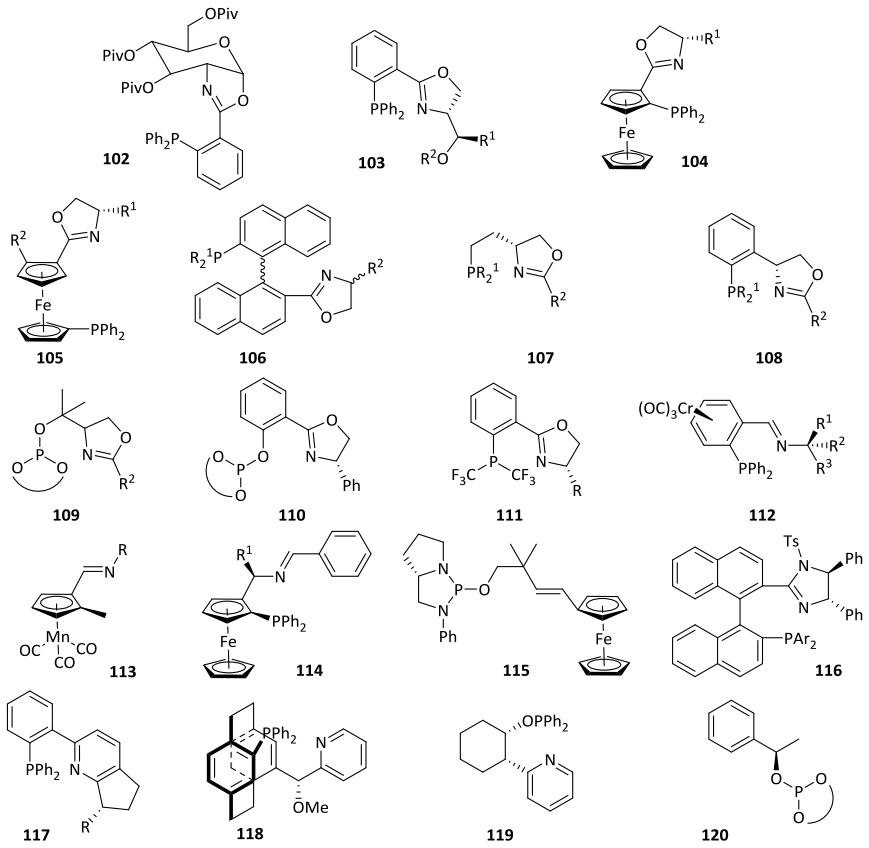


Figure 1.26. Selected successful P,N-ligands applied in the asymmetric Pd-catalyzed allylic substitution reaction.

Phosphine-oxazoline ligands **107**[86] and **108**[38b,87] (Figure 1.26) were also successfully applied in the Pd-allylic alkylation reaction of model substrate **S1** (ee's up to 98%). Ligand **107** also provided promising enantioselectivities in the allylic substitution of unhindered substrate **S2** (ee's up to 80%) and the cyclic substrate **S4** (ee's up to 79%).[86]

Phosphite-oxazoline ligands **109** (Figure 1.26) were designed to overcome the problem of regioselectivity in the allylic alkylation of monosubstituted linear substrates.[88] 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 **S1**) and unhindered (ee's up to 70% for **S4**) 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 1.26, and replace the phosphine group by a bulky diphenyl phosphite moiety (ligands **110**; Figure 1.26).[89] The application of these ligands in the asymmetric Pd-catalyzed allylic substitution was very successful. Excellent activities (TOF's > 2400 mol

substrate * (mol Pd * h)$^{-1}$, regio (up to 99%) and enantioselectivities (ee's up to >99%) were obtained for hindered and unhindered disubstituted and also monosubstituted substrates using a broad range of nucleophiles. Furthermore, experimental and theoretical studies showed that ligands **110** 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 adopt the *Sa*,*S* configuration.[78f]

After this breakthrough, other biaryl phosphite-oxazoline ligands have been developed. For instance, ligands **26**[90] and **27** (X = O)[91] (Figure 1.26) 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 1.10) has expanded the range of unhindered allylic substrates that can be efficiently catalyzed with this ligand family.

More recently, the strong π-accepting ligands **111** (Figure 1.26) have also provided high regioselectivities (up to 96%) and enantioselectivities (up to 94%) in the Pd-catalyzed alkylation of monosubstituted allyl substrates.[78j]

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 **112**-**115** (Figure 1.26) in the Pd-alkylation of model substrate **S1**.[92] More recently, phosphine imidazoline ligands have been also developed. For example, ligand **116** (Figure 1.26) provided high yields and enantioselectivities in the substitution of **S1** with dimethyl malonate and 1-fluorobis-(phenylsulfonyl)methane (ee's up to 96% and 98%, respectively).[78h]

P,N-ligands containing a pyridine group as sp^2-N donor group have also been developed. Ligand **117**[93] provided ee's up to 96%. Jiang *et al.* prepared a pyridine ligand **118** based on paracyclophane backbone. This ligand was applied in the allylic alkylation of model substrate **S1** and dimethylmalonate as nucleophile, achieving enantioselectivities up to 97%.[94] Zhou *et al.* designed a cyclohexyl based phosphinite-pyridine ligand **119**, achieving excellent enantioselectivities when standard substrate **S1** was studied (ee's up to 95%).[95] Phosphite-pyridine **120** was successfully applied in the Pd-allylic substitution reaction, achieving excellent enantioselectivities (up to 99% ee) in a wide range of substrates (disubstituted **S1**-**S2**, cyclic **S3**-**S5**, monosubstituted **S6**-**S9** and trisubstituted **S10**-**S11**) and different C-, N- and O-nucleophiles.[78c]

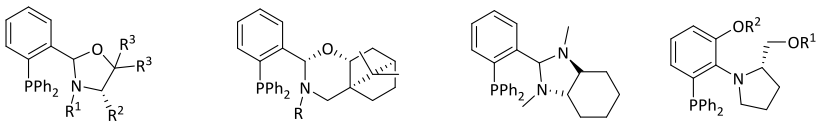
1.2.2.1.1. Phosphorus- sp^3-nitrogen ligands

Phosphine-based ligands

Although most of the phosphorus-nitrogen ligands applied in Pd-allylic substitution reaction have been phosphorus-sp^2-nitrogen ligands, some heterodonors sp^3-nitrogen

containing ligands have been successfully applied. These ligands can be divided mainly divided in four families:

The first ligands are variations of PHOX **101** ligand, where oxazoline moiety has been replaced by sp^3-nitrogen heterocycles such as oxazolidines **121**[96] (R^1= Me, Bu; R^2= ^{i}Pr, Ph, R^3= H, Ph), oxazinanes **122**[97] (R= Et, Pr, Bu, Bn), imidazolidines **123**[98] and **124**[99] (R^1= H, $SiMe_3$; R^2= Me, Et, Ph, OMe). All provided similar enantioselectivities in the Pd-allylic alkylation of standard substrate **S1** (ee's up to 99%).

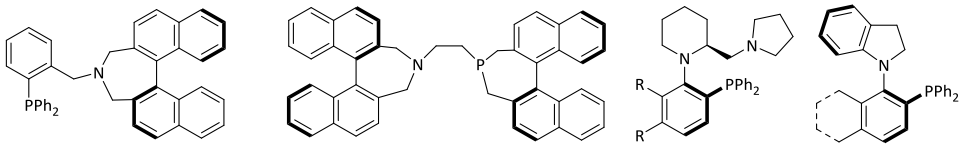


121 **122** **123** **124**

Figure 1.27. PHOX-type phosphine-sp^3 nitrogen ligands **121**-**124**.

In this second case, the enantioselectivity is provided from the axially chiral moieties: Azepine-type P,N ligands **125** and **126** have been successfully applied for the model substrate **S1** (ee's up to 97%) but poor results were obtained for unhindered substrate **S2**.[100]

Mino *et al.* developed amino-phosphine **127** (R= OMe, Naph) which presented axial chirality. These ligands provided excellent results in the allylic alkylation of model substrate **S1** (ee's up to 99%) with a wide range of C-nucleophiles derived from dimethyl malonate.[101]

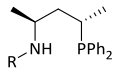


125 **126** **127** **128**

Figure 1.28. Axially chiral phosphine-amine ligands **125**-**128**.

Amino-phosphine **128** provided excellent results (ee's up to 97%) for standard substrate **S1**. They also observed kinetic resolution phenomena, achieving also enantioenriched **S1** from the reaction mixture (ee's up to 98%), while attaining alkylated product in high levels of enantioselectivity.[102]

The third class of ligands are P,N with N-donor secondary amines **129** (R= Me, ^{n}Bu, Ph). These ligands provided excellent enantioselectivities for model substrate **S1** (ee's 96%).

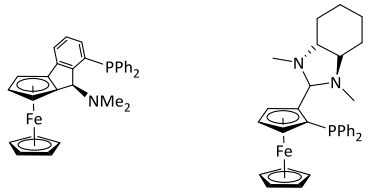


129

Figure 1.29. Phosphine-sp^3-amine ligand **129**.

Last ligand family has a planar chirality, which comes from ferrocenyl moiety. Fukuzawa *et al.* developed ferrocene-based phosphine-amine **130**. This ligand provided excellent enantioselectivities in the allylic alkylation and amination of standard substrate **S1** (ee's up to 96% and 90% respectively).[103]

Ligand **131**, developed by Kim and Jin[104], provided excellent enantioselectivities for the alkylation of model substrate **S1** (ee's up to >99%).



130 **131**

Figure 1.30. Selected ferrocene-based phosphine-sp^3-nitrogen ligands **130**-**131**.

Phosphinite/N-phosphine-based ligands.

Only two successful examples are reported in the literature. Ligand **132**, developed by Chan *et al.*, have been successfully applied in the allylic alkylation of model substrate **S1**, achieving enantioselectivities up to 95% ee. Authors found that secondary amines provided better enantioselectivities those tertiary amine-based ligands.

N-phosphine **133**, developed by Bujoli and Petit, also based on secondary amine moiety, exhibit a high enantioselectivity in the allylic alkylation of standard substrate **S1** (ee's up to 93%).[105]

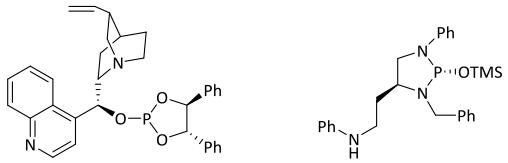
132 **133**

Figure 1.31. Selected phosphinite/aminophosphine-sp^3-nitrogen ligands **132**-**133**.

Phosphite-based ligands

As in phosphinite case, phosphite-based sp^3-nitrogen ligands have been poorly studied, and only two successful examples are present in the literature.

First example, reported by Zhang *et al*. is based on *chincona alkaloid*. Amino-phosphite **134** provided excellent results (ee's up to 94%) in allylic alkylation of standard substrate **S1** with a wide variety of carbon nucleophiles such as malonates and acetylacetones.[106] The second example, developed by Nemoto and Hamada,[107] is a unique case. Diaphabox ligand **135** is peculiar as the actual active species binding to the palladium is generated in situ. Ligand **135** comes from the P(V) analogue, which is reduced to P^{III} by BSA, achieving P-stereogenic phosphite-type ligand. This ligand provided excellent enantioselectivities for benchmark substrate **S1** (ee's up to 99%).



134 **135**

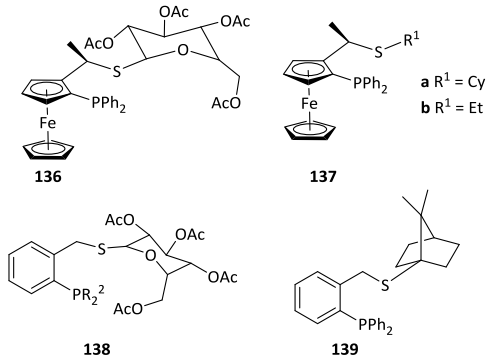
Figure 1.32. Phosphite-sp^3-nitrogen ligands **134**-**135**.

1.2.2.1.1. 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-thioether 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.



136 **137** **138** **139**

Figure 1.33. Chiral phosphine-thioether ligands **136**-**139**.

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 1.33) in 1996.[108] Ligand **136** bearing thyoglicose functionality afforded the alkylated product with an enantioselectivity of 88%. Changing the carbohydrate substituent for a cyclohexyl (**137a**) or an ethyl group (**137b**) (Figure 1.33) 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 **138a**-**b** (Figure 1.33) resulted in a low asymmetric induction (ee's up to 64%).[109] Thus, the combination of the two stereogenic fragments was crucial for achieving good levels of enantioselectivity. Low enantiomeric excesses were also obtained with a similar thioether-phosphine ligand **139** using a stereogenic norborneol

fragment (Figure 1.33), but the authors attributed their catalytic performance to the size chain between sulfur donor and the stereogenic unit.

The catalytic results using ferrocenyl phosphine-thioether ligands **138**-**142** (Figure 1.34) indicated that enantioselectivity is better when the phosphine group is attached to the Cp ring (ligands **138**-**140**) rather than when is attached to the thioether unit (ligands **141** and **142**) (Figure 1.34). Furthermore, by comparing ligands **138**-**140**, 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 1.34). The structural studies of a 1,3-diphenylallyl palladium complex containing ligand **138a**, [Pd(η^3-1,3-PhC_3H_3Ph)(**138a**)]PF_6, indicate that the small substituents on thioether groups favor the nucleophilic attack in the *cis* position to the S-donor moiety (Figure 1.34).[110]

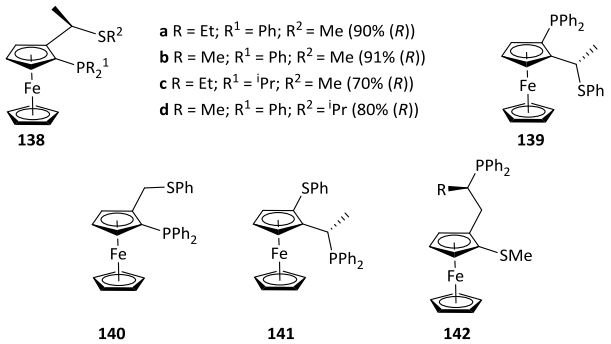


Figure 1.34. Ferrocenyl thioether-phosphine ligands **138**-**142**. This figure also shows the enantioselectivities obtained in the Pd-catalyzed asymmetric allylic alkylation of dimethyl malonate to **S10**.

Carretero et. al. reported a readily available family of enantiopure phosphine-thioether ferrocenes (Figure 1.35), having exclusively planar chirality. Ligands **143** and **144** were efficiently applied in the palladium-catalyzed allylic substitution of the model substrate **S10** (ee's up to 97%).[111] Catalytic results showed that ligands **143b**-**c** containing electron-withdrawing phosphines (Figure 1.35) provided high enantioselectivities in significantly shorter reaction times (20 min). A less sterically demanding thioether substituent in ligand **144** (Figure 1.35) resulted in a dramatically drop of the enantioselectivity (40% ee). Ligands **143** and **144** were also applied in the Pd-catalyzed allylic amination achieving the best ee's with ligands **143f**-**g** containing bulky phosphines (Figure 1.35) (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.

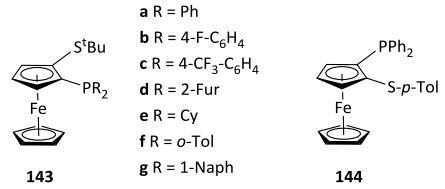


Figure 1.35. Ferrocenyl phosphine-thioether ligands **143** and **144** developed by Carretero *et al*.

Recently, a new class of ferrocenyl phosphine-thioether ligands with heterocyclic scaffolds has been reported by Chan and coworkers (Figure 1.36). Ligands **145**-**146** were initially applied in the enantioselective Pd-catalyzed indole alkylation of the 1,3-diphenylated substrate **S10**, achieving enantioselectivities up to 96% ee with ligand **146**, irrespective of the steric and electronic nature of indoles.[112] Later, ligands **145**-**147** (Figure 1.36) were applied in Pd-catalyzed allylic alkylation reactions using several malonate nucleophiles, providing enantioselectivities up to 96% ee with ligand **146**. Privileged ligand **146** was also examined in the Pd-allylic alkylation of cyclic allylic acetates and unsymmetrical allylic substrates, obtaining enantioselectivities up to 87% ee.[113]

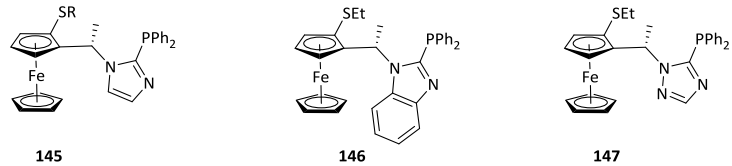


Figure 1.36. Phosphine-thioether ligands **145**-**147** based on ferrocene and heterocyclic scaffolds.

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 **148a**-**f** (Figure 1.37), 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 **148e** (up to 90% ee). It should be pointed out that ligand **148e** 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).[114]

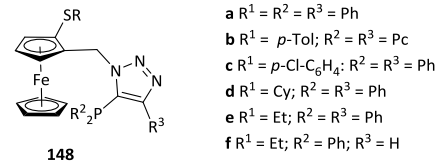
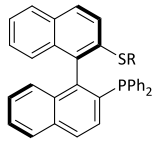


Figure 1.37. ThioclickFerrophos ligands **148**.

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 149a**-**d** (Figure 1.38) derived from enantiopure **BINOL** have

been reported by Kang[115], Gladiali[116] and Shi[117] with different alkyl groups on the sulfur atom. Kang and coworkers reported 91% ee for the product of usual allylic alkylation test by using ligand **149a**. Gladiali tested the isopropyl derivative **149b**, which led to the corresponding compound in quantitative yield in 60% ee. Shi obtained 77% and 33% ee, respectively, by using ligands **149c** and **149d**. Interestingly, they obtained a reversal of enantioselectivity between ligands **149a**, **149c**, and **149b**, **149d**. X-ray analyses and NMR studies confirmed a P,S-coordination as a metallocycle 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 arylthioether substituted **BINAPS** ligands **149e**-**h** and their alkyl counterpart **149i**.[118] After a first examination of ligand **149e** in the test reaction with **S10** (90% yield, 95% ee), ligands **149e**-**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, **149f** provided enantioselectivities up to 95% using different sterically and electronically substituted indoles.

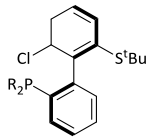


149

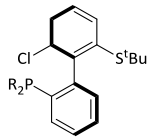
a R = Me
b R = ^{i}Pr
c R = Bn
d R = $CHPh_2$
e R = Ph
f R = 2-^{i}Pr-C_6H_4
g R = 2-Naph
h R = 3,5-Xyl
i R = Cy

Figure 1.38. Phosphine-thioether **BINAPS** ligands **149**.

Very recently, the synthesis of another axially chiral thioether-phosphine ligand has been reported.[119] Ligands **150** (Figure 1.39), 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 (**149**) above mentioned (ee's up to 94% were obtained with ligands **150**).



(*R*)-**150**



(*S*)-**150**

a R = Ph
b R = Cy

Figure 1.39. Axially chiral biphenyl-based phosphine-thioether ligands **150**.

Nakano and Hongo were the first to test the ability of oxathiane-type ligands to perform Pd-catalyzed allylic substitutions. They initially synthesized ligands **151**-**153** (Figure 1.40) and successfully used them in alkylation and amination reactions of substituted allyl acetates. Norbornane-based phosphine-oxathiane ligand **151** gave the highest level of enantioselectivity (ee's up to 94%) in the test reaction. Ligand **151** was also useful in the analogous allylic amination with either benzyl amine or potassium

phtalamide providing enantioselectivities up to 90% ee.[120] Later, taking into account the good catalytic performance obtained with ligand **151**, Nakano et. al reported a novel polymer-supported P-S type ligands **154a**-**e** (Figure 1.40) 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).[121] Additionally, the same authors developed a new xylofuranoside-based phosphinoxathiane ligand **155** (Figure 1.40), that provided also high enantioselectivities in the enantioselective Pd-catalyzed allylic substitution of **S10** (ee's up to 91%).[122]

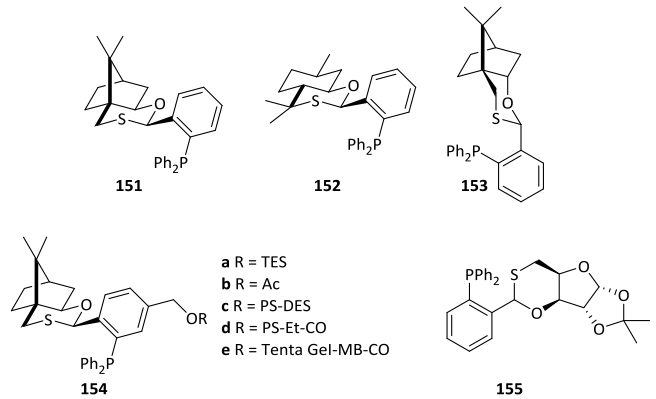


Figure 1.40. Phosphinooxathiane ligands **151**-**155**.

Cyclopropane-based phosphine-thioether ligands **17**-**19** (Figure 1.8) and related ligands **156**-**160** (Figure 1.41) 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 1.8) to have the optimal configuration for this reaction, giving the product in high yield and with good enantioselectivity (93% ee).[31]

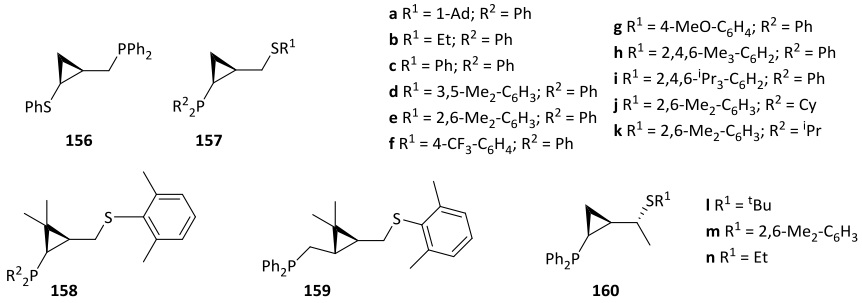


Figure 1.41. Cyclopropane-based thioether-phosphine ligands **156**-**160**.

A series of (*S*)-proline-derived phosphine ligands bearing thioether and selenoether functionalities (**161**-**165**; Figure 1.42) 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 **163a**-**g** resulted in higher values of

enantioselectivity, with a maximum of 88% ee for the ligand bearing a sterically hindered naphtyl group (**163g**). It should be noted that ligands **162** and **164**, bearing a selenium atom instead of sulfur, also induced good levels of enantioselectivities (ee's ranging from 79% to 86%).[123]

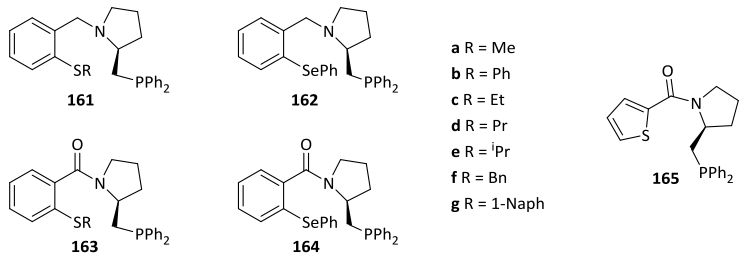


Figure 1.42. (*S*)-Proline-derived chiral ligands **161**-**165.**

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 **166**, Figure 1.43).[124] 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 **167**, Figure 1.43).[125] Ligands **167** have been applied in the Pd-catalyzed allylic alkylation of substrates **S10**, **S11** and **S13** (Figure 1.21). 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.

a R^1 = ^{t}Bu; R^2 = Ph; n = 1
b R^1 = ^{t}Bu; R^2 = Ph; n = 2
c R^1 = ^{t}Bu; R^2 = Tol; n = 1
d R^1 = ^{t}Bu; R^2 = Bn; n = 1
e R^1 = Ad; R^2 = Ph; n = 1

a R^3 = Ph; R^4 = *o*-An; n = 1
b R^3 = Ph; R^4 = *o*-Tol; n = 1
c R^3 = Ph; R^4 = *o*-bi-C_6H_4; n = 1
d R^3 = Ph; R^4 = Fc; n = 1
e R^3 = Ph; R^4 = *m*-Xyl; n = 1
f R^3 = Ph; R^4 = *o*-Anth; n = 2
g R^3 = Et; R^4 = *o*-Anth; n = 1
h R^3 = ^{t}Bu; R^4 = *o*-Anth; n = 1
i R^3 = Bn; R^4 = *o*-Anth; n = 1
j R^3 = *p*-Anth; R^4 = *o*-Anth; n = 1
k R^3 = *o*-Anth; R^4 = *o*-Anth; n = 1
l R^3 = 3,5-Me_2-C_6H_3; R^4 = *o*-Anth; n = 1
m R^3 = 4-CF_3-C_6H_4; R^4 = *o*-Anth; n = 1
n R^3 = Ph; R^4 = *o*-Anth; n = 0
o R^3 = ^{t}Bu; R^4 = *o*-Anth; n = 0

Figure 1.43. *P*-chirogenic phosphine-thioether ligands **166** and **167**.

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.[126] Ligands **2**-**4** (Figure 1.3), also applied in the Rh-catalyzed hydrogenation of enamides,[26] and related ligands **168**-**173** (Figure 1.44) 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 1.45). Hence, ligand **3g** contains a bulky substituent in both backbone and thioether group that controls the sulfur inversion. A similar optimization of the ligand structure for the Pd-catalyzed allylic substitution of cycloalkenyl acetates showed that **171c** afforded the highest enantioselectivities (91-97% ee) (Figure 1.46). Moreover, sulfur and nitrogen containing heterocyclic substrates underwent enantioselective allylic alkylation and amination using ligand **171c** to afford 3-substituted piperidines and dihydrothiopyrans in enantioselectivities up to 94% ee (Figure 1.46). 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 1.45). 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.

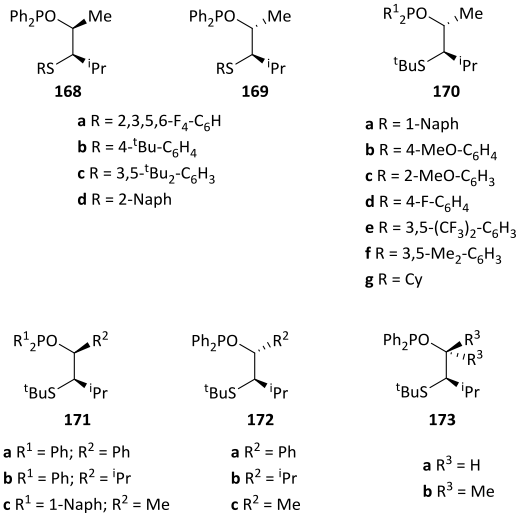


Figure 1.44. Phosphinite-thioether ligands **168**-**173** developed by Evans and coworkers.

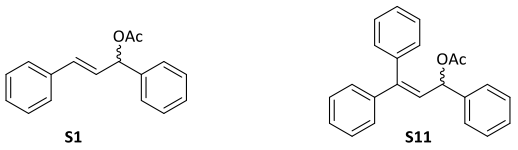


Figure 1.45. Summary of the best results obtained by using ligands **2**-**3g** in the Pd-allylic alkylation and amination of symmetrical and unsymmetrical linear substrates **S1** and **S11**.

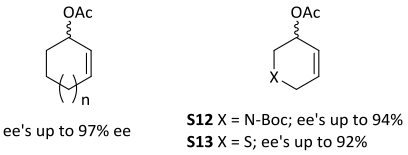


Figure 1.46. Summary of the best results obtained by using ligands **171c** in the Pd-allylic alkylation and amination of cyclic and heterocyclic substrates **S3**-**S5** and **S12**-**S13**.

The series of above mentioned furanoside phosphinite-thioether ligands **5** (Figure 1.4) and ligands **174** (Figure 1.47) bearing a more variety of thioether substituents, were applied in the Pd-catalyzed allylic substitution of mono- and disubstituted linear and cyclic substrates (ee's up to 95%).[127] 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 **174a** were used.

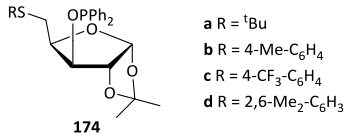
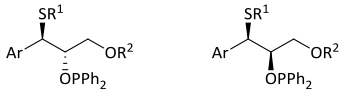


Figure 1.47. Phosphinite-thioether ligands **174** with furanoside backbone.

At the same time, the phosphinite-thioether ligands **6** and **7** with a pyranoside backbone (Figure 1.5) 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*-butyl group was present in the thioether moiety. Both enantiomers of the products were obtained by using ligand **7b**.[28a,b,128]

More recently, Pericàs and coworkers applied the previously mentioned phosphinite-thioether ligands **9a**-**m** (Figure 1.6) and related ligands **175a**-**f** and **176a**,**e** (Figure 1.48), to Pd-catalyzed allylic substitution reactions.[129] 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 **175a** and **176b** 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).



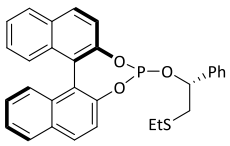
a Ar = Ph; R^1 = Ad; R^2 = Tr
b Ar = Mes; R^1 = Cy; R^2 = Me
c Ar = Mes; R^1 = ^{t}Bu; R^2 = Me
d Ar = Mes; R^1 = Ad; R^2 = Me
e Ar = Mes; R^1 = ^{t}Bu; R^2 = Tr
f Ar = Mes; R^1 = Ad; R^2 = Tr

Figure 1.48. Arylglicidol derived thioether-phosphinite ligands **175** and **176**.

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.

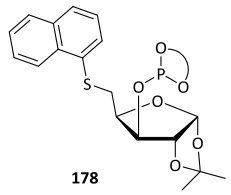
The first one was the binaphtyl phosphite-thioether ligand **177** (Figure 1.49), reported by Pregosin and coworkers. Yields up to 70% were reached, but in all cases, both the region and enantioselectivities were moderate.[130]



177

Figure 1.49. Binaphtyl phosphite-thioether ligand **177**.

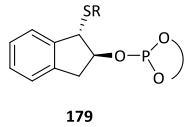
In 2001 thioether-phosphite ligands **32**-**34a** and **32d** with a furanoside backbone (Figure 1.11) were applied in the Pd-catalyzed allylic alkylation and amination substitution reactions providing only moderate enantioselectivities (up to 58% and 67% ee, respectively).[131] It was not until 2014 that the high efficiency of this sugar-based backbone has been demonstrated in this catalytic process. Ligands bearing bulkier thioether substituents (**38**, Figure 1.11; **178**, Figure 1.50) and enantiopure biaryl-phosphite moieties (**e** and **f**, Figure 1.11) and also their analogous ligands having the opposite configuration in C-3 (**39** and **42**, Figure 1.11) have been successfully applied in the Pd-catalyzed allylic substitution.[5c] Ligand **178f** 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 **178f** 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 1.50). Furthermore, the potential application of this P,S-system has been proven by simple tandem reactions, involving allylic alkylation/ringclosing metathesis or allylic alkylation/cycloisomerization of 1,6-enyne reactions, with no loss of enantiomeric excess.



178

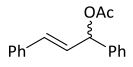
Figure 1.50. Phosphite-thioether ligands-type **178**.

Recently, Pericàs and coworkers have been synthesized phosphite-thioether indane-based ligands **179** (Figure 1.51) and were applied in 40 compounds involving linear and cyclic substrates and a broad range C-, N- and O-nucleophiles (ee's up to 99%). The results were maintained using the propylene carbonate as green solvent. In comparison with previous furanoside-based P,S ligands, which have emerged as some of the most successful catalyst for this process, the new P,S ligand also provided a better activity and a wider nucleophile scope (i.e., including the addition of pyrroles and a broader range of amines).[5g]

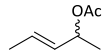


179

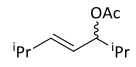
a R = ^{i}Pr
b R = Pr
c R = ^{t}Bu
d R = Ph
e R = 2,6-Me_2-C_6H_3
f R = 4-CF_3-C_6H_4
g R = 4-OMe-C_6H_4
h R = 9-ant



C-Nu; ee's from 92% to > 99%
N-Nu; > 99% ee
O-Nu; ee's from 85% to 98%



C-Nu; ee's from 82% to 92%



C-Nu; 99% ee's

C-Nu; ee's from 87% to 98%
N-Nu; 94% ee
O-Nu; 98% ee

C-Nu; ee's from 95% to >99%

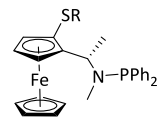
C-Nu; ee's from 99% to >99%

Figure 1.51. Phosphite-thioether ligands **179**.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-**179f** system.

N-phosphine-thioether ligands

In 2006 Chan and coworkers developed a series of ferrocene *N*-phosphine-thioether ligands **180a**-**c** (Figure 1.52) and successfully applied them in the asymmetric allylic substitution of **S10** (ee's up to 93%).[132] Later, the same authors expanded this family with ligands containing bulkier thioether substituents (**180d**-**e**) (Figure 1.52). Ligands **180a**-**e** were tested in the Pd-catalyzed allylic substitution of substrate **S1** with aliphatic alcohols. Ligand **180e** 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.[133]



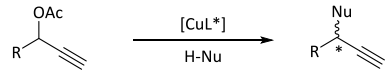
180

a R = Et
b R = ^{t}Bu
c R = Ph
d R = ^{i}Pr
e R = Cy

Figure 1.52. Ferrocene N-thioether-phosphine ligands **180**.

1.3. Asymmetric Cu-catalyzed propargylic substitution

Propargylic compounds are common motif in many natural products, fine chemicals and synthetic pharmaceuticals. The π-nucleophilic character of the triple bond makes it a versatile entity for further chemical transformations. In addition, for terminal acetylidenes, the triple bond is accompanied by a fairly acidic terminal acetylenic hydrogen converting these propargylic compounds in a highly potential for a wide variety of transformations.[134]

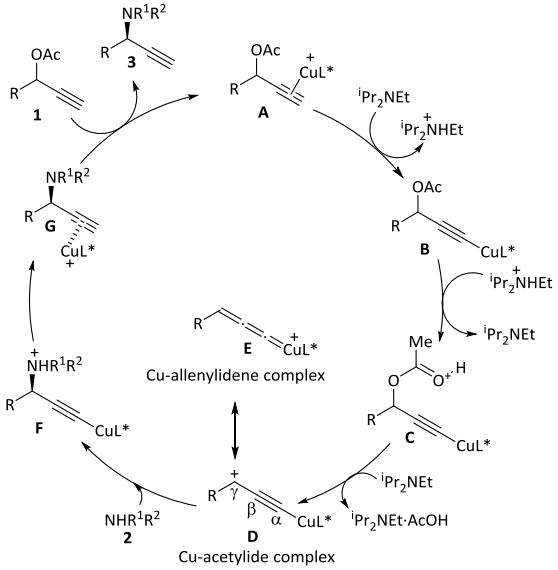


Scheme 1.7. Asymmetric Cu-catalyzed propargylic substitution reaction.

Whereas the metal-catalyzed asymmetric allylic substitution is broad studied, the transition-metal-catalyzed propargylic substitution reaction is much less developed. The Nicholas reaction has been used as an effective method for propargylic substitution reactions of propargylic alcohol and their derivatives with a variety of nucleophiles to give the corresponding propargylic substituted products.[135] However, this reaction has some drawbacks; it needs a stoichiomeric amount of toxic $Co_2(CO)_8$, which significantly limits its application, and the reaction process requires multiple steps to obtain the desired propargylic products.[135-136] For these reasons the transition-metal-catalyzed propargylic substitution is required to overcome these limitations. Several transition-metal have been applied in the current reaction; Pd, Cu, Ti and Ru are some examples. In this thesis we focused on copper-catalyzed propargylic substitution because of among various catalysts used in propargylic substitution reaction, copper catalysts show several advantages; a) low cost of the catalyst precursors, b) low toxicity, c) mild reaction condition, d) broad substrate scope and e) excellent enantioselectivities have been achieved. A wide range of nucleophiles such as carbon, nitrogen and oxygen[137] have been studied in this reaction. This thesis was focused on the application of amines (N-nucleophile) and enamines (C-nucleophile) which will be explained in more detail in the following sections.

1.3.1. Mechanism

The proposed mechanism for the Cu-catalyzed propargylic substitution using nitrogen nucleophiles was largely investigated by Nishibayashi.[138] It was similar to previous reaction pathway proposed by van Maarseveen[139], and it is shown in the Scheme 1.8.



Scheme 1.8. Proposed reaction pathway for Cu-catalyzed propargylic amination.

The experimental results revealed that copper-allenylidene complex should be the key intermediate. This conclusion is also supported by density functional theory calculations for the model reaction. The π-alkyne complex (**A**) is transformed into copper-acetylide complex (**C**), via protonation of specie (**B**).[140] Copper-allenylidene complex (**D**) is formed by elimination of an acetyl moiety from the copper-acetylide complex (**C**). *N*,*N*-Diisoproylethylamine promotes these deprotonation and protonation processes. Copper-acetylide complex (**D**), which bear a cationic *γ*-carbon, and the key intermediate copper-allenylidene complex (**E**) are in resonance structure. The nucleophilic attack of the amine on the *γ*-carbon atom provides Cu-acetylide complex (**F**). Copper-π-alkyne complex (**G**) was transformed from (**F**) due to the high acidity of the proton in the conjugated amine which promotes the shift of the hydrogen atom. The ligand exchange between the product and the substrate regenerates the initial π-alkene complex (**A**). Unfortunately, whereas silver- and gold-allenylidene complex have been experimentally isolated,[141] the copper-allenylidene complex have not been isolated yet.

DFT calculations for the model reaction system between propargylic acetate and dimethylamine in presence of $[Cu(PPh_3)_2(MeOH)]^+$, carried out by Sakata, Nishibayashi and coworkers, shown the importance of the Lewis base molecule (methanol or trimethylamine) to promote the propargylic amination.[138]

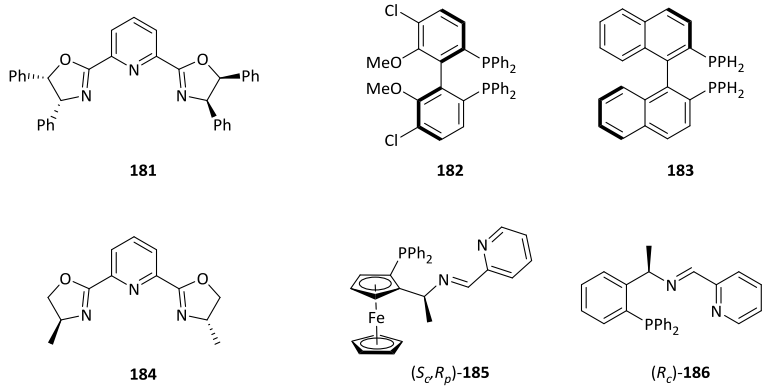
1.3.2. Ligands

1.3.2.1. Asymmetric Cu-catalyzed propargylic amination of propargylic esters

The use of propargylic amines as a versatile building blocks and intermediates for organic synthesis is extended.[142] Last years, the copper-catalyzed propargylic amination have suffered great progress becoming one of the most attractive strategies for the preparation of propargilyc amines.[140,143]

In 1994, Murahashi and coworkers reported a highly effective Cu-catalyzed amination of propargylic esters and phosphates with several amines under mild reaction conditions.[144] They found that a terminal acetylenic proton was needed for this reaction. It suggested that copper-acetylide complex should be formed as key intermediate (see above). Even though, they just got racemic products at this stage, this work sets the stage for an enantioselective version.

First asymmetric Cu-catalyzed propargylic amination was reported by van Maarseveen and Nishibayashi research groups independently in 2008. In both cases high activities and good enantioselectivities were obtained for the amination of aromatic propargylic acetates. The differences between both methods are the structure of the chiral ligand and the type of amine used. Regarding to van Maarseveen report, they used diPh-pybox **181** (Figure 1.53) in combination with CuI as a catalyst, and primary amines proved to be more suitable nucleophiles (up to 88% ee).[139]



181 **182** **183**

184 (S_c,R_p)-**185** (R_c)-**186**

Figure 1.53. Selected ligands for Cu-catalyzed amination of propargylic acetates.

On the other hand, Nishibayashi group applied the complex of $CuOTf{\cdot}1/2C_6H_5$ with an atropoisomeric diphosphine ligand Cl-MeO-BIPHEP **182** (Figure 1.53) as the catalysts and only secondary amines worked as suitable nucleophiles (up to 98% ee).[145] Despite this good results, the successfully substrates application was limited to aromatic propargylic acetates. In order to extend the substrate scope Nishibayashi's group used BINAP ligand **183** (Figure 1.53) with $(CuOTf)_2{\cdot}C_6H_5$ to substituted aliphatic propargylic alcohol derivatives with secondary amines achieving excellent enantioselectivities (up to 90% ee).[146] The leaving group of the substrates was

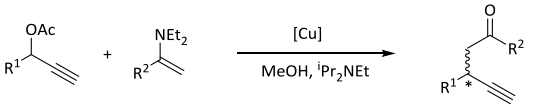
pentafluorobenzoate instead of acetate group. This modification was found to be necessary to promote the amination of aliphatic propargylic esters with secondary amines. However, primary amines were less efficient in this catalytic system. On the other hand, the copper-catalyzed enantioselective amination of non-aromatic propargylic esters with primary amines could be realized by van Maarseveen's method, in which good yields and high enantioselectivities were achieved by the use of CuI with Me-pybox **184** (Figure 1.53) (up to 99% ee).[147] Some secondary amines were also tested, however, only moderate enantioselectivities were achieved.

It was not until 2012, when Hu and coworkers demonstrated that chiral tridentate P,N,N-ligands, ($S_c R_p$)-**185** and (*R*)-**186**, were highly efficient for the Cu-catalyzed asymmetric propargylic amination of propargylic acetates.[148] Both primary and secondary amines were found suitable nucleophiles, providing the corresponding propargylic amines in high yields and with excellent enantioselectivities (up to 97% ee for secondary amines, and up to 96% ee for primary amines) using CuCl/($S_c R_p$)-**185** complex. Moreover, $Cu(OAc)_2 \cdot H_2O$/(*R*)-**186** catalytic system has been successfully applied in the amination of aliphatic propargylic acetates using both primary and secondary amines obtaining good enantioselectivities (up to 93% ee for secondary amines, and up to 81% ee for primary amines). It was noteworthy that this catalytic system was the first successfully example in which both primary and secondary amines could be used as efficient nucleophiles for the highly enantioselectivity catalytic propargylic amination of both aliphatic and aromatic propargylic acetates.

Since then, some advances have been developed applying this successful method. In 2014, Nishibayashi and co-workers disclosed a copper-catalyzed asymmetric intramolecular propargylic amination of propargylic acetates bearing a secondary amine moiety at suitable position.[149] The catalytic sequential reaction using transition metal complexes have been attracted much attention due to the advantage of simplicity and facility in the preparation of complex and useful compounds. Some cycloaddition reactions based on the Cu-catalyzed amination of propargylic acetates have been also developed.[150]

1.3.2.2. Asymmetric Cu-catalyzed propargylic alkylation of enamines

Despite the recent developments in the asymmetric catalytic propargylic substitution some versions of the reaction are still a challenge, in particular, the use of carbon-nucleophile. Among various carbon nucleophiles used,[151] enamine is a quite attractive one, because it can provides very useful propargylic ketones.[140,143]

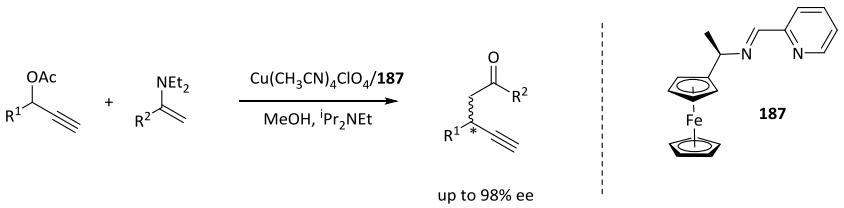


Scheme 1.9. Asymmetric Cu-catalyzed propargylic alkylation of enamines.

The first asymmetric Cu-catalyzed alkylation involving enamides was reported by Hou and co-workers in 2009.[152] 5 mol% of $Cu(CH_3CN)_4ClO_4$/(*R*)-Cl-MeO-BIPHEH **182**

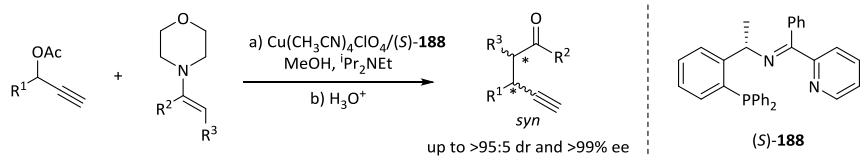
catalytic system was used to achieve in good yields and good enantioselectivities (up to 91% ee) a series of β-ethynyl ketones. The aliphatic enamine derived from cyclohexanone was also examinated, providing the chiral product in 33% yield and 72% ee when a propargylic benzoate instead of the acetate was used.

In order to improve the enantioselectivities obtained in the previous work, Guo's research group reported an enantioselective Cu-catalyzed propargylic alkylation using enamines with propargylic esters In presence of chiral ferrocene-based tridentate P,N,N ligand **187** to afford the desired propargylic ketone in good yields and excellent enantioselectivities (up to 98% ee) under mild reaction conditions (Scheme 1.10). [153]



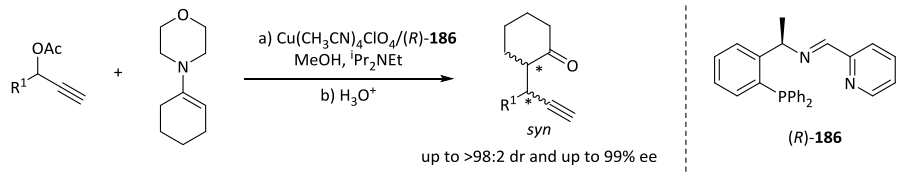
Scheme 1.10. Cu-catalyzed enantioselective propargylic substitution of propargylic acetates with enamines involving ferrocene-based tridentate P,N,N-ligand **187**.

In 2014, Hu and co-workers applied a bulky and structurally rigid tridentate ketamine P,N,N-ligand (*S*)-**188** in a highly diastereo-/enantioselective copper-catalyzed propargylic alkylation of morpholine-derived acyclic ketone enamine with propargylic esters to afford two vicinal tertiary stereocenters, in excellent diastereo- and enantioselectivities (up to >95:5 dr and >99% ee) (Scheme 1.11).[154]



Scheme 1.11. Cu-catalyzed diastereo-/enantioselective propargylic alkylation of acyclic ketone enamine with propargylic acetates involving tridentate P,N,N-ligand (*S*)-**188**.

Recently, based on the results obtained on the asymmetric propargylic alkylation involving acyclic enamines (Scheme 1.11), Hu and co-workers, tried to expand the enamine nucleophilic scope, using more challenging cyclic enamines (Scheme 1.12).[155] Employing 1-phenylethylamine-derived tridentate P,N,N-ligand (*R*)-**186**, good-to-excellent diastereo- and enantioselectivities (up to >98:2 dr and up to 99% ee) have been achieved for a wide range of substrates.



Scheme 1.12. Cu-catalyzed diastereo-/enantioselective propargylic alkylation of cyclic ketone enamine with propargylic acetates involving tridentate P,N,N-ligand (*R*)-**186**.

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Chapter 2

OBJECTIVES

UNIVERSITAT ROVIRA I VIRGILI
SUSTAINABLE AND COST-EFFECTIVE DEVELOPMENT OF CHIRAL METAL-CATALYSTS FOR C-H AND C-X BOND FORMING REACTIONS
Carlota Borràs Noguera

2. OBJECTIVES

This thesis is focused 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 cyclohexane-based phosphite/phosphinite-thioether ligands **L1**-**L2a**-**g** (Figure 2.1) in the Ir-catalyzed hydrogenation of minimally functionalized olefins. A DFT study has been performed in order to better understand their catalytic behavior.

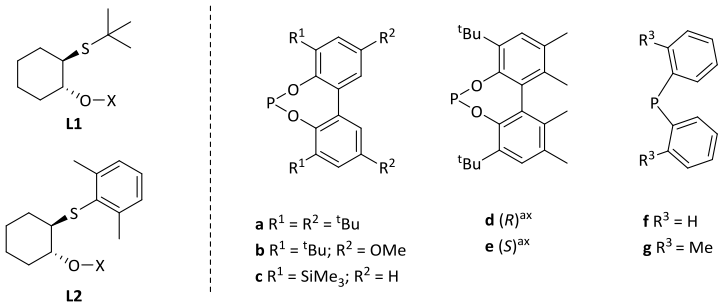


Figure 2.1. Phosphite/phosphinite-thioether ligands **L1**-**L2a-g**.

2. To synthesize and apply binaphtyl-based phosphite-thioether ligands **L3**-**L6a**-**c** (Figure 2.2) in the asymmetric Ir-catalyzed hydrogenation of minimally functionalized olefins.

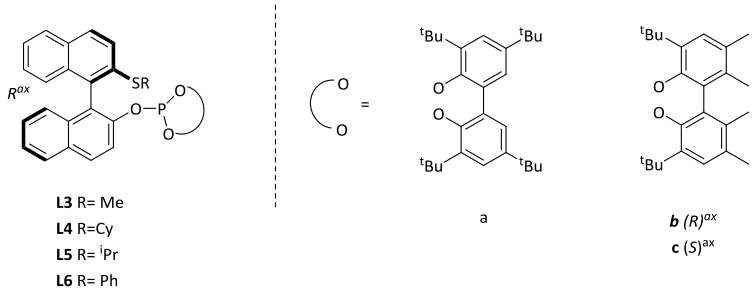


Figure 2.2. Binaphtyl-based phosphite-thioether ligands **L3**-**L6a**-**c**.

3. To synthesize and apply carbohydrate-derived phosphite-thioether/selenoether ligands **L7**-**L30a**-**g** (Figure 2.3) in the Ir- and Rh-catalyzed hydrogenation of minimally functionalized and functionalized olefins respectively, and in the Pd-catalyzed allylic substitution reactions.

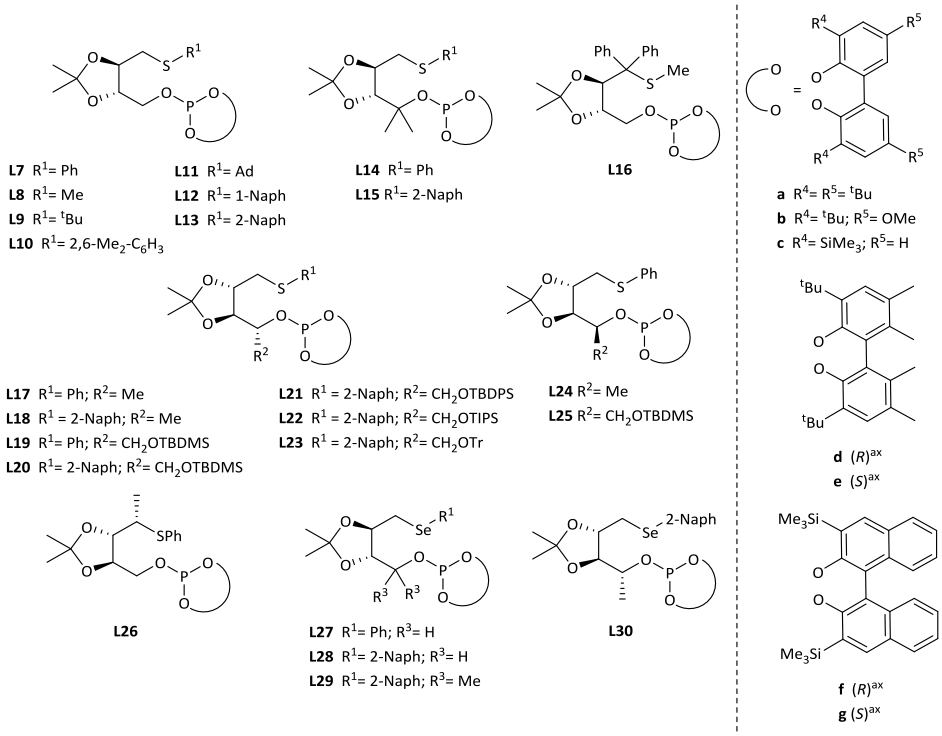


Figure 2.3. Sugar-based phosphite-thioether/selenoether ligand library **L7**-**L30a**-**g**.

4. To synthesize and apply carbene/phosphinite/phosphite-thioether compounds **L31**H·Br and **L32**-**L33** (Figure 2.4) in the asymmetric Ir-catalyzed hydrogenation of minimally functionalized olefins.

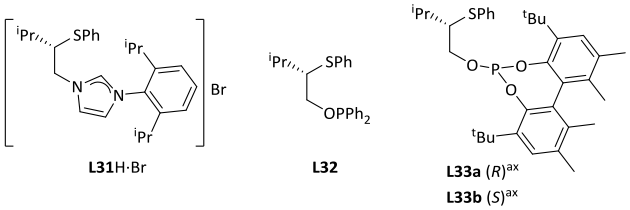


Figure 2.4. Bidentated S-NHC ligands **L31**-**L33**.

5. To synthesize and apply pyrrolidine-based P,O and P,S ligands **L34**-**L44** (Figure 2.5) in asymmetric Ir-catalyzed hydrogenation of minimally functionalized olefins.

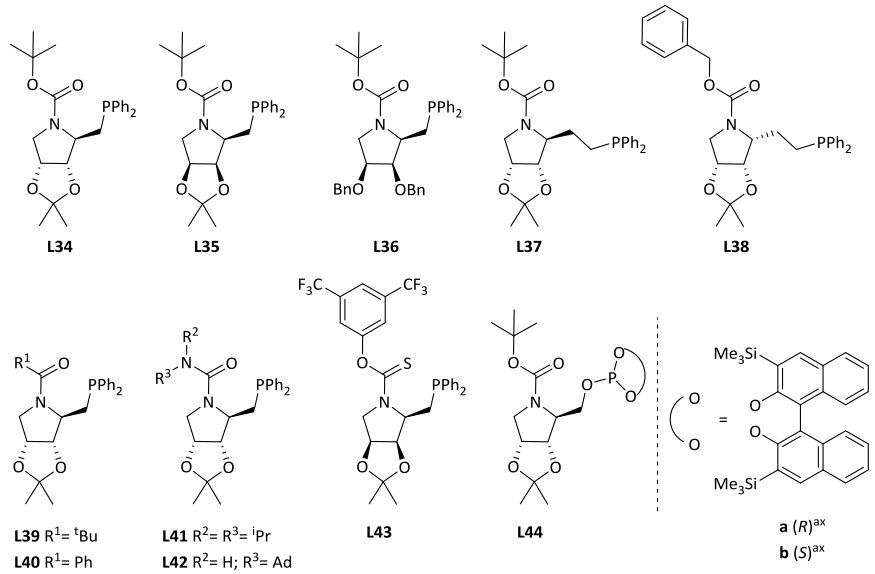


Figure 2.5. Pyrrolidine-based P,O/S ligands **L34**-**L44**.

6. To synthesize tridentated P,N,N ligands **L45**-**L48** (Figure 2.6) for the asymmetric Ir-catalyzed hydrogenation of simple ketones.

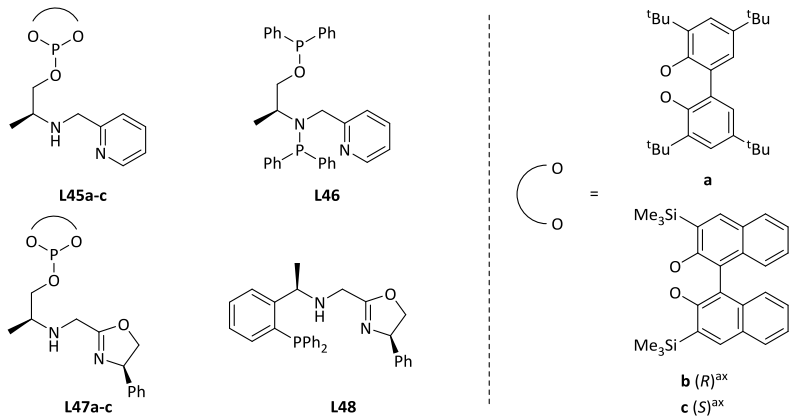


Figure 2.6. P,N,N-ligand library **L45**-**L48**.

7. To synthesize and apply pyrrolidine-based amino-phosphite/phosphinite/phosphine ligands **L49**-**L55a**-**d** (Figure 2.7) in the Pd-catalyzed allylic substitution reactions.

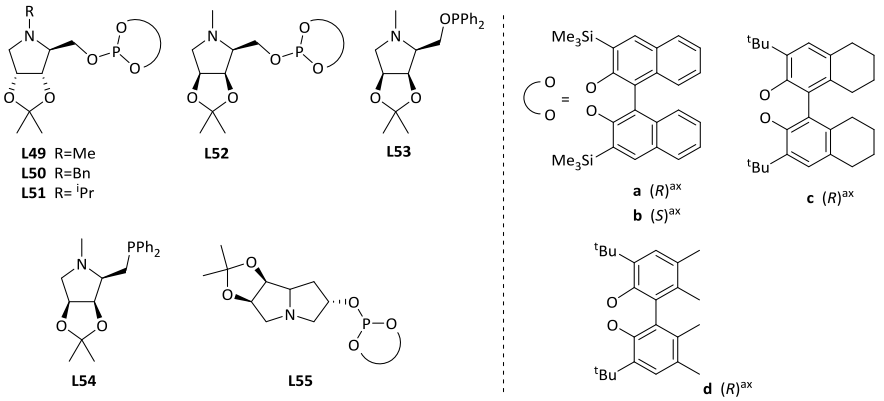


Figure 2.7. Amino-phosphite/phosphinite/phosphine ligands **L49**-**L55**.

8. To synthesize and apply tridentated phosphine-imino-based ligands **L56**-**L61** (Figure 2.8) in the asymmetric Cu-catalyzed propargylic substitution reactions.

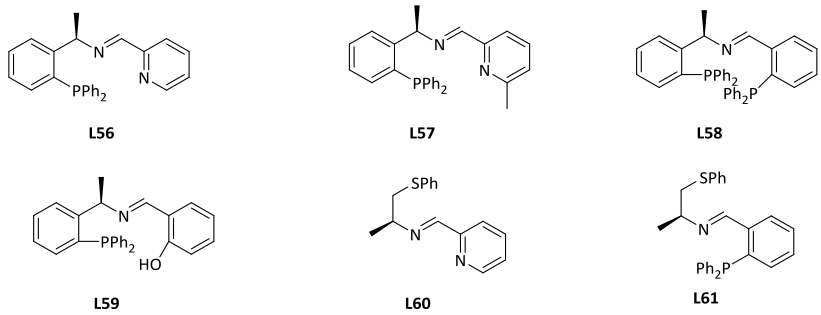
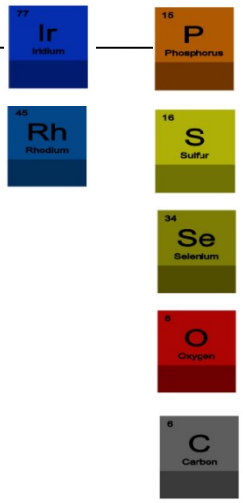


Figure 2.8. Chiral tridentated imine-based ligand family **L56**-**L61**.

Chapter 3

ASYMMETRIC HYDROGENATION REACTIONS



UNIVERSITAT ROVIRA I VIRGILI
SUSTAINABLE AND COST-EFFECTIVE DEVELOPMENT OF CHIRAL METAL-CATALYSTS FOR C-H AND C-X BOND FORMING REACTIONS
Carlota Borràs Noguera

3.1. Ir-catalyzed asymmetric hydrogenation with simple cyclohexane-based P/S ligands: In situ HP-NMR and DFT calculations for the characterization of reaction intermediates.

Carlota Borràs, Maria Biosca, Oscar Pàmies and Montserrat Diéguez in *Organometallics* **2015**, *34*, 5321.

Abstract: *We report a reduced but structurally valuable phosphite/phosphinite-thioether ligand library for the Ir-hydrogenation of 40 minimally functionalized alkenes, including relevant examples with poorly coordinative groups. We found that enantiomeric excesses are mainly dependent on the substrate structure and on some ligand parameters (i.e. the type of thioether/phosphorous moieties and the configuration of the phosphite group), whereas the substituents of the biaryl phosphite moiety had little impact. By tuning the ligand parameters we were able to find highly selective catalysts for a range of substrates (ee's up to 99%). These phosphite/phosphinite-thioether ligands have a simple backbone and thus yield simple NMR spectra that reduce signal overlap and facilitate the identification of relevant intermediates. Therefore, by combining HP-NMR spectroscopy and theoretical studies, we were also able to identify the catalytically competent Ir-dihydride alkene species, which made it possible to explain the enantioselectivity obtained.*

3.1.1. Introduction

Over the last four decades, the increasing demand for enantiopure compounds for agrochemicals, pharmaceuticals and materials has stimulated the search for efficient methodologies for their preparation.[1] Because of its high selectivity and perfect atom-economic nature, transition-metal-catalyzed asymmetric hydrogenation is one of the most powerful and versatile approaches for preparing a wide range of enantiopure compounds.[1-2] This field has been dominated by the Rh/Ru-catalyzed asymmetric hydrogenation of substrates with a good coordination group close to the C-C double bond.[1-3] Today, an impressive range of ligands are being applied to transform a wide range of functionalized substrates. In contrast, the asymmetric hydrogenation of substrates that do not have an adjacent coordinative polar group – minimally functionalized olefins – is much less developed, despite the fact that it constitutes an easy way to create complex compounds from simple olefins.[4] In this respect, Ir-catalyzed asymmetric hydrogenation has emerged as an effective and easy method for reducing minimally functionalized olefins. Since Pfaltz applied Ir/phosphine-oxazoline PHOX chiral catalysts in 1998,[5] some of the most efficient reported chiral ligands have been mixed P-oxazoline ligands. Several successful phosphine/phosphinite/carbene-oxazoline ligands have been prepared by modifying the chiral backbone.[6] Our group has contributed to the Ir-hydrogenation of minimally functionalized olefins with an

improved series of ligands. We have shown that phosphite groups improve the ligand's efficiency. Mixed phosphite-oxazoline ligands have been shown to be exceptionally effective, providing better substrate versatility than earlier Ir-phosphinite/phosphine-oxazoline catalysts.[7] Despite the advances achieved with Ir/P-oxazoline catalysts, the activity and enantioselectivity in the reduction of some relevant minimally functionalized olefins still need to be improved. To this end, research has progressed towards mixed ligands with groups that are more robust than oxazolines (pyridines,[8] amides,[9] thiazoles,[10] oxazoles,[11] etc.). In this context, we recently reported the use of non-N-donor mixed ligands – phosphite/phosphinite-thioether – in the enantioselective Ir-catalyzed reduction of minimally functionalized olefins.[12] The coordination of the thioether moiety to the iridium not only exerts steric and electronic effects by means of the change in the thioether groups, but also creates a new stereogenic center with a substituent that is very close to the iridium atom and therefore strongly shields one of the faces of the coordination sphere. In this context, two families of Ir/P-S catalysts were shown to hydrogenate a large variety of olefins with enantioselectivities comparable to the best ones reported to date.[12b,c] Despite this success, the performance of this new class of ligands must be further studied for this process by screening new readily accessible thioether-containing ligands and studying the species responsible for the catalytic performance under hydrogenation conditions. No experimental studies of the mechanism and the nature of the relevant catalytic intermediates under hydrogenation conditions have yet been carried out. The mechanistic proposals using phosphorus-thioether ligands are based on our previous work using DFT investigation.[12c] Therefore, in this paper we report a reduced but structurally valuable library of phosphite/phosphinite-thioether ligands **L1**-**L2a**-**g**[13] (Figure 3.1.1) for the Ir-hydrogenation of 40 minimally functionalized alkenes, including some specific examples with poorly coordinative groups. We also investigated the key iridium intermediate complexes under hydrogenation conditions to explain the origin of the enantioselectivity. By combining high pressure NMR (HP-NMR) spectroscopy and theoretical studies we were able to identify the catalytically competent Ir-dihydride alkene species.

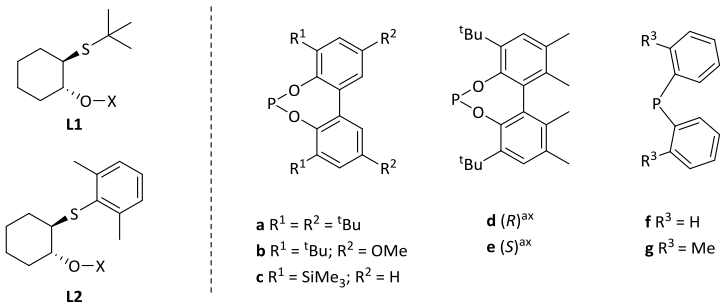


Figure 3.1.1. Phosphite/phosphinite-thioether ligands **L1**-**L2a**-**g**.

Phosphite/phosphinite-thioether ligands **L1**-**L2a**-**g** have been selected for this work because they have the following advantages: (a) they are synthesized in only two steps from commercially accessible cyclohexene oxide; (b) they benefit from the robustness of the thioether group; (c) a simple tuning of the thioether and phosphite/phosphinite moieties (**a**-**g**) provides control over the chiral cavity; and (d) their backbone is simple, thus yielding simple NMR spectra that reduce the overlap signals and facilitate the identification of relevant intermediates by HPNMR. For the purpose of this work, only two thioether substituents, *tert*-butyl and 2,6-dimethylphenyl, were used because previous work with Ir/P-thioether catalysts showed that these bulky substituents made it possible to achieve high enantioselectivities.[12b,c]

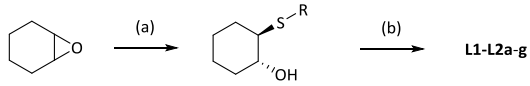
3.1.2. Results and discussion

3.1.2.1. Synthesis of ligands

The synthesis of ligands **L1**-**L2a**-**g** is shown in Scheme 3.1.1. The new ligands **L1**-**L2a**-**e** and **L2f**,**g** are prepared in only two steps from readily available cyclohexene oxide. The first step (Scheme 3.1.1, step a) consists of the enantioselective desymmetrization of cyclohexene oxide with the corresponding thiol using (*R*)-GaLibis(binaphtoxide) complex (GaLB-(*R*)), in keeping with Shibasaki's method.[14] Desymmetrization using *tert*-buthylthiol provided the desired cyclohexanol-thioether **1** in >99% ee.[13a,b] However, desymmetrization using 2,6-dimethylbenzenethiol led to poor enantiocontrol (43% ee). Further enantiomer resolution by using semipreparative chiral HPLC gave access to both enantiomers of the corresponding hydroxyl-thioether (**2** and *ent*-**2**). In the last step of the ligand synthesis process (Scheme 3.1.1 step b), cyclohexanol-thioether intermediates **1**-**2** were functionalized with different phosphite (**a**-**e**) or phosphinite moieties (**f**-**g**). Therefore, treating enantiopure hydroxyl-thioethers **1**-**2** with 1 equiv. of either the appropriate *in situ* formed phosphorochloridite ($ClP(OR)_2$, $(OR)_2$=**a**-**e**) or the required chlorophosphine ($ClPR_2$, R= **f**-**g**) provided the desired phosphite-thioether (**L1**-**L2a**-**e**) and phosphinite-thioether (**L1**-**L2f**-**g**) ligands.

All ligands were isolated in good yields as white solids (phosphite-thioether ligands **L1**-**L2a**-**e**) or colorless oils (phosphinite-thioether ligands **L1**-**L2f**-**g**) after purification on neutral alumina. They were found to be stable in air and resistant to hydrolysis, so they were further manipulated and stored in air. The elemental analyses and mass spectrometry were in agreement with the assigned structures. The ligands were also further characterized by $^{31}P\{^1H\}$, ^1H and $^{13}C\{^1H\}$ NMR spectroscopy. The spectral assignments were based on information from bidimensional ^1H-^1H and ^{13}C-^1H experiments. The $^{31}P\{^1H\}$ NMR spectra showed one singlet for each compound. The expected diastereoisomeric mixtures using tropoisomeric biphenyl phosphite moieties (a-c) were not detected by low-temperature $^{31}P\{^1H\}$ NMR, which is consistent with the fast ring inversions in the biphenylphosphorus moieties on the NMR time-scale.[15] ^1H

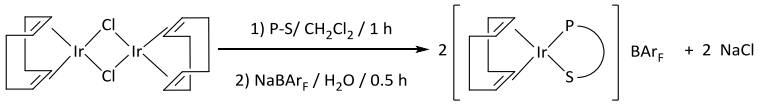
and $^{13}C\{^1H\}$ NMR spectra showed the expected pattern for the cyclohexane backbone and the phosphite/phosphinite moieties. Concerning the protons of the cyclohexane ring, we found the signals of the corresponding diastereomeric methylene protons and the expected two signals for the methine protons. The methine protons adjacent to the sulfur atom appear at a lower chemical shift than the methine protons adjacent to the oxygen atom because the sulfur atom is less electron withdrawing than the oxygen atom. Finally, the ^1H and $^{13}C\{^1H\}$ NMR spectra also showed the expected pattern for the thioether groups.



Scheme 3.1.1. Synthesis of ligands **L1**-**L2a**-**g**. Reaction conditions: (a) GaLB-(*R*), RSH, toluene, molecular sieves 4 Å. For compounds **2** and *ent*-**2** semipreparative chiral HPLC was further needed; (b) $ClP(OR)_2$, Py, toluene or $ClPR_2/NEt_3$/toluene.

3.1.2.2. Synthesis of Ir-catalysts precursors

The reaction of the corresponding phosphite/phosphinite-thioether ligand **L1**-**L2a**-**g** with $[Ir(\mu\text{-}Cl)(cod)]_2$ in dichloromethane for one hour followed by *in situ* chlorine abstraction with $NaBAr_F$ produced the desired cationic catalyst precursors [Ir(cod)(**L1**-**L2a**-**g**)]BAr_F (**3**-**12**; Scheme 3.1.2). These complexes were obtained in excellent yields and in pure form as orange-red solids. They were stable to air, so they were further manipulated and stored in air.



3 P-S = **L1a**
4 P-S = **L1b**
5 P-S = **L1c**
6 P-S = **L1d**
7 P-S = **L1e**
8 P-S = **L1f**
9 P-S = **L2d**
10 P-S = **L2e**
11 P-S = **L2f**
12 P-S = **L2g**

Scheme 3.1.2. Synthesis of [Ir(cod)(**L1**-**L2a**-**g**)]BAr_F (**3**-**12**).

The complexes were characterized by elemental analysis, mass spectrometry and $^{31}P\{^1H\}$, ^1H and $^{13}C\{^1H\}$ NMR spectroscopy. For all complexes, the elemental analysis of C, H and S matched with the expected stoichiometry. The TOF-MS (ESI+) spectra show the highest ions at m/z, which correspond to the loss of the non-coordinated BAr_F anion from the mononuclear species [Ir(cod)(**L1**-**L2a**-**g**)]BAr_F. The $^{31}P\{^1H\}$ NMR spectra exhibited a sharp signal in all cases. However, for complexes **3**-**5**, the ^{31}P VT-NMR spectra (+35 °C to -80 °C) showed that the signals became broader when the temperature was lowered. This behavior has been attributed to the

tropoisomerization of the biphenyl phosphite moieties (**a**-**c**), which led to a mixture of diastereoisomeric species in solution. This is supported by the fact that the $^{31}P\{^{1}H\}$ VT-NMR spectra of related complexes containing ligands with enantiomerically pure biphenyl moieties (**L1**-**L2d**-**e**) showed a single isomer in all cases, which rules out the possibility of the S-coordination being responsible for the diastereoisomeric species in complexes [Ir(cod)(**L1a**-**c**)]BAr_F.

Crystals suitable for X-ray diffraction analysis of the [Ir(**L1a**)(cod)]BAr_F complex were obtained by means of the slow diffusion of diethyl ether in a chloroform solution (Figure 3.1.2). It should be pointed out that only the diastereoisomer containing an *R*-disposition of the biaryl phosphite group crystallized out of the two observed diastereoisomers in solution (see above).

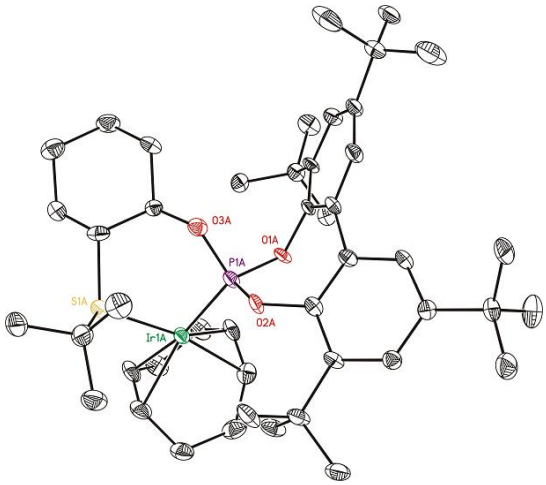


Figure 3.1.2. X-Ray structure of [Ir(**L1a**)(cod)]BAr_F complex **3** (hydrogens and BAr_F anion have been omitted for clarity).

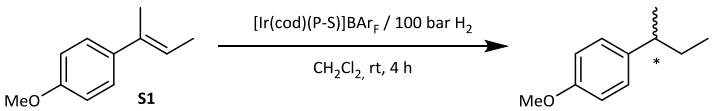
The crystal structure clearly indicates the bidentate coordination of the P,S ligand through both donor atoms with a twist-boat conformation of the chelate ring. As expected, the large variations in the Ir-carbon bond distances *trans* the phosphite and thioether (c.a. 0.1 Å) point to the difference in *trans* influence between the two donor groups. The structure also shows a pseudoaxial disposition of the thioether substituent as previously observed by the analogue rhodium complex ([Rh(cod)(**L1f**)]BF_4).[13c] However, this behavior contrasts with the pseudoequatorial disposition of the thioether substituent in our previous Ir-structures containing arylglycidol-derived phosphite-thioether ligands, which also form a six-membered chelate ring.[12c] For this latter case, Ir/phosphite-thioethers catalysts have always provided much lower enantioselectivities in the reduction of minimally functionalized olefins than related Ir/phosphinite-thioether analogues, in which the thioether substituent adopts a pseudoaxial disposition. This, together with the fact that phosphite-thioether ligand reported in the present paper provided high enantioselectivities in several substrates (see below), could indicate that the disposition of the thioether substituent in the

catalyst precursors has a relevant effect on the stereochemical outcome of the reaction.[16]

3.2.2.3. Asymmetric hydrogenation

Initially we tested the capacity of ligands **L1**-**L2a**-**g** by applying them in the reduction of the trisubstituted substrate **S1** model (Table 3.1.1). Excellent activities were obtained in all cases. However, the value of enantioselectivity depended on the type of thioether/phosphorous moieties and the configuration of the phosphite group, while the substituents of the biaryl phosphite moiety had little impact.

Table 3.1.1. Ir-catalyzed hydrogenation of **S1** using ligand library **L1**-**L2a**-**g.**[a]



Entry	Ligand	% Conv[b]	% ee[b]
1	**L1a**	100	19 (*R*)
2	**L1b**	100	18 (*R*)
3	**L1c**	100	18 (*R*)
4	**L1d**	100	42 (*S*)
5	**L1e**	100	86 (*R*)
6	**L1f**	100	60 (*R*)
7	**L2d**	100	5 (S)
8	**L2e**	100	36 (*R*)
9	**L2f**	100	69 (*R*)
10	**L2g**	100	61 (*R*)
11[c]	**L1e**	100	86 (*R*)
12[d]	**L1e**	81	85 (*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. [c] Reaction carried out using 0.25 mol% of Ir-catalyst precursor. [d] PC as solvent.

The effect on enantioselectivity of replacing the phosphite moiety with a phosphinite group depends on the thioether substituent. Thus, while for ligands **L1**, containing a *tert*-butyl thioether substituent, the addition of a phosphinite led to lower enantioselectivities (Table 3.1.1, entries 5 vs. 6), enantioselectivities increased for ligands **L2** with a 2,6-dimethylphenyl group (Table 3.1.1, entries 8 vs. 9). The results also show that a chiral phosphite moiety is needed for high enantioselectivity (entries 1-3 vs. 4-5). This indicates that, in contrast to previous xylofuranoside-based thioether-phosphite ligands,[12b] the simple cyclohexane-backbone is not able to control the tropoisomerization of the biaryl phosphite groups (**a**-**c**) in the active species, as has been found for [Ir(cod)(**L1a**-**c**)]BAr$_F$ precatalysts (see above). Therefore, it is not surprising that low enantioselectivities were obtained for this substrate with Ir/**L1a**-**c**

catalysts (entries 1-3). We also found a cooperative effect between the configuration of the cyclohexane-backbone and the configuration of the biaryl phosphite group (entries 4, 5, 7 and 8). This led to a matched combination with ligands containing an *S*-biaryl phosphite moiety (**e**; entries 5 and 8). The best enantioselectivity was therefore obtained with ligand **L1e** (ee's up to 86%; entry 5).

We also performed this reaction at a low catalyst loading (0.25 mol%) using Ir/**L1e**, which provided the best result, and enantioselectivity was maintained (Table 3.1.1, entry 11). Advantageously, the use of propylene carbonate (PC) as an environmentally friendly alternative solvent[17] to dichloromethane didn´t affected the stereochemical outcome of the reaction (entry 12).

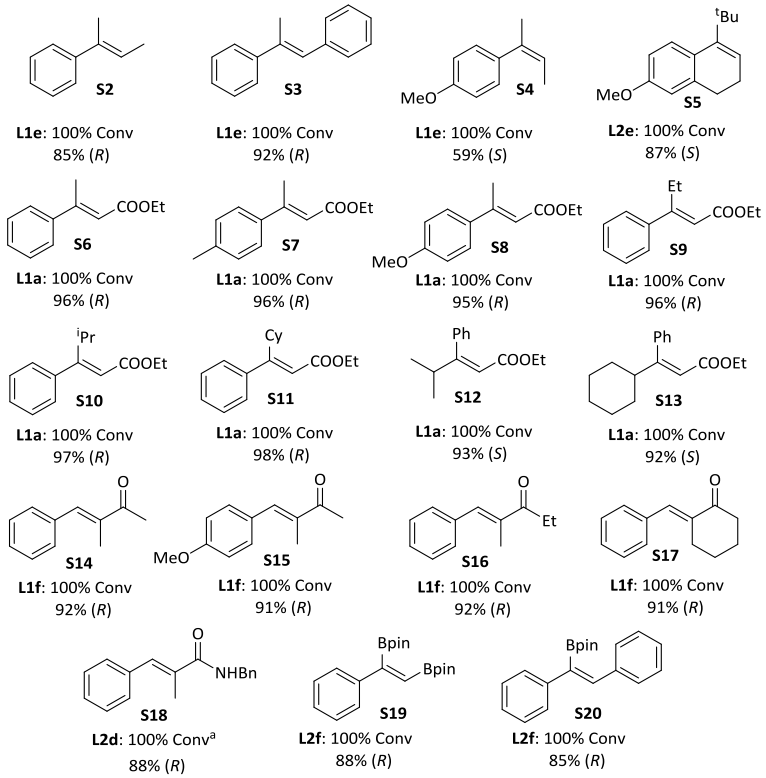


Figure 3.1.3. Asymmetric hydrogenation of trisubstituted substrates **S2**-**S20**. Reaction conditions: 1 mol % catalyst precursor, CH_2Cl_2 as solvent, 100 bar H_2, 4 h. [a] Reaction carried out for 18 h.

To further establish the scope of Ir/**L1**-**L2a**-**g** catalysts, we chose a representative family of substrates, some of which contain neighboring polar groups. The results are summarized in Figure 3.1.3. We found that the ligand parameters must be selected specifically for each substrate with the aim of obtaining the highest enantioselectivity. We initially considered the reduction of substrates **S2**-**S3**, which are related to **S1**. We found that enantioselectivities are relatively unaffected by varying the electronic and steric properties of the substrate (ee's between 85% and 92%). For both substrates the highest enantioselectivities were also obtained with Ir/**L1e** catalyst. The reduction of

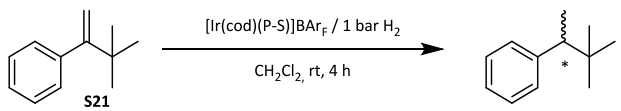
more challenging *Z*-isomers (model **S4** and **S5**), which are hydrogenated much less enantioselectively than *E*-isomers, also proceeded smoothly. We were pleased to see that for the more demanding *Z*-substrate **S5**, enantioselectivity (87% ee) was higher than for the *Z*-**S4** model.

We then went on to study the reduction of a range of key trisubstituted olefins with poorly coordinative groups. Their hydrogenation is of particular importance because they can be further converted into relevant intermediates for synthesizing more complex chiral molecules. Interestingly, the hydrogenation of a very large series of α,β-unsaturated esters **S6**-**S13** proceeded with high enantioselectivities (ee's up to 98%), comparable to the best reported to date.[18] However, unlike previous **S1**-**S4** substrates, the effect of the ligand parameters on enantioselectivity is slightly different. Therefore, regardless of the thioether substituent, the presence of a biaryl phosphite moiety is highly beneficial and the tropoisomerization of the flexible biaryl phosphite moieties (**a**-**c**) is efficiently controlled. The best enantioselectivities were obtained using the Ir/**L1a**-**c** and Ir/**L1e** catalytic systems. Advantageously, the ee's were independent of the electronic nature of the substrate phenyl ring (**S6**-**S8**) and the steric nature of the alkyl substituent (**S6**, **S9**-**S11**). Also noteworthy were the high enantioselectivities obtained using more demanding *Z*-isomers (**S12** and **S13**). Being able to reduce such a range of α,β-unsaturated esters with these high ee's is highly significant because the resulting chiral carboxylic ester derivatives are present in many relevant products. This method is a more sustainable way to prepare these chiral carboxylic esters than other regular methodologies.[19] Another relevant set of substrates that is receiving much consideration are the α,β-unsaturated enones. In the reduction of a range of α,β-unsaturated enones **S14**-**S17**, the highest enantioselectivities (ee's up to 92%) were obtained with Ir-**L1f** catalyst, which contains a diphenylphosphinite moiety with a *tert*-butyl thioether substituent. The reduction of these kinds of olefins is an elegant route for producing ketones with a chiral center in the α position of the carbonyl moiety. Nevertheless, they have been less investigated and hydrogenated with less success than other trisubstituted olefins[6i,6q,r,20]

These last results encouraged us to move on to the hydrogenation of other difficult olefins, such as enamide **S18**[6p,21] and alkenylboronic esters **S19**-**S20**.[7d,12c,22] Few catalysts can afford high enantioselectivities for these alkenes, so it was noteworthy that we could reach high enantioselectivities in all of them by carefully modification of the ligand parameters. In the reduction of enamide **S18**, the highest enantioselectivities (up to 88%) were therefore achieved using [Ir(cod)(**L2d**)]BAr_F, while for alkenylboronic esters the best enantioselectivities (ee's up to 85%) were obtained with [Ir(cod)(**L2f**)]BAr_F. The reduction of enamides and alkenylboronic esters is also of great interest because hydrogenated products can easily been transformed into high-value compounds such us benzylic acid derivatives and chiral boron compounds.

Finally, we focused on the reduction of a more demanding type of substrate: 1,1-disubstituted olefins. Unlike trisubstituted olefins, 1,1-disubstituted olefins have not been successfully hydrogenated until very recently.[4a,e,h] This is because most of the successful catalysts developed for the reduction of trisubstituted substrates fail either to control the face-selective coordination of the less hindered disubstituted substrate or to suppress the isomerization of the olefin that leads to the formation of the more stable *E*-trisubstituted substrates, which in turn form the opposite enantiomer when hydrogenated. With the aim of evaluating the efficiency of ligands **L1**-**L2a**-**g** in hydrogenating this kind of substrate, we first studied the reduction of the model substrate **S21**. The results are shown in Table 3.1.2. We found that the substituents of the biaryl phosphite moiety have little impact on selectivity and that the presence of a chiral phosphite moiety (**d**-**e**) is needed for high enantioselectivity. However, in contrast to trisubstituted olefins, the best enantioselectivity was obtained with the ligand containing an *R*-biaryl phosphite moiety and 2,6-Me_2-C_6H_3 thioether substituent (ligand **L2d**, ee's up to 97%; entry 7). Interestingly, we also found that the configuration of the biaryl phosphite moiety controls the sense of enantioselectivity; therefore, both enantiomers of the reduction product can be obtained in high enantioselectivities under mild reaction conditions (entries 7 and 8).

Table 3.1.2. Ir-catalyzed hydrogenation of **S21** using ligand library **L1**-**L2a**-**g**.[a]



Entry	Ligand	% Conv[b]	% ee[b]
1	**L1a**	100	30 (*S*)
2	**L1b**	100	28 (*S*)
3	**L1c**	100	27 (*S*)
4	**L1d**	100	90 (*S*)
5	**L1e**	100	85 (*R*)
6	**L1f**	100	29 (*S*)
7	**L2d**	100	97 (S)
8	**L2e**	100	90 (R)
9	**L2f**	100	65 (S)
10	**L2g**	100	84 (S)

[a] Reactions carried out using 0.5 mmol of **S21** and 2 mol% of Ir-catalyst precursor.[b] Conversion and enantiomeric excesses determined by chiral GC.

The scope of Ir/**L1**-**L2a**-**g** catalysts was further studied by using other 1,1-disubstituted substrates (Figure 3.1.4, **S22**-**S40**).

Our results with several α-alkylstyrenes with different sterically demanding alkyl groups (**S21**-**S24**) showed that enantioselectivity is influenced by the alkyl substituents (ee's ranging from 34% to 97%). This behavior may be due to a competition between direct hydrogenation and isomerization. In line with this, the hydrogenation of **S21** with a *tert*-butyl group, which cannot isomerize, provided the highest enantioselectivity. However, face selectivity problems cannot be ignored.[4h] To address this issue, we carried out deuterium labeling experiments (Scheme 3.1.3) in which we reduced **S1** and **S24** with deuterium. In contrast to **S1**, the hydrogenation of **S24** led to the addition of deuterium not only at the expected positions (direct incorporation to the double bond), but also at the allylic position, which is in agreement of a competing isomerization pathway.[23] Accordingly, the mass spectra data of the corresponding deuterated product from **S24** showed species with more than two incorporated deuteriums.

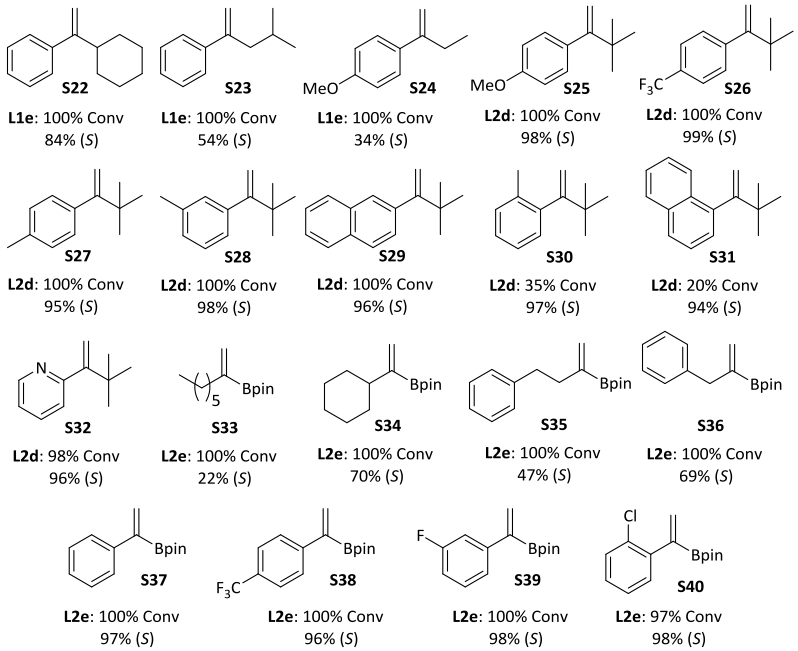
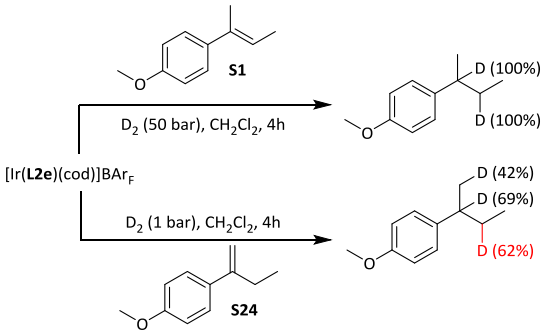


Figure 3.1.4. Asymmetric hydrogenation of 1,1-disubstituted olefins **S22**-**S40**. Reaction conditions: 1 mol % catalyst precursor, CH_2Cl_2 as solvent, 1 bar H_2, 4 h.

We next screened a wide range of α-*tert*-butylstyrene type substrates (**S25**-**S31**) to evaluate how the steric and electronic properties of the aryl group of the substrate affected enantioselectivity. Advantageously, we found that enantioselectivity (ee's up to 99%) is relatively insensitive to changes in the electronic and steric properties of the aryl group. N-containing heterocycles are present in many relevant compounds such us

pharmaceuticals and natural products. We were pleased to see that we could also obtained high enantioselectivities in both enantiomers of the reduction products of 2-(3,3-dimethylbut-1-en-2-yl)pyridine (**S32**).



Scheme 3.1.3. Deuterium labeling experiments with substrates **S1** and **S24**. The percentage of incorporation of deuterium atoms is shown in brackets. The results of the indirect addition of deuterium due to the isomerization process are shown in red.

Finally, due to the importance of chiral borane compounds, we wanted to see if the high enantioselectivities achieved in the reduction of trisubstituted alkenylboronic esters (Figure 3.1.3, substrate **S19**-**S20**) were retained for the even more challenging terminal analogues. The hydrogenation of such compounds using Ir-catalyst has recently emerged as a more sustainable alternative to the existing synthetic routes.[22a,b] However, high levels of enantioselectivity have only been obtained for alkyl-substituted terminal boronic esters such as **S33**-**S36**, and the hydrogenation of aryl-substituted boronic esters such as **S37** has yielded much lower enantioselectivities.[22a,b] Despite the moderate enantioselectivities achieved in the reduction of **S33**-**S36** using our new Ir-**L1**-**L2a**-**g** catalytic systems, we were pleased to find that a range of aryl-substituted terminal boronic esters **S37**-**S40** could be efficiently reduced using the Ir-**L2e** catalytic system. Interestingly, the substitution pattern in the aryl ring did not affect the stereochemical outcome of the reaction. This constitutes an important finding that overcomes the limitations previously encountered in the reduction of terminal aryl-substituted boronic esters and nicely complements the current state of the art.

In summary by efficiently selecting the ligand parameters of this reduced and simple readily available phosphite/phosphinite-thioether ligand family, we could obtain highly selective catalysts for a range of substrates, with enantioselectivities comparable in most cases to the best ones reported.

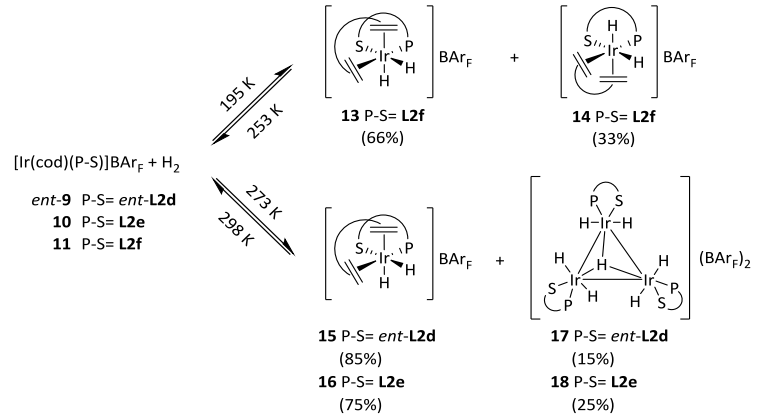
3.2.2.4. Mechanistic studies: study of reaction intermediates by in situ HP-NMR and theoretical studies

Computational and experimental research with P,N- and C,N- ligands showed that the hydrogenation of minimally functionalized olefins proceeds via and Ir^{III}/Ir^{V}

migratory-insertion/reductive-elimination catalytic cycle.[7e,24] Very recently, Pfaltz's group, based on mechanistic studies under hydrogenation conditions, was able to detect the Ir(III) dihydride alkene intermediates responsible for the catalytic performance for the first time.[25] They found that, similarly to the classical Halpern-mechanism for asymmetric hydrogenation with Rh-catalysts, the minor intermediate, which is less stable, is converted to the major product enantiomer.

Similarly, our previous DFT investigations using Ir-P/S ligands also agree with Ir^{III}/Ir^{V} pathway, with migratory insertion of the hydride as an enantioselective-determining step.[12c] However, there is a lack of experimental evidences to support the calculations. On the basis of these previous studies and in an effort to rationalize the enantioselectivity achieved with the Ir-P/thioether catalysts reported in this manuscript, we performed an HP-NMR study of the iridium intermediates formed under hydrogenation conditions, with the aim of identifying the catalytically competent Ir-dihydride alkene species.

For this study, we initially investigated the oxidative addition of hydrogen to the iridium catalyst precursors [Ir(cod)(P-S)]BAr_F (P-S = **L2f,** *ent*-**L2d** and **L2e**; Scheme 3.1.4). As models, we took complexes containing phosphinite-thioether ligand **L2f** and the phosphite-thioether ligands *ent*-**L2d** and **L2e**, respectively. These ligands contain different P-donor groups that can provide insight into their previously observed substantial effect on enantioselectivity (see above).



Scheme 3.1.4. Oxidative addition of H_2 to [Ir(cod)(P-S)]BAr_F complexes **11**, *ent*-**9** and **10**.

Bubbling H_2 in a CD_2Cl_2 solution of [Ir(cod)(**L2f**)]BAr_F (**11**) at -78 ˚C led to the formation of two dihydride species **13** and **14** in a 2:1 ratio (Scheme 4), which are unstable when warming up. The equilibrium shifts back to the starting olefin complex **11** at -20 ˚C. Both isomers of [Ir(H)$_2$(cod)(**L2f**)]BAr_F showed small phosphorus-hydride coupling constants ($^2J_{P\text{-}H} \leq 21.2$ Hz) that indicate that all the hydrides are *cis* to the phosphorus atom (Table 3.1.3).[13c,26]

Table 3.1.3. $^{31}P\{^{1}H\}$ and ^{1}H NMR data at the hydride region of dihydride species $[Ir(H)_2(cod)(L2f)]BAr_F$ (**13** and **14**), $[Ir(H)_2(cod)(ent\text{-}\mathbf{L2d})]BAr_F$ **15** and $[Ir(H)_2(cod)(\mathbf{L2e})]BAr_F$ **16**.

Compound	H^a	H^b	$^{31}P\{^{1}H\}$
$[Ir(H)_2(cod)(\mathbf{L2f})]BAr_F$ (**13**)	-12.2 (d, $^{2}J_{P\text{-}H}$= 18 Hz)	-14.4 (d, $^{2}J_{P\text{-}H}$= 16.8 Hz)	86.2 (s)
$[Ir(H)_2(cod)(\mathbf{L2f})]BAr_F$ (**14**)	-12.3 (d, $^{2}J_{P\text{-}H}$= 21.2 Hz)	-15.9 (d, $^{2}J_{P\text{-}H}$= 16.8 Hz)	87.5 (s)
$[Ir(H)_2(cod)(ent\text{-}\mathbf{L2d})]BAr_F$ (**15**)	-12.4 (d, $^{2}J_{P\text{-}H}$= 22.4 Hz)	-14.7 (s)	73.4 (s)
$[Ir(H)_2(cod)(\mathbf{L2e})]BAr_F$ (**16**)	-12.43 (d, $^{2}J_{P\text{-}H}$= 21.6 Hz)	-14.63 (s)	86.1 (s)

The 3D structure of both isomers of $[Ir(H)_2(cod)(\mathbf{L2f})]BAr_F$ were assigned by DFT and NMR studies. Table 3.1.4 shows the calculated DFT relative energies of the four possible isomers with all the hydrides *cis* to the phosphinite group. These four structures result from the up or down relative position of one of the hydrides and the two possible configurations at the sulfur center (the S atom becomes a stereogenic center upon coordination to the metal).

Table 3.1.4. Calculated energies (in kJ/mol) for dihydride complexes **13**-**16** containing ligands **L2f**, *ent*-**L2d** and **L2e**, respectively.

Intermediate	**L2f**	*ent*-**L2d**	**L2e**
 **A** *S* config on sulfur	0	0	0
 **B** *R* config on sulfur	20	18	29
 **C** *S* config on sulfur	25	27	35
 **D** *R* config on sulfur	12	29	30

The DFT calculations indicate that the most stable isomer **13** corresponds to intermediate **A** in which the hydride *trans* to the olefin (H^a) is pointing down with an *S* configuration at the S atom (Figure 3.1.5a). The minor isomer **14** has been assigned to intermediate **D** with the hydride *trans* to the olefin (H^a) pointing up and an *R* configuration at the S atom (Figure 3.1.5a). The assignments of the major and minor isomers of $[Ir(H)_2(cod)(\mathbf{L2f})]BAr_F$ were further confirmed by NOE experiments. The major isomer **13** therefore showed NOE contacts between the hydride *trans* to the olefin and the methine proton adjacent to the P group, while for the minor isomer **14**

this NOE interaction appeared with the methine proton adjacent to the thioether group (Figure 3.1.5b). The agreement between the NMR elucidation and the DFT calculations of structures of **13** and **14** validates the computational model used. The observed results may be compared with those obtained from the oxidative addition of H_2 to [Ir(cod)(**L1f**)]SbF_6, whose ligand differs from (**11**) by a *tert*-butyl thioether group instead of a 2,6-dimethylphenyl thioether moiety.[13c] The use of Evans and colleagues' ligand leads to a single dihydride species with high thermal stability which has the same structure of the major isomer **13**.

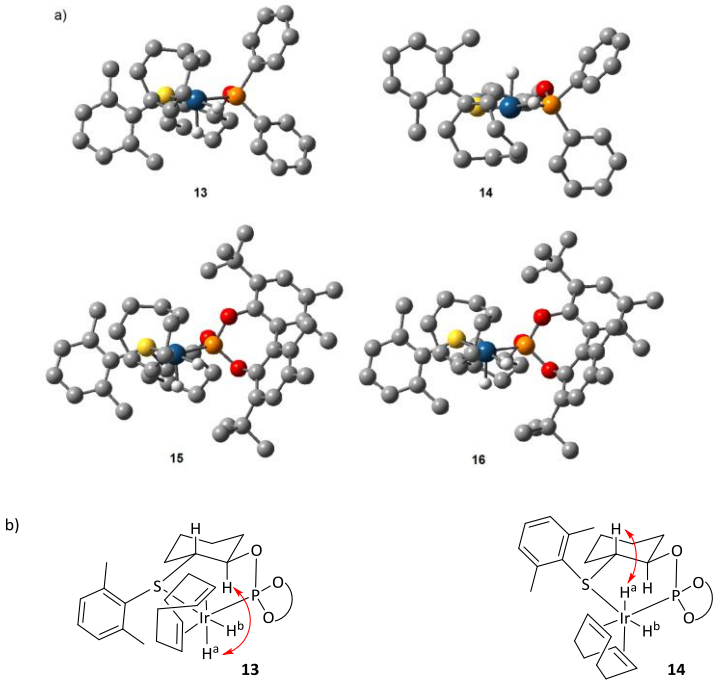
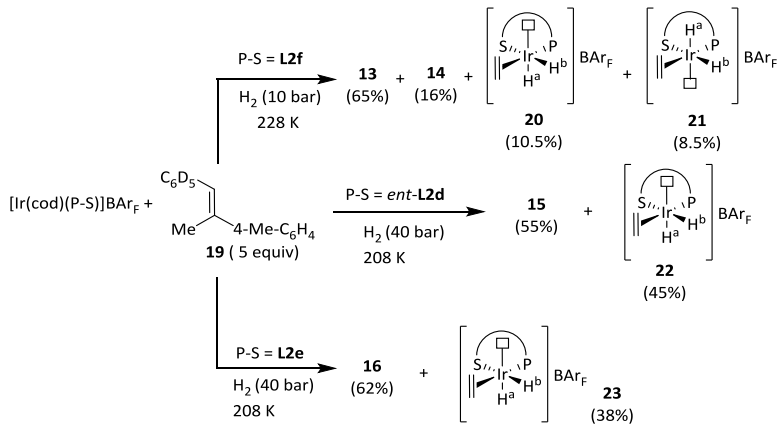


Figure 3.1.5. a) Calculated structures of dihydride [Ir(H)$_2$(cod)(P-S)]BAr_F complexes **13**-**16** (hydrogen atoms and BAr_F anion have been omitted for clarity). b) Relevant NOE contacts from the NOESY experiment of dihydride [Ir(H)$_2$(cod)(P-S)]BAr_F complexes **13** and **14**.

We next studied the oxidative addition of H_2 to [Ir(cod)(P-S)]BAr_F precursors containing phosphite-thioether ligands *ent*-**L2d** and **L2e** (compounds *ent*-**9** and **10**). Only one dihydride intermediate was detected for each and required up to 0 ˚C to push the equilibrium to the expected dihydride species (Scheme 3.1.4). The observed results contrast with [Ir(H)$_2$(cod)(**L2f**)]BAr_F where two dihydride species were observed and required -78 ˚C. Again, the NMR spectra of the dihydride intermediates of each complex indicated that they are *cis* to the phosphorus atom (Table 3.1.3). The final assignments of these dihydride intermediates were performed by DFT studies (Table 3.1.4). As observed for the previous diphosphinite analogue [Ir(H)$_2$(cod)(**L2f**)]BAr_F, dihydride compounds **15** and **16** correspond to intermediate **A** in which the hydride

trans to the olefin (H^a) is pointing down with an *S* configuration at the S atom (Figure 3.1.5a). It should be noted, that at 0 ˚C the cyclooctadiene of the catalyst precursors *ent*-**9** and **10** also hydrogenated, resulting in the concomitant formation of other species, that have been assigned to catalytically inactive trinuclear iridium hydrido species $[Ir_3(\mu_3\text{-}H)(H)_6(P\text{-}S)_3](BAr_F)_2$ **17** and **18** (Scheme 3.1.4).[27] These trinuclear iridium hydrido species **17** and **18** showed the expected pattern of the hydrides. Thus, for instance, for **17** the bridging m_3 hydride signal appeared at -5.62 ppm as quadruplet due to the coupling with the three phosphorus atoms, while the terminal hydride resonances appeared at -13.58 ppm and at -33.72 ppm as a singlet and a broad signal, respectively. The hydride resonances for **18** appeared at -4.48, -14.53 and -36.94 ppm, respectively.

We next investigated the reactivity of iridium precatalysts [Ir(cod)(**L2f**)]BAr_F **11**, [Ir(cod)(*ent*-**L2d**)]BAr_F *ent*-**9** and [Ir(cod)(**L2e**)]BAr_F **10** with H_2 in the presence of an alkene (Scheme 3.1.5). The alkene used was (*E*)-1-methyl-4-(1-phenylprop-1-en-2-yl)benzene-D_5 **19**, in accordance with the methodology recently described by Pfaltz and colleagues.[25]



Scheme 3.1.5. Reactivity of [Ir(cod)(P-S)]BAr_F complexes with olefin **19** under hydrogenation conditions.

Under 10 bar of H_2 at -45 ˚C, the reaction of **11** with five equiv. of **19** led to the formation of four dihydride complexes in a ratio 6:1.5:1:0.8 (Scheme 3.1.5). The two most abundant complexes were unambiguously assigned to the two dihydrides **13** and **14** described above. The minor isomers were assigned to the elusive dihydride intermediate species $[Ir(H)_2(\mathbf{19})(\mathbf{L2f})]BAr_F$ **20** and **21**, in which the alkene is coordinated (Table 3.1.5).

The alkene coordination to iridium in these dihydride intermediate species **20** and **21** was verified by ^{1}H-NMR, which showed a significant low-frequency shift of the olefinic proton of the alkene **19** from 6.82 to *ca* 4.8 ppm. Interestingly, in the ^{1}H-NMR spectra of species **20** and **21** one of the hydrides appeared high-field shifted (between -25.6 and -28.5 ppm). This is characteristic of a hydride ligand positioned *trans* to the

coordination site which is either vacant or engaged in a C-H agostic interaction.[25] As for $[Ir(H)_2(cod)(\mathbf{L2f})]BAr_F$ complexes **13** and **14**, dihydride alkene intermediate species **20** and **21** also show a small phosphorus-hydride coupling constant ($^2J_{P\text{-}H} \leq 27.6$ Hz), which indicates that all the hydrides are *cis* to the phosphorus atom. This behavior is not unexpected because early theoretical calculations on Ir(III) dihydride alkene intermediates showed the alkene coordinated *trans* to the phosphorus donor group.[24]

Table 3.1.5. $^{31}P\{^1H\}$ and ^1H NMR data at the hydride region of dihydride alkene species $[Ir(H)_2(\mathbf{19})(\mathbf{L2f})]BAr_F$ (**20** and **21**), $[Ir(H)_2(\mathbf{19})(\textit{ent}\text{-}\mathbf{L2d})]BAr_F$ **22** and $[Ir(H)_2(\mathbf{19})(\mathbf{L2e})]BAr_F$ **23**.

Compound	H[a]	H[b]	$^{31}P\{^1H\}$
$[Ir(H)_2(\mathbf{19})(\mathbf{L2f})]BAr_F$ (**20**)	-28.52 (d, $^2J_{P\text{-}H}$= 26 Hz)	-16.41 (d,$^2J_{P\text{-}H}$= 17.2 Hz)	75.2 (s)
$[Ir(H)_2(\mathbf{19})(\mathbf{L2f})]BAr_F$ (**21**)	-25.59 (d, $^2J_{P\text{-}H}$= 27.6 Hz)	-16.23 (d, $^2J_{P\text{-}H}$= 15.6 Hz)	84.1 (s)
$[Ir(H)_2(\mathbf{19})(\textit{ent}\text{-}\mathbf{L2d})]BAr_F$ (**22**)	-25.67 (d, $^2J_{P\text{-}H}$= 34.8 z)	-16.19 (s)	76.3 (s)
$[Ir(H)_2(\mathbf{19})(\mathbf{L2e})]BAr_F$ (**23**)	-27.22 (d, $^2J_{P\text{-}H}$= 32.1Hz)	-16.74 (d, $^2J_{P\text{-}H}$= 7.2 Hz)	77.4 (s)

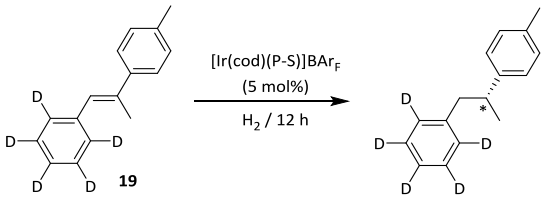
On the other hand, the reaction of iridium precatalysts $[Ir(cod)(\textit{ent}\text{-}\mathbf{L2d})]BAr_F$ and $[Ir(cod)(\mathbf{L2e})]BAr_F$ with five equiv. of **19** under optimized reaction conditions (40 bar of H_2 at -65 ˚C) led to the formation for each complex of two hydride species at a ratio of 1.2:1 and 1.6:1, respectively (Scheme 3.1.5). In both cases, the major isomers were assigned to the corresponding dihydride complexes $[Ir(H)_2(cod)(P\text{-}S)]BAr_F$ **15** and **16**, whereas the minor isomers were attributed to $[Ir(H)_2(\mathbf{19})(P\text{-}S)]BAr_F$ intermediate species (**22** and **23**) in which the alkene is coordinated (Table 3.1.5).

The assignments of the 3D structure of both isomers of $[Ir(H)_2(\mathbf{19})(\mathbf{L2f})]BAr_F$ **20** and **21** and of the isomer of each complex of $[Ir(H)_2(\mathbf{19})(\textit{ent}\text{-}\mathbf{L2d})]BAr_F$ **22** and $[Ir(H)_2(\mathbf{19})(\mathbf{L2e})]BAr_F$ **23** were performed by DFT studies. Unfortunately, due to signal overlap in the ^1H NMR, these studies could not be validated by NOE experiments. The DFT relative energies of the sixteen possible isomers with all the hydrides *cis* to the phosphinite/phosphite group are shown in Table 3.1.6. These isomers result from varying the relative position of one of the hydrides, the coordination of two enantiotopic olefin faces, the two possible configurations at the sulfur center and the relative position of the vacant site (up or down). The results indicate that the observed major (**20**) and minor (**21**) isomers of the olefinic dihydride intermediates $[Ir(H)_2(\mathbf{19})(\mathbf{L2f})]BAr_F$ adopt structures **K** and **A**, respectively, while intermediates **22** adopts an **L** structure and intermediate **23** adopts an **K** structure.

Table 3.1.6. Calculated energies (in kJ/mol) for dihydride olefin complexes **20**-**23** containing ligands **L2f**, *ent*-**L2d** and **L2e**, respectively.

Intermediate	**L2f**	*ent*-**L2d**	**L2e**	Intermediate	**L2f**	*ent*-**L2d**	**L2e**
 **A** *R* config on sulfur	0.9	13.2	2.2	 **I** *R* config on sulfur	16.1	20.8	13.0
 **B** *S* config on sulfur	16.2	21.7	20.3	 **J** *S* config on sulfur	15.4	19.3	21.4
 **C** *R* config on sulfur	48.3	11.8	12.0	 **K** *R* config on sulfur	0	12.9	0
 **D** *S* config on sulfur	26.5	6.7	24.1	 **L** *S* config on sulfur	5.7	0	7.3
 **E** *R* config on sulfur	-	44.4	32.0	 **M** *R* config on sulfur	-	33.3	25.8
 **F** *S* config on sulfur	35.4	33.5	49.2	 **N** *S* config on sulfur	17.8	19.7	22.6
 **G** *R* config on sulfur	18.3	29.9	30.1	 **O** *R* config on sulfur	18.9	31.1	31.1
 **H** *S* config on sulfur	36.1	36.9	47.3	 **P** *S* config on sulfur	32.8	32.5	37.1

With these mechanistic results in hand, we next screened precatalysts [Ir(cod)(**L2f**)]BAr_F **11**, [Ir(cod)(*ent*-**L2d**)]BAr_F *ent*-**9** and [Ir(cod)(**L2e**)]BAr_F **10** with substrate **19** under the conditions used for the HP-NMR analysis. The results are shown in Scheme 3.1.6. For precatalyst [Ir(cod)(**L2f**)]BAr_F **11** the configuration of the product obtained from hydrogenation is *R* (Scheme 3.1.6), which requires coordination of the substrate as determined for the minor isomer **21**. This result therefore indicates that the hydrogenation of substrate **19** with the Ir/**L2f** catalytic system follows the Halpern-type mechanism in which the less stable isomer **21** reacts faster than the major intermediate **20**, and it is converted into the major product enantiomer. The same behavior is obtained using precatalysts [Ir(cod)(*ent*-**L2d**)]BAr_F *ent*-**9** and [Ir(cod)(**L2e**)]BAr_F **10**. Thus, the configuration of the hydrogenated products are *R*, while the expected from the detected isomers of **22** and **23** is *S*.



P-S	p_{H2} (bar)	T (K)	%ee
L2f	10	228	65 (*R*)
ent-**L2d**	40	208	8 (*R*)
L2e	40	208	34 (*R*)

Scheme 3.1.6. Asymmetric hydrogenation of **19** using precatalysts [Ir(cod)(**L2f**)]BAr$_F$ **11,** [Ir(cod)(*ent*-**L2d**)]BAr$_F$ *ent*-**9** and [Ir(cod)(**L2e**)]BAr$_F$ **10** under HP-NMR conditions.

From this we can conclude that in order to obtain the highest enantioselectivity the amount of the minor faster reacting isomer has to be enhanced and/or the energy difference, and therefore the reaction rates, between both TS resulting from the major and minor isomers observed has to be increased. Accordingly, the lowest enantioselectivities obtained with precatalysts [Ir(cod)(*ent*-**L2d**)]BAr$_F$ *ent*-**9** and [Ir(cod)(**L2e**)]BAr$_F$ **10** in comparison with [Ir(cod)(**L2f**)]BAr$_F$ **11** can been explained by the lower population of the faster reacting olefinic dihydride isomer.

3.1.3. Conclusions

We report a reduced but structurally valuable phosphite/phosphinite-thioether ligand library for the Ir-hydrogenation of 40 minimally functionalized alkenes, including some relevant examples with poorly coordinative groups. These phosphite/phosphinite-thioether ligands are synthesized in only two steps from commercially accessible cyclohexene oxide. They also benefit from the robustness of the thioether group and the additional control of the chiral cavity by tuning the thioether and phosphite/phosphinite moieties. With a simple tuning of these ligand parameters we developed highly selective catalysts for a range of substrates with enantioselectivities up to 99%, including a variety of olefins that have recently caught attention because their hydrogenated compounds can lead to high-value chemicals. Moreover, these catalysts extend the state-of-the-art with the successful reduction, for the first time, of terminal aryl-substituted boronic esters. It is also remarkable that these thioether-phosphite/phosphinite ligands have a simple backbone and thus their NMR spectra are simple, with reduced signal overlap, which facilitates the identification of relevant intermediates. Therefore, by combining HP-NMR spectroscopy and theoretical studies, we were able to identify the catalytically competent Ir-dihydride alkene species, which made it possible to explain the enantioselectivity obtained. We found that, similarly to the classical Halpern-mechanism for asymmetric hydrogenation with Rh-catalysts, the minor intermediate, which is less stable, is converted to the major product enantiomer.

3.1.4. Experimental Part

3.1.4.1. General remarks

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 or H_3PO_4 (^{31}P) as an external standard. ^{1}H and ^{13}C assignments were made on the basis of ^{1}H-^{1}H gCOSY, ^{1}H-^{13}C gHSQC and NOESY experiments. The GaLB-(*R*) solution was prepared in accordance with a method published in the literature.[14] Phosphorochloridites were easily prepared in one step from the corresponding biphenols.[28] Enantiopure hydroxyl-thioether compound **1**[13b] thioether-phosphinite ligand **L1f**[13b] and (*E*)-1-methyl-4-(1-phenylprop-1-en-2-yl)benzene-D5 **19**[25] were prepared as previously described.

3.1.4.2. Computational details

The geometries of all intermediates were optimized using the Gaussian 09 program,[29] employing the B3LYP[30] density functional and the LANL2DZ[31] basis set for iridium and the 6-31G* basis set for all other elements.[32] Solvation correction was applied in the course of the optimizations using the PCM model with the default parameters for dichloromethane.[33] The complexes were treated with charge +1 and in the single state. No symmetry constraints were applied. The energies were further refined by performing single point calculations using the above mentioned parameters, with the exception that the 6-311+G**[34] basis set was used for all elements except iridium, and by applying dispersion correction using DFT-D3[35] model. All energies reported are Gibbs free energies at 298.15 K and calculated as $G_{reported} = G_{6\text{-}31G^*} + (E_{6\text{-}311+G^{**}} - E_{6\text{-}31G^*}) + E_{DFT\text{-}D3}$.

3.1.4.3. General procedure for the preparation of the thioether-phosphite ligands L1-L2a-e

The corresponding phosphorochloridite (1.1 mmol) produced *in situ* was dissolved in toluene (5 mL) and pyridine (3.8 mmol, 0.3 mL) was added. The corresponding hydroxyl-thioether (1 mmol) was azeotropically dried with toluene (3x1 mL) and dissolved in toluene (5 mL) to which pyridine (3.8 mmol, 0.3 mL) was added. The solution was transferred slowly at 0 ˚C to the phosphorochloridite solution. The reaction mixture was stirred overnight at 80 ˚C, and the pyridine salts were removed by filtration. The evaporation of the solvent yielded a white foam, which was purified by flash chromatography in alumina (eluent: toluene/triethylamine – 100:1) to produce the corresponding ligand as a white solid.

L1a: Yield: 423 mg (67%). ^{31}P NMR (C_6D_6), δ: 146.3. ^{1}H NMR (C_6D_6), δ: 1.23 (b, 2H, CH_2), 1.26 (s, 9H, CH_3, S^tBu), 1.34 (s, 9H, CH_3, ^tBu), 1.38 (s, 9H, CH_3, ^tBu), 1.55 (m, 1H,

CH_2), 1.69 (m, 3H, CH_2), 1.72 (s, 18H, CH_3, ^tBu), 1.84 (m, 2H, CH_2), 2.38 (m, 1H, CH_2), 3.19 (b, 1H, CH-S), 4.75 (b, 1H, CH-O), 7.42 (m, 2H, CH=), 7.69 (m, 2H, CH=).^{13}C NMR (C_6D_6), δ: 20.2 (CH_2), 22.1 (CH_2), 29.2 (b, CH_2), 29.8 (b, CH_2), 30.9 (CH_3, S^tBu), 31.1 (CH_3, ^tBu), 31.2 (CH_3, ^tBu), 31.3 (CH_3, ^tBu), 34.2 (C, ^tBu), 34.3 (C, ^tBu), 35.3 (C, ^tBu), 35.4 (C, ^tBu), 43.0 (CH-S), 44.2 (C, S^tBu), 76.7 (b, CH-O, $^2J_{C\text{-}P}$=7.7Hz), 123.9-146.2 (aromatic carbons). Anal. calcd. (%) for $C_{38}H_{59}O_3PS$: C 72.80, H 9.49, S 5.11; found: C 72.71, H 9.44, S 5.06. MS HR-ESI [found 649.3811, $C_{38}H_{59}O_3PS$ $(M\text{-}Na)^+$ requires 649.3815].

L1b: Yield: 410 mg (71%). ^{31}P NMR (C_6D_6), δ: 146.0. ^{1}H NMR (C_6D_6), δ: 1.22 (s, 9H, CH_3, S^tBu), 1.32 (b, 2H, CH_2), 1.55 (s, 9H, CH_3, ^tBu), 1.56 (s, 9H, CH_3, ^tBu), 1.63 (b, 3H, CH_2), 1.83 (m, 1H, CH_2), 1.94 (m, 1H, CH_2), 2.31 (m, 1H, CH_2), 3.14 (b, 1H, CH-S), 3.31 (s, 3H, CH_3-O), 3.34 (s, 3H, CH_3-O), 4.73 (b, 1H, CH-O), 6.65-7.18 (4H, CH=). ^{13}C NMR (C_6D_6), δ: 20.1 (CH_2), 21.9 (CH_2), 29.4 (b, CH_2), 29.6 (b, CH_2), 30.8 (CH_3, ^tBu), 30.9 (CH_3, ^tBu), 35.1 (C, ^tBu), 35.3 (C, ^tBu), 43.0 (CH-S), 44.0 (C, S^tBu), 54.6 (CH_3-O), 54.7 (CH_3-O), 76.6 (d, CH-O, $^2J_{C\text{-}P}$=8.6Hz), 113.0-155.9 (aromatic carbons). Anal. calcd. (%) for $C_{32}H_{47}O_5PS$: C 66.87, H 8.24, S 5.58; found: C 66.85, H 8.22, S 5.55. MS HR-ESI [found 597.2768, $C_{32}H_{47}O_5PS$ $(M\text{-}Na)^+$ requires 597.2774].

L1c: Yield: 343 mg (63%). ^{31}P NMR (C_6D_6), δ: 142.3. ^{1}H NMR (C_6D_6), δ: 0.44 (s, 9H, CH_3Si), 0.47 (s, 9H, CH_3Si), 1.13 (s, 9H, CH_3,S ^tBu), 1.25 (m, 2H, CH_2), 1.48-1.72 (b, 5H, CH_2), 2.21 (m, 1H, CH_2), 2.97 (m, 1H, CH-S), 4.52 (m, 1H, CH-O), 7.03-7.42 (6H, CH=). ^{13}C NMR (C_6D_6), δ: 0.0 (CH_3Si), 0.1 (CH_3Si), 20.8 (CH_2), 22.5 (CH_2), 29.7 (b, CH_2), 30.4 (b, CH_2), 31.0 (CH_3,^tBu), 43.0 (CH-S), 44.5 (C, S^tBu), 76.9 (d, CH-O, $^2J_{C\text{-}P}$=3.1Hz), 124.5-155.2 (aromatic carbons). Anal. calcd. (%) for $C_{28}H_{43}O_3PSSi_2$: C 61.50, H 7.93, S 5.86; found: C 61.47, H 7.92, S 5.83. MS HR-ESI [found 569.2098, $C_{28}H_{43}O_3PSSi_2$ $(M\text{-}Na)^+$ requires 569.2101].

L1d: Yield: 399 mg (69%). ^{31}P NMR (C_6D_6), δ: 143.7. ^{1}H NMR (C_6D_6), δ: 1.21 (s, 9H, CH_3,S^tBu), 1.30 (b, 2H, CH_2), 1.60 (s, 9H, CH_3, ^tBu), 1.62 (b, 3H, CH_2), 1.66 (s, 9H, CH_3, ^tBu), 1.70 (s, 3H, CH_3), 1.72 (s, 3H, CH_3), 1.93 (b, 2H, CH_2), 2.04 (s, 3H, CH_3), 2.07 (s, 3H, CH_3), 2.32 (m, 1H, CH_2), 3.05 (b, CH-S), 4.76 (m, 1H, CH-O), 7.24 (s, 1H, CH=), 7.25 (s, 1H, CH=).^{13}C NMR (C_6D_6), δ: 16.2 (CH_3), 16.4 (CH_3), 19.5 (CH_2), 19.9 (CH_3), 20.0 (CH_3), 21.2 (CH_2), 27.8 (b, CH_2), 28.2 (b, CH_2), 30.8 (CH_3, S^tBu), 31.2 (d, CH_3, ^tBu, $J_{C\text{-}P}$= 5.5Hz), 31.6 (CH_3, ^tBu), 34.5 (C, ^tBu), 34.7 (C, ^tBu), 43.0 (CH-S), 43.9 (C, S^tBu), 76.1 (d, CH-O, $^2J_{C\text{-}P}$=14.7 Hz), 125.2-145.8 (aromatic carbons). Anal. calcd. (%) for $C_{34}H_{51}O_3PS$: C 71.54, H 9.01, S 5.62; found: C 71.52, H 8.99, S 5.58. MS HR-ESI [found 593.3187, $C_{34}H_{51}O_3PS$ $(M\text{-}Na)^+$ requires 593.3189].

L1e: Yield: 404 mg (70%). ^{31}P NMR (C_6D_6), δ: 133.6. ^{1}H NMR (C_6D_6), δ: 1.19 (s, 9H, CH_3, S^tBu), 1.26 (b, 1H, CH_2), 1.56 (b, 1H, CH_2) 1.60 (s, 9H, CH_3, ^tBu), 1.61 (s, 9H, CH_3, ^tBu), 1.60-1.75 (b, 5H, CH_2), 1.69 (s, 3H, CH_3), 1.77 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 2.09 (s, 3H, CH_3), 2.27 (m, 1H, CH_2), 3.19 (m, 1H, CH-S), 4.48 (m, 1H, CH-O), 7.22 (s, 1H, CH=), 7.24 (s, 1H, CH=). ^{13}C NMR (C_6D_6), δ: 16.8 (CH_3), 17.2 (CH_3), 20.6 (CH_3), 20.7 (CH_3), 20.8 (CH_2), 22.6 (CH_2), 29.8 (CH_2), 30.3 (CH_2), 31.6 (CH_3, S^tBu), 31.9 (d, CH_3, ^tBu, $J_{C\text{-}P}$=5.6Hz), 32.1 (CH_3, ^tBu), 35.2 (C, ^tBu), 35.4 (C, ^tBu), 43.6 (CH-S), 44.5 (C, S^tBu), 77.6 (d, CH-O, $^2J_{C\text{-}}$

$_P$=2.1Hz), 128-146.7 (aromatic carbons). Anal. calcd. (%) for $C_{34}H_{51}O_3PS$: C 71.54, H 9.01, S 5.62; found: C 71.50, H 9.02, S 5.59. MS HR-ESI [found 593.3183, $C_{34}H_{51}O_3PS$ $(M\text{-}Na)^+$ requires 593.3189].

L2d: Yield: 392 mg (63%). ^{31}P NMR (C_6D_6), δ: 141.7. ^1H NMR (C_6D_6), δ: 1.19 (m, 1H, CH_2), 1.26 (m, 1H, CH_2), 1.49 (s, 9H, CH_3, ^{t}Bu), 1.56 (s, 9H, CH_3, ^{t}Bu), 1.57 (b, 3H, CH_2), 1.68 (s, 6H, CH_3), 1.89 (m, 1H, CH_2), 2.01 (b, 1H, CH_2), 2.03 (s, 3H, CH_3-Ph), 2.05 (s, 3H, CH_3-Ph), 2.19 (m, 1H, CH_2), 2.45 (s, 6H, CH_3), 3.20 (m, 1H, CH-S), 4.60 (m, 1H, CH-O), 6.93-7.20 (m, 5H, CH=).^{13}C NMR (C_6D_6), δ: 16.9 (CH_3), 17.1 (CH_3), 20.7 (CH_3), 21.2 (CH_2), 22.2 (CH_2), 22.9 (CH_3-Ph), 27.7 (b, CH_2), 29.3 (b, CH_2), 31.7 (d, CH_3, ^{t}Bu, $J_{C\text{-}P}$=5.3Hz), 32.6 (CH_3, ^{t}Bu), 35.0 (C, ^{t}Bu), 35.3 (C, ^{t}Bu), 52.2 (CH-S), 76.2 (d, CH-O, $^2J_{C\text{-}P}$= 15.3 Hz), 126.0-146.4 (aromatic carbons). Anal. calcd. (%) for $C_{38}H_{51}O_3PS$: C 73.75, H 8.32, S 5.18; found: C 73.72, H 8.31, S 5.16. MS HR-ESI [found 641.3186, $C_{38}H_{51}O_3PS$ $(M\text{-}Na)^+$ requires 641.3189].

L2e: Yield: 344 mg (56%). ^{31}P NMR (C_6D_6), δ: 137.0. ^1H NMR (C_6D_6), δ: 1.31 (m, 1H, CH_2), 1.42 (m, 1H, CH_2), 1.75 (m, 1H, CH_2), 1.81 (s, 9H, CH_3, ^{t}Bu), 1.83 (s, 9H, CH_3, ^{t}Bu), 1.84 (b, 3H, CH_2), 1.94 (s, 3H, CH_3), 2.01 (s, 3H, CH_3), 2.18 (m, 2H, CH_2), 2.29 (s, 3H, CH_3), 2.33 (s, 3H, CH_3), 2.75 (s, 6H, CH_3-Ph), 3.51 (m, 1H, CH-S), 4.79 (m, 1H, CH-O), 7.17-7.50 (m, 5H, CH=). ^{13}C NMR (C_6D_6), δ: 16.2 (CH_3), 16.5 (CH_3), 20.0 (CH_3), 21.0 (CH_2), 21.2 (CH_2), 22.3 (CH_3-Ph), 28.3 (b, CH_2), 30.2 (b, CH_2), 31.2 (d, CH_3, ^{t}Bu, $J_{C\text{-}P}$=5.4Hz), 31.5 (CH_3, ^{t}Bu), 34.5 (C, ^{t}Bu), 34.7 (C, ^{t}Bu), 51.4 (CH-S), 75.2 (d, CH-O, $^2J_{C\text{-}P}$=1.8 Hz), 125.3-143.2 (aromatic carbons). Anal. calcd. (%) for $C_{38}H_{51}O_3PS$: C 73.75, H 8.32, S 5.18; found: C 73.72, H 8.30, S 5.15. MS HR-ESI [found 641.3184, $C_{38}H_{51}O_3PS$ $(M\text{-}Na)^+$ requires 641.3189].

3.1.4.4. General procedure for the preparation of the thioether-phosphinite ligands L2f-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 a colorless oil.

L2f: Yield: 307 mg (73%). ^{31}P NMR (C_6D_6), δ: 108.8. ^1H NMR (C_6D_6), δ: 0.85 (m, 1H, CH_2), 1.01 (m, 1H, CH_2), 1.32 (m, 2H, CH_2), 1.44 (m, 2H, CH_2), 1.71 (m, 1H, CH_2), 2.02 (m, 1H, CH_2), 2.46 (s, 6H, CH_3-Ph), 3.17 (m, 1H, CH-S), 4.03 (m, 1H, CH-O), 6.9-7.7 (m, 13H, CH=). ^{13}C NMR (C_6D_6), δ: 22.2 (CH_3-Ph), 22.8 (b, CH_2), 23.7 (b, CH_2), 30.2 (b, CH_2), 32.5 (b, CH_2), 52.0 (CH-S), 81.1 (d, CH-O, $^2J_{C\text{-}P}$=21.4 Hz), 127.3-143.8 (aromatic carbons). Anal. calcd. (%) for $C_{26}H_{29}OPS$: C 74.26, H 6.95, S 7.62; found: C 74.33, H 6.96, S 7.59. MS HR-ESI [found 443.1563, $C_{26}H_{29}OPS$ $(M\text{-}Na)^+$ requires 443.1569].

L2g: Yield: 363 mg (81%). ^{31}P NMR (C_6D_6), δ: 95.2. ^1H NMR (C_6D_6), δ: 0.95 (m, 1H, CH_2), 1.09 (m, 1H, CH_2), 1.37 (m, 2H, CH_2), 1.49 (m, 2H, CH_2), 1.76 (m, 1H, CH_2), 2.05

(m, 1H, CH_2), 2.28 (s, 3H, CH_3-Ph), 2.38 (s, 3H, CH_3-Ph), 2.42 (s, 6H, CH_3-Ph), 3.09 (m, 1H, CH-S), 4.00 (m, 1H, CH-O), 6.8-7.8 (m, 11H, CH=). ^{13}C NMR (C_6D_6), δ: 20.2 (CH_3-Ph), 20.5 (CH_3-Ph), 22.1 (CH_3-Ph), 22.5 (b, CH_2), 23.3 (b, CH_2), 29.7 (b, CH_2), 31.6 (b, CH_2), 52.0 (CH-S), 80.1 (d, CH-O, $^2J_{C\text{-}P}$=16.2 Hz), 125.7-143.3 (aromatic carbons). Anal. calcd. (%) for $C_{28}H_{33}OPS$: C 74.97, H 7.41, S 7.15; found: C 75.08, H 7.42, S 7.10. MS HR-ESI [found 471.1878, $C_{28}H_{33}OPS$ (M-Na)$^+$ requires 471.1882].

3.1.4.5. General procedure for the preparation of [Ir(cod)(P-S)]BAr_F (P-S=L1-L2a-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, $NaBAr_F$ (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 silica and the solvent was evaporated, resulting in the product as a red-orange solid.

[Ir(cod)(L1a)]BAr_F (3): Yield: 123 mg (93). ^{31}P NMR (C_6D_6), δ: 99.9. ^{1}H NMR (C_6D_6), δ: 1.33 (s, 9H, CH_3, ^{t}Bu), 1.36 (s, 9H, CH_3, ^{t}Bu), 1.49 (s, 9H, CH_3, ^{t}Bu), 1.52 (s, 9H, CH_3, ^{t}Bu), 1.61 (s, 9H, CH_3, S^{t}Bu), 1.76 (b, 2H, CH_2), 1.82 (b, 2H, CH_2), 1.95 (m, 2H, CH_2), 2.01 (m, 2H, CH_2, cod), 2.14 (m, 2H, CH_2), 2.21 (m, 2H, CH_2, cod), 2.30 (m, 2H, CH_2, cod), 2.38 (m, 2H, CH_2, cod), 2.72 (m, 1H, CH-S), 4.21 (m, 1H, CH-O), 4.61 (b, 1H, CH=, cod), 4.88 (m, 2H, CH=, cod), 5.76 (b, 1H, CH=, cod), 6.97-7.76 (m, 16H, CH=, Ar). ^{13}C NMR (C_6D_6), δ: 23.9 (CH_2), 25.8 (CH_2), 26.8 (b, CH_2, cod), 29.9 (b, CH_2, cod), 30.3 (b, CH_2, cod), 31.2 (CH_2), 31.3 (CH_3, ^{t}Bu), 31.4 (CH_3, ^{t}Bu), 31.5 (CH_3, ^{t}Bu), 31.5 (CH_3, ^{t}Bu), 32.0 (CH_3, S^{t}Bu), 33.6 (b, CH_2, cod), 34.9 (b, CH_2, cod), 35.7 (C, ^{t}Bu), 36.0 (C, ^{t}Bu), 47.6 (CH-S), 58.8 (C, S^{t}Bu), 77.4 (CH=, cod), 78.0 (CH-O), 78.0 (b, CH=, cod), 99.4 (d, $J_{C\text{-}P}$= 20.36 Hz, CH=, cod), 110.7 (d, $J_{C\text{-}P}$= 14.01 Hz, CH=, cod), 117.7 (b, CH=, BAr_F), 120.6-131.2 (aromatic carbons), 134.9 (b, CH=, BAr_F), 138.1-149.3 (aromatic carbons), 161.8 (q, $^1J_{C\text{-}B}$ = 49.4 Hz, C-B, BAr_F). Anal. calcd. (%) for $C_{78}H_{83}BF_{24}IrO_3PS$: C 52.32, H 4.67, S 1.79; found: C 52.29, H 4.66, S 1.75. MS HR-ESI [found 927.4487, $C_{46}H_{71}IrO_3PS$ (M-BAr_F)$^+$ requires 927.4491].

[Ir(cod)(L1b)]BAr_F (4): Yield: 116 mg (90%). ^{31}P NMR (C_6D_6), δ: 102.9. ^{1}H NMR (C_6D_6), δ: 1.44 (s, 9H, CH_3, ^{t}Bu), 1.51 (s, 9H, CH_3, ^{t}Bu), 1.59 (s, 9H, CH_3, ^{t}Bu), 1.79 (m, 4H, CH_2), 2.00 (m, 2H, CH_2, cod), 2.11 (m, 2H, CH_2, cod), 2.20 (m, 2H, CH_2), 2.12 (m, 2H, CH_2, cod), 2.29 (m, 2H, CH_2, cod), 2.32 (m, 2H, CH_2), 2.75 (m, 1H, CH-S), 3.80 (s, 3H, CH_3-O), 3.84 (s, 3H, CH_3-O), 4.24 (m, 1H, CH-O), 4.77 (b, 2H, CH=, cod), 4.91 (m, 1H, CH=, cod), 5.73 (b, 1H, CH=, cod), 6.52-7.70 (m, 16H, CH=, Ar). ^{13}C NMR (C_6D_6), δ: 23.8 (CH_2), 25.8 (CH_2) 27.2 (CH_2, cod), 29.9 (CH_2, cod), 30.7 (CH_2), 31.2 (CH_3, ^{t}Bu), 31.8 (CH_3, ^{t}Bu), 31.9 (CH_3, ^{t}Bu), 33.9 (b, CH_2, cod), 34.1 (b, CH_2, cod), 35.2 (CH_2), 35.9 (C, ^{t}Bu), 36.1 (C, ^{t}Bu), 47.7 (CH-S), 55.8 (CH_3-O), 55.9 (CH_3-O), 58.5 (C, S^{t}Bu), 75.8 (CH=, cod), 77.4 (CH-O), 79.5 (CH=, cod), 99.7 (d, $J_{C\text{-}P}$= 19.56 Hz, CH=, cod), 111.0 (d, $J_{C\text{-}P}$=13.30 Hz, CH=, cod), 112.9-115.6 (aromatic carbons), 117.6 (b, CH=, BAr_F), 120.6-131.9 (aromatic

carbons), 135.0 (b, CH=, BAr_F), 140.4-157.3 (aromatic carbons), 161.9 (q, $^1J_{C-B}$ = 49.4 Hz, C-B, BAr_F). Anal. calcd. (%) for $C_{72}H_{71}BF_{24}IrO_5PS$: C 49.75, H 4.12, S 1.84; found: C 49.61, H 4.10, S 1.79. MS HR-ESI [found 875.3447, $C_{40}H_{59}IrO_5PS$ $(M\text{-}BAr_F)^+$ requires 875.3450].

[Ir(cod)(L1c)]BAr_F (5): Yield: 115 mg (91%). ^{31}P NMR (C_6D_6), δ: 99.0. ^{1}H NMR (C_6D_6), δ: 0.44 (s, 18H, CH_3, $SiMe_3$), 1.57 (s, 9H, CH_3, S^tBu), 1.79 (b, 4H, CH_2, CH_3), 1.96 (m, 2H, CH_2, cod), 2.09 (m, 2H, CH_2, cod), 2.20 (m, 4H, CH_2 and CH_2, cod), 2.20 (m, 4H, CH_2 and CH_2, cod), 2.66 (m, 1H, CH-S), 4.14 (m, 1H, CH=, cod), 4.69 (b, 1H, CH=, cod), 4.92 (m, 2H, CH=, cod, CH-O), 5.90 (b, 1h, CH=, cod), 7.23-7.70 (m, 18H, CH=, Ar). ^{13}C NMR (C_6D_6), δ: 0.7 (CH_3, $SiMe_3$), 1.0 (CH_3, $SiMe_3$), 24.1 (CH_2), 25.9 (CH_2), 26.8 (CH_2, cod), 30.3 (CH_2, cod), 31.2 (CH_2), 31.7 (CH_3, S^tBu), 33.4 (d, J_{C-P}= 6.25 Hz, CH_2, cod), 34.7 (d, J_{C-P}= 5.54 Hz, CH_2, cod), 34.9 (CH_2), 47.6 (CH-S), 58.8 (C, S^tBu), 76.9 (CH=, cod), 77.4 (CH-O), 78.5 (CH=, cod), 99.9 (d, J_{C-P}= 20.36 Hz, CH=, cod), 111.6 (d, J_{C-P}= 14.11 Hz, CH=, cod), 117.6 (b, CH=, BAr_F), 120.7-133.1 (aromatic carbons), 134.9 (b, CH=, BAr_F), 135.8-154.1 (aromatic carbons), 161.9 (q, $^1J_{C-B}$ = 49.2 Hz, C-B, BAr_F). Anal. calcd. (%) for $C_{68}H_{67}BF_{24}IrO_3PSSi_2$: C 47.75, H 3.95, S 1.87; found: C 47.68, H 3.92, S 1.84. MS HR-ESI [found 847.2773, $C_{36}H_{55}IrO_3PSSi_2$ $(M\text{-}BAr_F)^+$ requires 847.2777].

[Ir(cod)(L1d)]BAr_F (6): Yield: 119 mg (93%). ^{31}P NMR ($CDCl_3$), δ: 99.8. ^{1}H NMR ($CDCl_3$), δ: 1.38 (b, 2H, CH_2), 1.44 (s, 9H, CH_3, ^{t}Bu), 1.53 (s, 9H, CH_3, ^{t}Bu), 1.56 (m, 2H, CH_2), 1.57 (s, 9H, CH_3, ^{t}Bu), 1.64 (s, 3H, CH_3), 1.75 (b, 6H, CH_2), 1.84 (s, 3H, CH_3), 2.1-2.2 (b, 6H, CH_2), 2.23 (s, 3H, CH_3), 2.25 (s, 3H, CH_3), 2.69 (m, 1H, CH-S), 4.24 (m, 1H, CH=, cod), 4.36 (m, 1H, CH=, cod), 4.91 (m, 2H, CH=, cod and CH-O), 5.59 (m, 1H, CH=, cod), 7.17-7.70 (m, 14H, CH=, Ar). ^{13}C NMR ($CDCl_3$), δ: 16.4 (CH_3-Ph), 16.7 (CH_3-Ph), 20.3 (CH_3-Ph), 20.6 (CH_3-Ph), 23.7 (CH_2), 25.8 (CH_2), 27.8 (b, CH_2), 29.2 (CH_2), 31.2 (CH_3, ^{t}Bu), 31.2 (b, CH_2), 31.7 (CH_3, ^{t}Bu), 31.9 (CH_3, ^{t}Bu), 33.2 (b, CH_2), 34.7 (b, CH_2), 35.2 (C, ^{t}Bu), 35.3 (C, ^{t}Bu), 35.5 (C, ^{t}Bu), 47.7 (CH-S), 57.6 (C, S^tBu), 74.1 (b, CH=, cod), 77.7 (b, CH=, cod), 81.6 (CH-O), 99.2 (d, J_{C-P}= 19.7 Hz, CH=, cod), 110.4 (d, J_{C-P}= 14.0 Hz, CH=, cod), 117.6 (b, CH=, BAr_F), 123.3-134.4 (aromatic carbons), 134.9 (b, CH=, BAr_F), 135.9-143.9 (aromatic carbons), 161.9 (q, $^1J_{C-B}$ = 49.4 Hz, C-B, BAr_F). Anal. calcd. (%) for $C_{74}H_{75}BF_{24}IrO_3PS$: C 51.25, H 4.36, S 1.85; found: C 51.05, H 4.34, S 1.82. MS HR-ESI [found 871.3861, $C_{42}H_{63}IrO_3PS$ $(M\text{-}BAr_F)^+$ requires 871.3865].

[Ir(cod)(L1e)]BAr_F (7): Yield: 118 mg (92%). ^{31}P NMR (C_6D_6), δ: 94.6. ^{1}H NMR ($CDCl_3$), δ: 1.4-1.6 (b, 4H, CH_2), 1.40 (s, 9H, CH_3, ^{t}Bu), 1.56 (s, 9H, CH_3, ^{t}Bu), 1.6-1.9 (m, 6H, CH_2), 1.62 (s, 3H, CH_3), 1.64 (s, 9H, CH_3, ^{t}Bu), 1.85 (s, 3H, CH_3), 2.1-2.4 (b, 6H, CH_2), 2.25 (s, 3H, CH_3), 2.29 (s, 3H, CH_3), 2.81 (m, 1H, CH-S), 4.12 (m, 1H, CH=, cod), 4.55 (m, 1H, CH=, cod), 4.92 (m, 2H, CH=, cod and CH-O), 5.98 (m, 1H, CH=, cod), 7.12-7.70 (m, 14H, CH=, Ar). ^{13}C NMR ($CDCl_3$), δ: 16.7 (CH_3-Ph), 20.2 (CH_3-Ph), 20.7 (CH_3-Ph), 24.4 (CH_2), 25.1 (CH_2), 25.8 (b, CH_2), 30.1 (CH_2), 30.8 (CH_3, ^{t}Bu), 31.6 (b, CH_2), 32.0 (CH_3, ^{t}Bu), 32.2 (CH_3, ^{t}Bu), 33.7 (b, CH_2), 34.2 (b, CH_2), 34.7 (b, CH_2), 35.2 (C, ^{t}Bu), 36.4 (C, ^{t}Bu), 46.8 (CH-S), 57.9 (C, S^tBu), 61.9 (b, CH=, cod), 63.4 (b, CH=, cod), 79.6 (CH-O), 97.6 (d, J_{C-P}= 18.4 Hz, CH=, cod), 110.2 (d, J_{C-P}= 16.1 Hz, CH=, cod), 117.7 (b, CH=, BAr_F), 120.6-134.6 (aromatic carbons), 134.9 (b, CH=, BAr_F), 137.2-144.2 (aromatic carbons), 161.8 (q, $^1J_{C-B}$

= 49.4 Hz, C-B, BAr_F). Anal. calcd. (%) for $C_{74}H_{75}BF_{24}IrO_3PS$: C 51.25, H 4.36, S 1.85; found: C 51.11, H 4.35, S 1.82. MS HR-ESI [found 871.3863, $C_{42}H_{63}IrO_3PS$ $(M\text{-}BAr_F)^+$ requires 871.3865].

[Ir(cod)(L1f)]BAr_F (8): Yield: 103 mg (91%). ^{31}P NMR (C_6D_6), δ: 100.9. ^1H NMR (C_6D_6), δ: 1.24 (s, 9H, CH_3, S^tBu), 1.37 (m, 2H, CH_2), 1.49 (m, 2H, CH_2), 1.79 (m, 2H, CH_2, cod), 1.86 (m, 2H, CH_2), 2.03 (m, 2H, CH_2, cod), 2.17 (m, 2H, CH_2, cod), 2.28 (m, 2H, CH_2, cod), 2.37 (m, 2H, CH_2), 2.76 (m, 1H, CH-S), 3.37 (b, 1H, CH-O), 4.20 (m, 2H, CH=, cod), 4.81 (m, 1H, CH=, cod), 5.48 (b, 1H, CH=, cod), 7.16-7.70 (m, 22H, CH=, Ar). ^{13}C NMR (C_6D_6), δ: 24.3 (CH_2), 25.9 (CH_2), 28.0 (CH_2, cod), 31.3 (CH_3, S^tBu), 31.8 (CH_2), 34.0 (CH_2, cod), 35.0 (CH_2, cod), 35.4 (CH_2), 48.7 (CH-S), 59.4 (C, S^tBu), 74.7 (CH=, cod), 77.4 (CH-O), 83.3 (CH=, cod), 96.1 (d, $J_{C\text{-}P}$= 13.31 Hz, CH=, cod), 104.8 (d, $J_{C\text{-}P}$= 11.79 Hz, CH=, cod), 117.6 (b, CH=, BAr_F), 120.7-134.7 (aromatic carbons), 134.9 (b, CH=, BAr_F), 135.3 (C), 161.9 (q, $^1J_{C\text{-}B}$ = 49.2 Hz, C-B, BAr_F). Anal. calcd. (%) for $C_{62}H_{53}BF_{24}IrOPS$: C 48.48, H 3.48, S 2.09; found: C 48.21, H 3.46, S 2.02. MS HR-ESI [found 673.2239, $C_{30}H_{41}IrOPS$ $(M\text{-}BAr_F)^+$ requires 673.2245].

[Ir(cod)(L2d)]BAr_F (9): Yield: 125 mg (95%). ^{31}P NMR (C_6D_6), δ: 88.7. ^1H NMR (C_6D_6), δ:1.15 (m, 1H, CH_2), 1.27 (b, 1H, CH_2), 1.47 (s, 9H, CH_3, ^{t}Bu), 1.62 (m, 1H, CH_2), 1.64 (s, 9H, CH_3, ^{t}Bu), 1.74 (m, 2H, CH_2), 1.76 (s, 6H, CH_3), 1.84 (m, 3H, CH_2), 1.97 (m, 4H, CH_2 and CH_2, cod), 2.01 (m, 4H, CH_2 and CH_2, cod), 2.26 (s, 3H, CH_3), 2.27 (s, 3H, CH_3), 2.70 (s, 3H, CH_3), 2.72 (s, 3H, CH_3), 3.26 (b, 1H, CH-S), 3.53 (m, 1H, CH=, cod), 4.40 (m, 1H, CH=, cod), 4.54 (m, 2H, CH=, cod), 4.74 (m, 1H, CH-O), 7.20-7.71 (m, 17H, CH=, Ar). ^{13}C NMR (C_6D_6), δ: 16.6 (CH_3), 16.6 (CH_3), 20.3 (CH_3-Ph), 20.3 (CH_3-Ph), 23.6 (CH_3), 23.8 (CH_3), 25.4 (CH_2), 27.6 (b, CH_2, cod), 29.3 (CH_2), 29.7 (CH_2), 31.6 (CH_3, ^{t}Bu), 31.8 (b, CH_2, cod), 32.3 (CH_3, ^{t}Bu), 33.7 (b, CH_2, cod), 34.8 (b, CH_2), 34.9 (C, ^{t}Bu), 35.0 (C, ^{t}Bu), 50.9 (d, $J_{C\text{-}P}$= 5.44 Hz, CH=, cod), 66.9 (CH-S), 76.9 (CH-O), 82.1 (b, CH=, cod), 102.4 (d, $J_{C\text{-}P}$= 15.6 Hz, CH=, cod), 104.0 (d, $J_{C\text{-}P}$= 14.82 Hz, CH=, cod), 117.4 (b, CH=, BAr_F), 120.4-134.1 (aromatic carbons), 134.8 (b, CH=, BAr_F), 135.7-144.9 (aromatic carbons), 161.7 (q, $^1J_{C\text{-}B}$ = 49.0 Hz, C-B, BAr_F). Anal. calcd. (%) for $C_{78}H_{75}BF_{24}IrO_3PS$: C 52.56, H 4.24, S 1.80; found: C 52.34, H 4.22, S 1.77. MS HR-ESI [found 919.3858, $C_{46}H_{63}IrO_3PS$ $(M\text{-}BAr_F)^+$ requires 919.3865].

[Ir(cod)(L2e)]BAr_F (10): Yield: 122 mg (93%). ^{31}P NMR (C_6D_6), δ: 88.8. ^1H NMR (C_6D_6), δ: 1.38 (s, 9H, CH_3, ^{t}Bu), 1.55 (m, 2H, CH_2, cod), 1.57 (s, 9H, CH_3, ^{t}Bu), 1.66 (s, 3H, CH_3), 1.72 (b, 2H, CH_2), 1.75 (s, 3H, CH_3), 1.81 (m, 2H, CH_2, cod), 1.90-2.03 (m, 6H, CH_2), 2.10 (m, 2H, CH_2, cod), 2.17 (s, 3H, CH_3-Ph), 2.20 (s, 3H, CH_3-Ph), 2.25 (m, 2H, CH_2, cod), 2.42 (s, 3H, CH_3), 2.68 (m, 1H, CH-S), 2.88 (s, 3H, CH_3), 3.25 (m, 1H, CH=, cod), 3.81 (m, 1H, CH=, cod), 4.32 (m, 1H, CH=, cod), 4.46 (m, 1H, CH-O), 4.86 (m, 1H, CH=, cod), 7.07-7.64 (m, 17H, CH=, Ar). ^{13}C NMR (C_6D_6), δ: 16.4 (CH_3), 16.6 (CH_3), 20.3 (CH_3-Ph), 20.4 (CH_3-Ph), 22.6 (CH_3), 22.8 (CH_3), 25.4 (CH_2), 26.5 (b, CH_2, cod), 29.7 (CH_2), 29.9 (CH_2), 30.3 (CH_2), 31.4 (b, CH_2, cod), 31.7 (CH_3, ^{t}Bu), 32.8 (CH_3, ^{t}Bu), 34.2 (b, CH_2, cod), 34.6 (b, CH_2, cod), 34.8 (C, ^{t}Bu), 35.3 (C, ^{t}Bu), 52.6 (CH=, cod), 66.2 (CH-S), 76.2 (CH-O), 78.3 (b, CH=, cod), 102.3 (d, $J_{C\text{-}P}$= 14.11 Hz, CH=, cod), 105.3 (d, $J_{C\text{-}P}$= 16.43 Hz, CH=,

cod), 117.5 (b, CH=, BAr_F), 120.4-134.4 (aromatic carbons), 134.8 (b, CH=, BAr_F), 135.4-143.5 (aromatic carbons), 161.5 (q, $^1J_{C-B}$ = 49.2 Hz, C-B, BAr_F). Anal. calcd. (%) for $C_{78}H_{75}BF_{24}IrO_3PS$: C 52.56, H 4.24, S 1.80; found: C 52.38, H 4.23, S 1.79. MS HR-ESI [found 919.3861, $C_{46}H_{63}IrO_3PS$ $(M\text{-}BAr_F)^+$ requires 919.3865].

[Ir(cod)(L2f)]BAr_F (11): Yield: 107 mg (91%). ^{31}P NMR (C_6D_6), δ: 99.0. ^{1}H NMR (C_6D_6), δ: 1.27 (b, 2H, CH_2), 1.56 (m, 2H, CH_2, cod), 1.68 (b, 2H, CH_2), 1.83 (m, 2H, CH_2, cod), 1.91 (m, 2H, CH_2, cod), 2.08 (m, 2H, CH_2, cod), 2.36 (m, 4H, CH_2), 2.63 (s, 3H, CH_3-Ph), 3.05 (s, 3H, CH_3-Ph), 3.12 (b, 1H, CH=, cod), 3.43 (m, 2H, CH-S, CH=, cod), 3.70 (b, 2H, CH-O, CH=, cod) 5.01 (b, 1H, CH=, cod), 7.17-8.03 (m, 25H, CH=, Ar). ^{13}C NMR (C_6D_6), δ: 22.8 (CH_3-Ph), 23.5 (CH_3-Ph), 25.4 (CH_2), 27.5 (b, CH_2, cod), 29.7 (b, CH_2), 30.2 (CH_2), 30.3 (CH_2), 31.2 (b, CH_2, cod), 33.0 (b, CH_2, cod), 35.0 (b, CH_2, cod), 51.3 (CH=, cod), 67.4 (CH-S), 75.9 (CH-O), 77.8 (CH=, cod), 94.1 (d, J_{C-P}= 9.37 Hz, CH=, cod), 98.5 (d, J_{C-P}= 13.20 Hz, CH=, cod), 117.5 (b, CH=, BAr_F), 120.4-133.9 (aromatic carbons), 134.8 (b, CH=, BAr_F), 134.9-143.2 (aromatic carbons), 161.5 (q, $^1J_{C-B}$ = 49.4 Hz, C-B, BAr_F). Anal. calcd. (%) for $C_{66}H_{53}BF_{24}IrOPS$: C 50.04, H 3.37, S 2.02 found: C 49.98, H 3.35, S 1.98. MS HR-ESI [found 721.2240, $C_{34}H_{41}IrOPS$ $(M\text{-}BAr_F)^+$ requires 721.2245].

[Ir(cod)(L2g)]BAr_F (12): Yield: 112 mg (94%). ^{31}P NMR (C_6D_6), δ: 101.6. ^{1}H NMR (C_6D_6), δ: 1.40 (m , 2H, CH_2), 1.50 (m, 2H, CH_2), 1.61 (m, 2H, CH_2), 1.79-2.01 (m, 6H, CH_2 and CH_2, cod), 2.08 (s, 3H, CH_3), 2.17 (m, 4H, CH_2, cod), 2.41 (s, 3H, CH_3), 2.56 (b, 1H, CH=, cod), 2.82 (s, 3H, CH_3-Ph), 2.90 (s, 3H, CH_3-Ph), 3.08 (b, 1H, CH-S), 3.47 (m, 1H, CH=, cod), 3.66 (m, 2H, CH-O, CH=, cod), 4.70 (b, 1H, CH=, cod), 6.62-8.95 (m, 23H, CH=, Ar). ^{13}C NMR (C_6D_6), δ: 21.7 (d, J_{C-P}= 3.0 Hz, CH_3), 22.5 (d, J_{C-P}= 7.0 Hz, CH_3-Ph), 22.7 (d, J_{C-P}= 3.0 Hz, CH_3-Ph), 23.4 (b, CH_3), 25.5 (CH_2), 27.8 (b, CH_2, cod), 29.6 (CH_2), 29.7 (CH_2), 30.3 (CH_2), 31.2 (CH_2, cod), 33.0 (, CH_2, cod), 35.7 (d, J_{C-P}= 7.0 Hz, CH_2, cod), 50.8 (CH=, cod), 68.0 (CH-S), 76.5 (CH-O), 78.8 (b, CH=, cod), 96.9 (d, J_{C-P}= 9.4 Hz, CH=, cod), 98.1 (d, J_{C-P}= 13.3 Hz, CH=, cod), 117.5 (b, CH=, BAr_F), 120.5-133.9 (aromatic carbons), 134.8 (b, CH=, BAr_F), 139.9-143.4 (aromatic carbons), 161.5 (q, $^1J_{C-B}$ = 49.2 Hz, C-B, BAr_F). Anal. calcd. (%) for $C_{68}H_{57}BF_{24}IrOPS$: C 50.66, H 3.56, S 1.99 found: C 50.34, H 3.53, S 1.93. MS HR-ESI [found 749.2553, $C_{36}H_{45}IrOPS$ $(M\text{-}BAr_F)^+$ requires 749.2558].

3.1.4.6. Preparation of (1R, 2R)-2-(2,6-dimethylphenylthio)cyclohexanol (2)

A mixture of a 0.05 M solution of GaLB-(*R*) (2.0 mL, 0.10 mmol) and powdered MS 4 Å (200 mg) was stirred at room temperature for 30 min and then evaporated *in vacuo* to remove THF. Toluene (2.0 mL) and cyclohexene oxide (101 µL, 1.00 mmol) were added to the residue, and then 2,6-dimethylbenzenethiol (160 µL, 1.20 mmol) was added in one portion. The mixture was stirred at room temperature for 9 h, then diluted with diethyl ether (30 mL) and filtered over a celite pad. The filtrate was washed successively with 5% *aq*. citric acid (10 mL), sat. *aq*. $NaHCO_3$ (10 mL), and brine (10 mL), dried over $MgSO_4$ and then evaporated *in vacuo.* The residue was purified by flash chromatography (SiO_2, hexane/acetone (20:1)) to yield the desired thioether-alcohol as a mixture of enantiomers. Further enantiomeric resolution by using

semipreparative chiral HPLC (Daicel CHIRACEL OD, 3% 2-propanol in hexanes, 5 mL·min^{-1}, 23 min (**2**)) gave access to desired enantiomer hydroxyl-thioether **2** as a white solid. Yield: 69 mg (29%). ^{1}H NMR (C_6D_6), δ: 1.16 (m, 1H, CH_2), 1.24 (m, 2H, CH_2), 1.31 (m, 1H, CH_2), 1.63 (m, 1H, CH_2), 1.73 (m, 1H, CH_2), 1.88 (m, 1H, CH_2), 2.12 (m, 1H, CH_2), 2.58 (s, 6H, CH_3-Ph), 2.63 (b, 1H, OH), 2.72 (m, 1H, CH-O), 3.56 (m, 1H, CH-S), 7.13 (b, 3H, CH=). ^{13}C NMR (C_6D_6), δ: 22.6 (CH_3), 24.2 (CH_2), 25.8 (CH_2), 32.5 (CH_2), 34.1 (CH_2), 56.4 (CH-O), 73.9 (CH-S), 128.3 (CH=), 132.0 (C), 143.5 (CH=). Anal. calcd. (%) for $C_{14}H_{20}OS$: C 71.14, H 8.53, S 13.56; found: C 71.07, H 8.56, S 13.48. MS HR-ESI [found 236.1232, $C_{14}H_{20}OS$ requires 236.1235].

3.1.4.7. In situ preparation of [Ir(H)$_2$(cod)(L1-L2a-g)]BAr$_F$

In a typical experiment hydrogen was bubbled through a CD_2Cl_2 solution of the desired [Ir(cod)(P-S)]BAr_F catalyst precursor (6.2 mmol) to the desired temperature for 15-30 min. The reaction mixture was analyzed by NMR spectroscopy at the desired temperature.

3.1.4.8. In situ HP-NMR hydrogenation experiments using (E)-1-methyl-4-(1-phenylprop-1-en-2-yl)benzene-D5 19

The desired [Ir(cod)(P-S)]BAr_F catalyst precursor (6.2 mmol) and (*E*)-1-methyl-4-(1-phenylprop-1-en-2-yl)benzene-D5 (5.9 mg, 27.7 mmol, 4.5 equiv.) were added to an oven-dried Schlenk tube and dissolved in CD_2Cl_2 (0.6 ml). The solution was transferred to a HPNMR sapphire tube (ϕ = 5 mm) and cooled to 195 K. The HPNMR was pressurized to the desired pressure of hydrogen gas. The reaction mixture was analyzed by NMR spectroscopy at the desired temperature.

3.1.4.9. 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. It was then 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**,[11] **S2**,[36] **S3**-**S4**,[11] **S5**,[37] **S6**,[11] **S7**-**S9**,[6l] **S10**,[38] **S11**,[39] **S12**,[37] **S13**,[38] **S14**-**S17**,[6i] **S18**,[20a] **S19**,[21d] **S20**,[21a] **S21**,[11] **S22**,[7c] **S23**,[35] **S24**,[11] **S25**-**S31**,[40] **S32**,[11] **S33**-**S37**,[21a] **S38**,[41] **S39**[42] and **S40**[43] were determined using the conditions previously described.

3.1.5. Acknowledgments

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3.2. Ir-catalyzed asymmetric hydrogenation of minimally functionalized alkenes using binaphthyl-based phosphite-thioether ligands

Carlota Borràs, Isidro Pastor, Oscar Pàmies and Montserrat Diéguez preliminary results.

Abstract: *Eight binaphtyl-based phosphite-thioether ligands (**L3**-**L6a**-**c**) have been prepared by easily modulate of the thioether substituent and biaryl phosphite moieties, from commercially available (R)-BINOL. These ligands have been examined in the Ir-catalyzed asymmetric hydrogenation of minimally functionalized alkenes. Depending on the olefin geometry and its substitution pattern different ligands are required to reach the highest enantioselectivity. In some significantly cases, the chiral hydrogenated products were isolated with ee's within 74-99%. It is noteworthy the excellent results obtained in the hydrogenation of lactone (up to >99% ee) and lactame substrates (up to 97% ee), enolphosphinates (up to 95% ee) and alkenyl boronic esters (up to 98% ee).*

3.2.1. Introduction

In this chapter, we wish to give a new push to the catalytic potential of simple phosphite-thioether ligands in the hydrogenation of minimally functionalized olefins by screening novel and readily available thioether-containing compounds. For this purpose we designed a small but structurally valuable library of phosphite-thioether ligands **L3**-**L6a**-**c** (Figure 3.2.1). They are based on the successful use of ligands with a chiral binapthalene scaffold, such as BINAP[1], in several M-catalyzed asymmetric processes. With ligands **L3**-**L6a**-**c**, we investigated the effect on catalytic performance of systematically changing the electronic and steric properties of the thioether substituent (**L3**-**L6**) and the configuration of the biaryl phosphite moiety (**a**-**c**).[2]

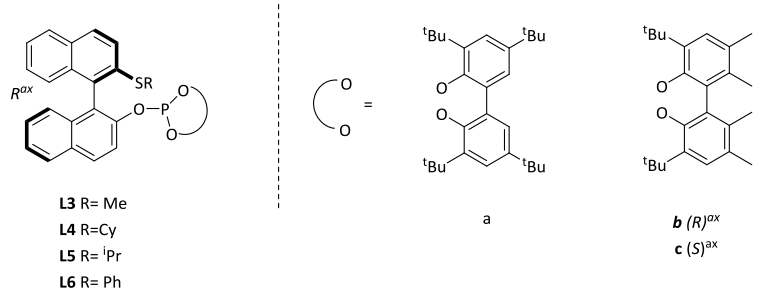


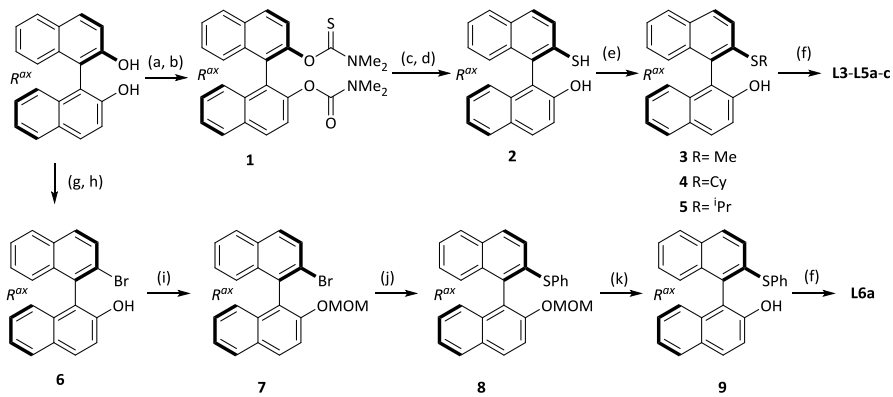
Figure 3.2.1. Phosphite-thioether ligands **L3**-**L6a**-**c**.

3.2.2. Results and discussion

3.2.2.1. Synthesis of ligands

A library of phosphite-thioether ligands **L3**-**L6a**-**g** was prepared as outlined in Scheme 3.2.1 from hydroxyl-thioether compounds **3**-**5** and **9**, which are easily synthesized from the commercially available (*R*)-BINOL. Compounds **3**-**5** have been prepared following the procedure reported by Woodward and coworkers.[3] In this respect, addition of $Me_2NC(S)Cl$ to commercially (*R*)-BINOL in presence of triethylamine and DMAP and the subsequent addition of $Me_2NC(O)Cl$ allowed the isolation of enantiomerically pure compound **1** (Scheme 3.2.1; steps a and b)**.** The purified compound **1** was used in the thermal Newmann rearrangement and after a simple recrystallization (to ensure enantiomeric purity) it was hydrolyzed with potassium hydroxide to yield **2** (Scheme 3.2.1; steps c and d). Finally, compounds **3**-**5** were easily obtained by treating thiol **2** with the appropriate alkylating agent (Scheme 3.2.1; step e).

However, for the synthesis of the corresponding hydroxyl-thioether compound **9**, with an aryl thioether group rather than an alkyl one, we used another route developed by Hagiwara's group. First, compound **6** was synthesized as previously described (Scheme 3.2.1; steps g and h).[4] Then, the protection of alcohol **6** using chloromethyl methylether in presence of sodium hydride and THF as a solvent was carried out (step i). The resulting protected compound **7** was transformed to the thioether intermediate **8** at low temperature using phenyl disulphide and *n*-buthyllithium (step j). Finally, compound **8** was treated with Amberlyst 15 resin to afford the desired hydroxyl-thioether **9** (step k).

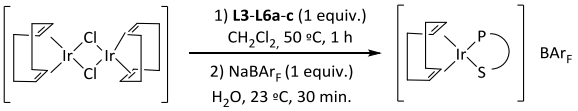


Scheme. 3.2.1. Synthesis of ligands **L3**-**L6a**-**c**. a) $Me_2NC(S)Cl$, NEt_3, DMAP, CH_2Cl_2; b) $Me_2NC(O)Cl$, NEt_3, DMAP, CH_2Cl_2; c) 250 ˚C; d) KOH, H_2O/MeOH; e) *n*-BuLi, RX, THF; f) $ClP(OR)_2$; $(OR)_2$ = **a**-**c**, NEt_3, toluene; g) HY Zeolith CBV400, dichlorobenzene; h) Li, 1,1,2,2-tetrabromoethane, toluene/Et_2O; i) NaH, MOMCl, THF; j) *n*-BuLi, PhSSPh, THF; k) Amberlyst 15 resin, MeOH.

The last step is common for all of the ligands. It consists in the reaction of the corresponding hydroxyl-thioether compounds **3**-**5** and **9**, in the presence of a base, with one equivalent of the desired biaryl phosphochloridite ($Cl(OR)_2$; $P(OR)_2$ = **a**-**c**) to provide phosphite-thioether ligands **L3**-**L6a**-**c** (Scheme 3.2.1; step f). All of the ligands are stable in air at room temperature and to hydrolysis. They were isolated in low-to-moderated yields as white solids after purification by neutral alumina. HRMS-ESI spectra agreed with the assigned structures. The ^{1}H, ^{31}P and ^{13}C NMR spectra were as expected for these ligands.

3.2.2.2. Synthesis of Ir-catalyst precursors

The catalyst precursors were prepared by refluxing a dichloromethane solution of the appropriate ligand (**L3**-**L6a**-**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 3.2.2). All complexes were isolated as air-stable orange solids after purification. The complexes were characterized by HRSM-ESI, ^{31}P NMR, ^{1}H NMR and ^{13}C NMR. 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 molecular species. NMR spectra showed the expected pattern for these complexes. In all cases, one singlet in the VT-^{31}P-{^{1}H} NMR spectra (in CD_2Cl_2, +35 to -85 ˚C) was observed.



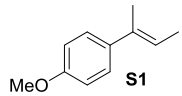
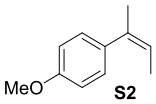
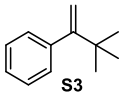
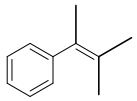
Scheme 3.2.2. Synthesis of catalyst precursors [Ir(cod)(**L3**-**L6a**-**c**)]BAr_F.

3.2.2.3. Ir-catalyzed hydrogenation

The asymmetric hydrogenation of minimally functionalized olefins is highly dependent on the olefin geometry and its substitution pattern.[5] In this respect, *Z*-trisubstituted olefins are commonly hydrogenated less enantioselectively than the related *E*-isomers. On the other hand, for di- and tetrasubstituted olefins enantioslectivities is much more difficult to control than in trisubstituted olefins. In order to evaluate the efficiency of ligands **L3**-**L6** in the hydrogenation of olefins with different geometry and substitution pattern, we initially tested them in the asymmetric reduction of trisubstituted substrates *E*-**S1** (the model olefin) and *Z*-**S2**, and in the hydrogenation of di- and tetrasubstituted olefins **S3** and **S4**, respectively (Table 3.2.1). The enantioselectivities were found to be dependent on the thioether substituent and the biaryl phosphite group. For all of them, we found that ligands with alkyl thioether moieties led to higher ee's than their counterparts with an aryl-thioether group (i.e. entries 1, 4 and 6 vs 8). For di- and tetrasubstituted olefins the

best enantioselectivities (ee's up to 92%) were achieved with a methyl-thioether substituent (entries 1 and 3) while for *E*-trisubstituted olefins a cyclohexyl-thioether substituent is needed for good enantioselectivity (ee's up to 83%, entry 5). However, for *Z*-trisubstituted olefins the type of alkyl-thioether substituent had little effect on enantioselectivity (entries 1-3 vs 4-7). Concerning the effect of the biaryl phosphite group, we found that for trisubstituted substrates an *S*-binaphthyl phosphite group (**c**) is needed to enhance enantioselectivity. In contrast, for di- and tetrasubstituted olefins similar enantioselectivities are obtained with ligands containing the achiral inexpensive biaryl phosphite (**a**) and the *S*-binaphthyl phophite (**c**) moieties (i.e. entry 1 vs 6). For these latter substrates, we can conclude that the ligand backbone together with the thioether moiety is able to control the tropoisomerism of the biaryl phosphite group.

Table 3.2.1. Ir-catalyzed hydrogenation of substrates **S1**-**S4**.[a]

		 **S1**	 **S2**	 **S3**	 **S4**
Entry	**L**	**% ee**[b]	**% ee**[b]	**% ee**[b]	**% ee**[b]
1	**L3a**	40 (*S*)	15 (*S*)	90 (*R*)	45 (*S*)
2	**L3b**	2 (*S*)	15 (*R*)	10 (*S*)	21 (*R*)
3	**L3c**	63 (*S*)	5 (*R*)	92 (*R*)	43 (*S*)
4	**L4a**	74 (*S*)	10 (*S*)	84 (*R*)	2 (*S*)
5	**L4c**	83 (*S*)	3 (*R*)	91 (*R*)	33 (*S*)
6	**L5a**	66 (*S*)	15 (*S*)	85 (*R*)	36 (*S*)
7	**L5c**	80 (*S*)	13 (*S*)	86 (*R*)	40 (*S*)
8	**L6a**	1 (*S*)	2 (*S*)	2 (*R*)	2 (*R*)

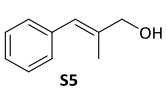
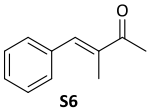
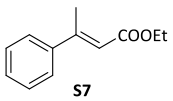
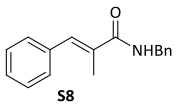
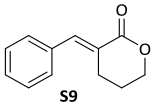
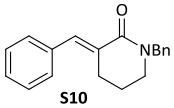
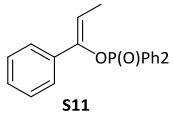
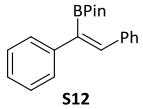
[a] Reactions conditions: 0.5 mmol of substrate, 2 mol% of Ir-catalyst precursor, P_{H2}= 100 bar (for substrates **S1**, **S2** and **S4**) or 1 bar (for substrate **S3**), rt, 18 h. Full conversions, measured by GC, were achieved in all cases. [b] Enantiomeric excesses determined by chiral GC.

Encouraged by the good enantioselectivities obtained in the reduction of tri- and disubstituted olefins we then focus in the hydrogenation of these types of substrates including examples containing neighboring polar groups. Results are shown in Table 3.2.2. We again found that the ligand components must be selected correctly to enhance the enantioselectivity for each substrate.

The reduction of allylic alcohol **S5** proceeded with similar good enantioselectivitiy (ee's up to 80%) than the achieved in the reduction of **S1**, although the best enantioselectivity is obtained with the ligand **L4a** that contain the achiral inexpensive biaryl phosphite (**a**). The Ir/**L3b** catalytic system can also hydrogenate the α,β-unsaturated enone **S6** with comparable high enantioselectivities (up to 84% ee). Higher enantioselectivities could be achieved with the same catalytic system, Ir/**L4a**, in the reduction of a relevant type of substrate: α,β-unsaturated ester **S7** (90% ee). Although, moderate enantioselectivity was achieved in the hydrogenation of an α,β-

unsaturated amide **S8**, excellent enantioselectivities were obtained in the reduction of lactone **S9**, lactame **S10**, enolphosphinate **S11** and alkenyl boronic ester **S12** as substrates (ee's up to 99%).

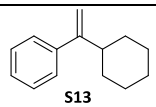
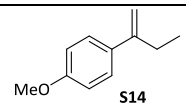
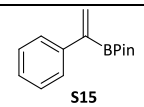
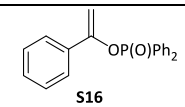
Table 3.2.2. Ir-catalyzed hydrogenation of trisubstituted substrates containing minimally coordinative groups **S5**-**S12**.[a]

		 **S5**	 **S6**	 **S7**	 **S8**
Entry	**L**	**% ee**[b]	**% ee**[b]	**% ee**[b]	**% ee**[b]
1	**L3a**	50 (*S*)	6 (*S*)	35 (*S*)	65 (*S*)
2	**L3b**	32 (*R*)	84 (*R*)	90 (*R*)	62 (*S*)
3	**L3c**	49 (*S*)	60 (*S*)	60 (*S*)	33 (*S*)
4	**L4a**	80 (*S*)	28 (*S*)	52 (*R*)	60 (*S*)
5	**L4c**	41 (*S*)	66 (*S*)	12 (*R*)	11 (*S*)
6	**L5a**	4 (*S*)	33 (*S*)	85 (*S*)	53 (*S*)
7	**L5c**	30 (*S*)	30 (*S*)	68 (*S*)	4 (*S*)
8	**L6a**	3 (*R*)	10 (*S*)	21 (*R*)	4 (*S*)
		 **S9**	 **S10**	 **S11**	 **S12**
9	**L3a**	99 (*R*)	96 (*R*)	20 (*R*)	40 (-)
10	**L3b**	>99 (*R*)	97 (*R*)	91 (*R*)	98 (+)
11	**L3c**	99 (*R*)	96 (*R*)	4 (*R*)	33 (-)
12	**L4a**	13 (*S*)	9 (*S*)	70 (*S*)	97 (+)
13	**L4c**	5 (*S*)	6 (*S*)	95 (*S*)	0
14	**L5a**	99 (*R*)	94 (*R*)	71 (*S*)	20 (-)
15	**L5c**	96 (*R*)	95 (*R*)	50 (*S*)	30 (+)
16	**L6a**	33 (*S*)	24 (*S*)	5 (*R*)	48 (-)

[a] Reactions conditions: 0.5 mmol of substrate, 2 mol% of Ir-catalyst precursor for substrates **S5**-**S8** and **S11** or 4 mol% for substrates **S9**, **S10** and **S11**, P_{H2}= 100 bar, rt, 24 h. Full conversions, measured by ^{1}H-NMR, were achieved in all cases. [b] Enantiomeric excesses determined by chiral HPLC.

Finally, we focus in the reduction of other disubstituted substrates (Table 3.2.3). By comparing the results obtained with **S3**, **S13** and **S14** we conclude that enantioselectivities are dependent on the nature of the alkyl chain of the substrate. This agrees with a competing isomerization pathway. Finally, we wanted to see if the excellent catalytic performance in the reduction of trisubstituted enol phosphinates and alkenylboronic esters was maintained for the even more challenging terminal analogues. While the hydrogenation of **S15** proceeds with low enantioselectivities, high enantioselectivities (ee's up to 96%) comparable to the best one reported in the literature could be achieved in the reduction of enol phosphinate **S16**.

Table 3.2.3. Ir-catalyzed hydrogenation of substrates **S1**-**S4**.[a]

		 S13	 S14	 S15	 S16
Entry	**L**	**% ee[b]**	**% ee[b]**	**% ee[b]**	**% ee[b]**
1	**L3a**	25 (*R*)	72 (*R*)	55 (*R*)	86 (*S*)
2	**L3b**	17 (*R*)	24 (*S*)	10 (*R*)	36 (*R*)
3	**L3c**	43 (*R*)	74 (*R*)	48 (*R*)	85 (*S*)
4	**L4a**	15 (*S*)	35 (*R*)	30 (*R*)	96 (*S*)
5	**L4c**	2 (*R*)	50 (*R*)	11 (*R*)	83 (*S*)
6	**L5a**	24 (*S*)	27 (*R*)	9 (*R*)	92 (*S*)
7	**L5c**	6 (*S*)	26 (*R*)	5 (*S*)	80 (*S*)
8	**L6a**	0	1 (*R*)	1 (*R*)	2 (*S*)

[a] Reactions conditions: 0.5 mmol of substrate, 2 mol% of Ir-catalyst precursor, P_{H2}= 1 bar (for substrates **S13**-**S15**) or 100 bar (for **S16**), rt, 18 h. Full conversions, measured by GC or ^{1}H-NMR, were achieved in all cases. [b] Enantiomeric excesses determined by chiral GC or HPLC.

3.2.3. Conclusions

A new binaphtyl-based phosphite-thioether ligand family (**L3**-**L6a**-**c**) was successfully synthesized from commercially available (*R*)-BINOL. The synthetic procedure used allowed the systematic variation of the substituents of the thioether and the biaryl phosphite moiety. Both groups have been found to be highly important for the enantioselectivity of the process. The presence of alkyl thioether groups was necessary to reach high levels of enantioselectivity. Depending on the olefin geometry and its substitution pattern different ligands are required to reach the highest enantioselective. In some significantly cases, the chiral hydrogenated products were isolated with ee's in the range of 74-99%. It is noteworthy the excellent results obtained in the hydrogenation of lactone (up to >99% ee) and lactame substrates (up to 97% ee), enolphosphinates (up to 95% ee) and alkenyl boronic esters (up to 98% ee).

3.2.4. Experimental part

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.[6] Compounds **1-2**[7], **3**[3], **5**[3] and **6**[4] were prepared as previously described. All other reagents were used as commercially available. ^{1}H, ^{13}C{^{1}H}, ^{31}P{^{1}H} NMR spectra experiments 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 done based on ^{1}H-^{1}H gCOSY and ^{1}H-^{13}C gHSQC experiments.

3.2.4.2 General procedure for the preparation of phosphite-thioether ligands L3-L6a-c

The corresponding phosphorochloridite (1.1 mmol) produced in situ was dissolved in toluene (5 mL) and triethylamine (2.2 mmol, 0.3 mL) was added. The corresponding hydroxyl-thioether **3**-**5** and **9** (1 mmol) was azeotropically dried with toluene (3x1 mL) and dissolved in toluene (5 mL) to which NEt_3 (2.2 mmol, 0.3 mL) was added. The solution was transferred slowly at 0 ^{o}C to the solution of the phosphorochloridite. The reaction mixture was stirred overnight at 80 ^{o}C, and the triethylamine salts were removed by filtration. Evaporation of the solvent gave a white foam, which was purified by flash chromatography in silica (eluent: toluene/triethylamine – 100:1) to produce the corresponding ligand as a white solid.

L3a: Yield: 129.1 mg (34%). ^{31}P NMR (C_6D_6), δ: 136.4 (s). ^{1}H NMR (C_6D_6), δ:1.31 (s, 9H, CH_3, ^{t}Bu), 1.33 (s, 18H, CH_3, ^{t}Bu), 1.49 (s, 9H, CH_3, ^{t}Bu), 1.98 (s, 3H, SCH_3), 7.05 (m, 2H, CH=), 7.20 (m, 2H, CH=), 7.38 (m, 6H, CH=), 7.62 (m, 5H, CH=), 7.78 (m, 2H, CH=). ^{13}C NMR (C_6D_6), δ: 15.3 (SCH_3), 29.7 (CH_3, ^{t}Bu), 29.9 (CH_3, ^{t}Bu), 31.0 (CH_3, ^{t}Bu), 31.1 (CH_3, ^{t}Bu), 31.3 (CH_3, ^{t}Bu), 31.4 (CH_3, ^{t}Bu), 34.4 (C, ^{t}Bu), 34.4 (C, ^{t}Bu), 35.3 (C, ^{t}Bu), 35,4 (C, ^{t}Bu), 122.9-147.4 (aromatic carbons). MS HR-ESI [found 777.3428, $C_{49}H_{55}O_3PS$ (M-Na)$^{+}$ requires 777.3502].

L3b: Yield: 115 mg (33%). ^{31}P NMR (C_6D_6), δ:131.4 (s). ^{1}H NMR (C_6D_6), δ: 1.37 (s, 9H, CH_3, ^{t}Bu), 1.43 (s, 9H, CH_3, ^{t}Bu), 1.67 (s, 3H, CH_3), 1.74 (s, 3H, CH_3), 1.94 (s, 3H, SCH_3), 2.02 (s, 3H, CH_3), 2.08 (s, 3H, CH_3), 6.98 (m, 6H, CH=), 7.31 (m, 3H, CH=), 7.50 (d, 1H, CH=, $^{3}J_{H-H}$= 8.3 Hz), 7.62 (m, 4H, CH=). ^{13}C NMR (C_6D_6), δ: 15.5 (SCH_3), 16.4 (CH_3, ^{t}Bu), 16.6 (CH_3, ^{t}Bu), 20.2 (CH_3, ^{t}Bu), 20.3 (CH_3, ^{t}Bu), 31.3 (CH_3, ^{t}Bu), 31.7 (CH_3, ^{t}Bu), 34.7 (C, ^{t}Bu), 34.7 (C, ^{t}Bu), 122.2-148.0 (aromatic carbons). MS HR-ESI [found 721.2871, $C_{45}H_{47}O_3PS$ (M-Na)$^{+}$ requires 721.2876].

L3c: Yield: 157 mg (45%). ^{31}P NMR (C_6D_6), δ: 132.1 (s). ^{1}H NMR (C_6D_6), δ: : 1.21 (s, 9H, CH_3, ^{t}Bu), 1.45 (s, 9H, CH_3, ^{t}Bu), 1.68 (s, 3H, CH_3), 1.71 (s, 3H, CH_3), 1.94 (s, 3H, SCH_3), 2.03 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 7.12 (m, 9H, CH=), 7.59 (m, 3H, CH=), 7.69 (d, 2H, CH=, $^{3}J_{H-H}$= 8.3 Hz) .^{13}C NMR (C_6D_6), δ: 15.3 (SCH_3), 16.3 (CH_3, ^{t}Bu), 16.5 (CH_3, ^{t}Bu), 20.0 (CH_3, ^{t}Bu), 20.1 (CH_3, ^{t}Bu), 31.1 (CH_3, ^{t}Bu), 31.3 (CH_3, ^{t}Bu), 34.5 (C, ^{t}Bu), 122.7-147.4 (aromatic carbons). MS HR-ESI [found 721.2879, $C_{45}H_{47}O_3PS$ (M-Na)$^{+}$ requires 721.2876].

L4a: Yield: 213 mg (52%). ^{31}P NMR (C_6D_6), δ: 135.5 (s). ^{1}H NMR (C_6D_6), δ: 1.01 (m, 5H, CH_2, SCy), 1.23 (s, 9H, CH_3, ^{t}Bu), 1.24 (s, 9H, CH_3, ^{t}Bu), 1.29 (s, 9H, CH_3, ^{t}Bu), 1.38 (m, 3H, CH_2, SCy), 1.44 (s, 9H, CH_3, ^{t}Bu), 1.71 (m, 1H, CH_2, SCy), 1.88 (m, 1H, CH_2, SCy), 3.05 (m, 1H, CH, SCy), 7.05 (m, 3H, CH=), 7.18 (m, 2H, CH=), 7.24 (m, 3H, CH=), 7.35 (m, 1H, CH=), 7.58 (m, 5H, CH=), 7.69 (m, 2H, CH=).^{13}C NMR (C_6D_6), δ: 25.6 (CH_2, SCy), 25.8 (CH_2, SCy), 25.9 (CH_2, SCy), 30.9 (CH_3, ^{t}Bu), 31.3 (CH_3, ^{t}Bu), 32.8 (CH_2, SCy), 33.3 (CH_2, SCy), 34.3 (C, ^{t}Bu), 34.4 (C, ^{t}Bu), 35.2 (C, ^{t}Bu), 35.3 (C, ^{t}Bu), 44.8 (CH, SCy), 122.6-147.7 (aromatic carbons). MS HR-ESI [found 845.4124, $C_{54}H_{63}O_3PS$ (M-Na)$^{+}$ requires 845.4128].

L4c: Yield: 179 mg (47%). ^{31}P NMR (C_6D_6), δ: 131.7 (s). ^{1}H NMR (C_6D_6), δ: 0.99 (m, 5H, CH_2, SCy), 1.24 (s, 9H, CH_3, ^{t}Bu), 1.26 (m, 1H, CH_2, SCy), 1.38 (m, 3H, CH_2, SCy), 1.44 (s, 9H, CH_3, ^{t}Bu), 1.64 (s, 3H, CH_3), 1.67 (s, 3H, CH_3), 1.90 (m, 1H, CH_2, SCy), 1.99 (s, 3H, CH_3), 2.02 (s, 3H, CH_3), 3.01 (m, 1H, CH, SCy), 6.92 (m, 2H, CH=), 7.00 (m, 3H, CH=), 7.11 (m, 5H, CH=), 7.54 (m, 2H, CH=), 7.64 (m, 2H, CH=). ^{13}C NMR (C_6D_6), δ: 16.3 (CH_3), 16.5 (CH_3), 20.0 (CH_3), 20.1 (CH_3), 25.6 (CH_2, SCy), 25.8 (CH_2, SCy), 25.9 (CH_2, SCy), 31.4 (CH_3, ^{t}Bu), 32.9 (CH_2, SCy), 33.2 (CH_2, SCy), 34.6 (C, ^{t}Bu), 44.8 (CH, SCy), 122.4-147.9 (aromatic carbons). MS HR-ESI [found 789.3500, $C_{50}H_{55}O_3PS$ $(M\text{-}Na)^+$ requires 789.3502].

L5a: Yield: 251 mg (64%). ^{31}P NMR (C_6D_6), δ: 135.6 (s). ^{1}H NMR (C_6D_6), δ: 0.90 (d, 3H, CH_3, S^{i}Pr, $^{3}J_{H\text{-}H}$= 6.6 Hz), 0.95 (d, 3H, CH_3, S^{i}Pr, $^{3}J_{H\text{-}H}$= 6.6 Hz), 1.21 (s, 9H, CH_3, ^{t}Bu), 1.22 (s, 9H, CH_3, ^{t}Bu), 1.27 (s, 9H, CH_3, ^{t}Bu), 1.41 (s, 9H, CH_3, ^{t}Bu), 3.18 (dt, 1H, CH, S^{i}Pr, $^{3}J_{H\text{-}H}$= 13.3 Hz, $^{3}J_{H\text{-}H}$= 6.7 Hz), 6.94 (m 3H, CH=), 7.11 (m, 5H, CH=), 7.23 (m, 1H, CH=), 7.31 (m, 2H, CH=), 7.52 (m, 4H, CH=), 7.67 (m, 1H, CH=).^{13}C NMR (C_6D_6), δ: 22.4 (CH_3, S^{i}Pr), 23.0 (CH_3, S^{i}Pr), 31.0 (CH_3, ^{t}Bu), 31.2 (CH_3, ^{t}Bu), 31.3 (CH_3, ^{t}Bu), 34.3 (C, ^{t}Bu), 34.4 (C, ^{t}Bu), 35.2 (C, ^{t}Bu), 35.3 (C, ^{t}Bu), 36.0 (CH, S^{i}Pr), 122.6-147.7 (aromatic carbons). MS HR-ESI [found 805.3813, $C_{51}H_{59}O_3PS$ $(M\text{-}Na)^+$ requires 805.3815].

L5c: Yield: 150 mg (41%). ^{31}P NMR (C_6D_6), δ: 131.7 (s). ^{1}H NMR (C_6D_6), δ: 0.89 (d, 3H, CH_3, S^{i}Pr, $^{3}J_{H\text{-}H}$= 6.6 Hz), 0.99 (d, 3H, CH_3, S^{i}Pr, $^{3}J_{H\text{-}H}$= 6.6 Hz), 1.21 (s, 9H, CH_3, ^{t}Bu), 1.43 (s, 9H, CH_3, ^{t}Bu), 1.63 (s, 3H, CH_3), 1.66 (s, 3H, CH_3), 1.98 (s, 3H, CH_3), 2.00 (s, 3H, CH_3), 3.16 (dt, 1H, CH, S^{i}Pr, $^{3}J_{H\text{-}H}$= 13.3 Hz, $^{3}J_{H\text{-}H}$= 6.6 Hz), 6.91 (m 2H, CH=), 7.04 (m, 6H, CH=), 7.41 (d, 1H, CH=, $^{3}J_{H\text{-}H}$= 8.8 Hz), 7.53 (m, 2H, CH=), 7.64 (m, 3H, CH=).^{13}C NMR (C_6D_6), δ: 16.3 (CH_3), 16.5 (CH_3), 20.1 (CH_3), 20.1 (CH_3), 22.4 (CH_3, S^{i}Pr), 22.9 (CH_3, S^{i}Pr), 31.3 (CH_3, ^{t}Bu), 31.4 (CH_3, ^{t}Bu), 34.5 (CH, S^{i}Pr), 36.0 (C, ^{t}Bu), 122.6-147.8 (aromatic carbons). MS HR-ESI [found 749.3186, $C_{47}H_{51}O_3PS$ $(M\text{-}Na)^+$ requires 749.3189].

L6a: Yield: 55 mg (11%). ^{31}P NMR (C_6D_6), δ: 135.4 (s). ^{1}H NMR (C_6D_6), δ: 1.22 (s, 18H, CH_3, ^{t}Bu), 1.24 (s, 9H, CH_3, ^{t}Bu), 1.28 (s, 9H, CH_3, ^{t}Bu), 6.79 (m, 3H, CH=), 6.94 (m, 3H, CH=), 7.05 (m, 1H, CH=), 7.14 (m, 1H, CH=), 7.28 (m, 2H, CH=), 7.33 (m, 3H, CH=), 7.40 (d, 1H, CH=, $^{3}J_{H\text{-}H}$= 8.7 Hz), 7.53 (m, 7H, CH=).^{13}C NMR (C_6D_6), δ: 30.9 (CH_3, ^{t}Bu), 31.2 (CH_3, ^{t}Bu), 34.2 (C, ^{t}Bu), 34.3 (C, ^{t}Bu), 35.2 (C, ^{t}Bu), 122.5-146.8 (aromatic carbons). MS HR-ESI [found 839.3655, $C_{50}H_{49}O_3PS$ $(M\text{-}Na)^+$ requires 839.3658].

3.2.4.3. Typical procedure for the preparation of [Ir(cod)(L3-L6a-c)]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 $MgSO_4$, the resulting crude was purified by flash chromatography on silica (CH_2Cl_2/hexane 1:1) to give the products as orange solids.

[Ir(cod)(L3a)]BAr$_F$. Yield: 32 mg (90%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ 98.7 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.74 (s, 9H, CH_3, ^{t}Bu), 1.31 (s, 9H, CH_3, ^{t}Bu), 1.37 (s, 9H, CH_3, ^{t}Bu) , 1.54 (s, 9H, CH_3, ^{t}Bu), 1.75 (m, 2H, CH_2, cod), 2.17 (m, 5H, CH_2, cod), 2.37 (m, 1H, CH_2, cod), 2.71 (s, 3H, CH_3, SMe), 3.42 (b, 1H, CH=, cod), 4.60 (b, 1H, CH=, cod), 5.32 (b, 1H, CH=, cod), 5.38 (b, 1H, CH=, cod), 7.08 (m, 2H, C=), 7.17 (m, 1H, CH=), 7.23 (m, 1H, CH=), 7.29 (b, 1H, CH=), 7.32 (m, 1H, CH=), 7.36 (m, 2H, CH=), 7.53 (m, 4H, CH=), 7.58 (m, 1H, CH=), 7.64 (m, 1H, CH=), 7.72 (m, 7H, CH=), 7.79 (d, 1H, CH=, $^3J_{H-H}$= 8.8 Hz), 7.89 (d, 1H, CH=, $^3J_{H-H}$= 9.0 Hz), 7.94 (d, 1H, CH=, $^3J_{H-H}$= 8.1 Hz), 8.01 (d, 1H, CH=, $^3J_{H-H}$= 8.2 Hz), 8.15 (d, 1H, CH=, $^3J_{H-H}$= 8.7 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 16.9 (CH_3, SMe), 28.6 (CH_2, cod), 29.7 (CH_2, cod), 30.4 (CH_2, cod), 30.8 (CH_3, ^{t}Bu), 31.3 (CH_3, ^{t}Bu), 31.4 (CH_3, ^{t}Bu), 31.5 (CH_2, cod), 32.5 (CH_3, ^{t}Bu), 32.9 (CH_2, cod), 34.8 (C, ^{t}Bu), 34.9 (C, ^{t}Bu), 35.0 (C, ^{t}Bu), 35.9 (C, ^{t}Bu), 69.8 (CH=, cod), 78.8 (CH=, cod), 97.4 (d, CH=, cod, J_{C-P}= 18.5 Hz), 98.9 (d, CH=, cod, J_{C-P}= 13.8 Hz), 117.4-149.6 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^1J_{C-B}$ =49.9 Hz). MS HR-ESI [found 1055.4170, $C_{57}H_{67}IrO_3PS$ $(M)^+$ requires 1055.4172].

[Ir(cod)(L3b)]BAr$_F$. Yield: 32 mg (93%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ 108.5 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.34 (s, 9H, CH_3, ^{t}Bu), 1.59 (s, 3H, CH_3), 1.62 (s, 9H, CH_3, ^{t}Bu), 1.67 (s, 3H, CH_3), 1.80 (m, 3H, CH_2, cod), 2.00 (m, 5H, CH_2, cod), 2.18 (s, 3H, CH_3), 2.24 (s, 3H, CH_3), 2.55 (s, 3H, CH_3, SMe), 3.27 (b, 1H, CH=, cod), 4.49 (b, 1H, CH=, cod), 4.69 (b, 1H, CH=, cod), 4.93 (b, 1H, CH=, cod), 6.84 (m, 1H, C=), 7.24 (m, 2H, CH=), 7.37 (m, 3H, CH=), 7.56 (m, 7H, CH=), 7.70 (m, 8H, CH=), 7.90 (d, 1H, CH=, $^3J_{H-H}$= 9.0 Hz), 7.99 (m, 2H, CH=), 8.15 (m, 2H, C=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 16.2 (CH_3), 16.3 (CH_3), 20.0 (CH_3), 20.1 (CH_3), 20.3 (CH_3, SMe), 27.7 (CH_2, cod), 30.1 (CH_2, cod), 31.1 (CH_2, cod), 32.1 (CH_3, ^{t}Bu), 32.7 (CH_3, ^{t}Bu), 33.7 (CH_2, cod), 33.8 (CH_2, cod), 34.8 (C, ^{t}Bu), 35.6 (C, ^{t}Bu), 68.9 (CH=, cod), 72.6 (CH=, cod), 98.0 (d, CH=, cod, J_{C-P}= 15.3 Hz), 100.3 (d, CH=, cod, J_{C-P}= 15.3 Hz), 117.4-146.7 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^1J_{C-B}$ =49.7 Hz). MS HR-ESI [found 999.3542, $C_{53}H_{59}IrO_3PS$ $(M)^+$ requires 999.3546].

[Ir(cod)(L3c)]BAr$_F$. Yield: 30 mg (89%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ 95.3 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.69 (s, 9H, CH_3, ^{t}Bu), 1.48 (s, 9H, CH_3, ^{t}Bu) , 1.69 (b, 2H, CH_2, cod), 1.82 (s, 3H, CH_3), 1.84 (s, 3H, CH_3), 2.00 (m, 2H, CH_2, cod), 2.14 (m, 3H, CH_2, cod), 2.24 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 2.35 (b, 1H, CH_2, cod), 2.69 (s, 3H, CH_3, SMe), 2.97 (b, 1H, CH=, cod), 4.51 (b, 1H, CH=, cod), 5.30 (b, 2H, CH=, cod), 7.05 (m, 3H, C=), 7.17 (d, 1H, CH=, $^3J_{H-H}$= 9.1 Hz), 7.27 (m, 1H, CH=), 7.35 (m, 2H, CH=), 7.51 (m, 7H, CH=), 7.63 (m, 1H, CH=), 7.71 (m, 8H, CH=), 7.77 (d, 1H, CH=, $^3J_{H-H}$= 8.8 Hz), 7.94 (m, 1H, C=), 8.14 (d, 1H, CH, $^3J_{H-H}$= 8.8 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 16.3 (CH_3), 16.6 (CH_3), 16.8 (CH_3, SMe), 20.3 (CH_3), 20.5 (CH_3), 28.7 (CH_2, cod), 30.1 (CH_2, cod), 31.0 (CH_3, ^{t}Bu), 31.9 (CH_2, cod), 32.5 (CH_3, ^{t}Bu), 32.7 (CH_2, cod), 34.4 (C, ^{t}Bu), 35.0 (C, ^{t}Bu), 69.8 (CH=, cod), 78.6 (CH=, cod), 97.1 (d, CH=, cod, J_{C-P}= 18.3 Hz), 98.5 (d, CH=, cod, J_{C-P}= 14.5 Hz), 117.4-147.3 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^1J_{C-B}$ =49.7 Hz). MS HR-ESI [found 999.3544, $C_{53}H_{59}IrO_3PS$ $(M)^+$ requires 999.3546].

[Ir(cod)(L4a)]BAr$_F$. Yield: 31 mg (87%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ 95.6 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.74 (s, 9H, CH_3, ^{t}Bu), 0.79 (b, 2H, CH_2, SCy), 1.09 (m, 1H, CH_2, SCy), 1.39 (s, 9H, CH_3, ^{t}Bu), 1.56 (s, 9H, CH_3, ^{t}Bu), 1.75 (b, 5H, CH_2, cod, CH_2, SCy), 2.08 (b, 2H, CH_2, cod), 2.43 (b, 2H, CH_2, cod), 3.55 (b, 1H, CH=, cod), 3.75 (b, 1H, CH, SCy), 4.40 (b, 1H, CH=, cod), 5.62 (b, 2H, CH=, cod), 7.07 (m, 3H, CH=), 7.22 (m, 4H, CH=), 7.35 (m, 3H, CH=), 7.49 (m, 5H, CH=), 7.59 (m, 1H, CH=), 7.64 (m, 1H, CH=), 7.72 (b, 7H, CH=), 7.81 (d, 1H, CH=, $^3J_{H-H}$= 8.8 Hz), 7.86 (d, 1H, CH=, $^3J_{H-H}$= 9.1 Hz), 7.93 (d, 1H, C=, $^3J_{H-H}$= 8.2 Hz), 8.00 (d, 1H, CH=, $^3J_{H-H}$= 8.3 Hz), 8.12 (d, 1H, CH=, $^3J_{H-H}$= 8.7 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 22.7 (CH_2, SCy), 24.7 (CH_2, SCy), 25.0 (CH_2, SCy), 25.4 (CH_2, SCy), 29.4 (CH_2, cod), 29.7 (CH_2, cod), 30.4 (CH_2, SCy), 30.8 (CH_3, ^{t}Bu), 31.3 (CH_3, ^{t}Bu), 31.4 (CH_3, ^{t}Bu), 32.1 (CH_2, cod), 32.5 (CH_2, cod), 32.6 (CH_3, ^{t}Bu), 34.8 (C, ^{t}Bu), 34.9 (C, ^{t}Bu), 35.0 (C, ^{t}Bu), 35.9 (C, ^{t}Bu), 46.0 (CH, SCy), 68.9 (CH=, cod), 75.6 (CH=, cod), 98.4 (d, CH=, cod, J_{C-P}= 17.9 Hz), 99.3 (d, CH=, cod, J_{C-P}= 14.2 Hz), 117.4-149.2 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^1J_{C-B}$ =49.9 Hz). MS HR-ESI [found 1123.4795, $C_{62}H_{75}IrO_3PS$ $(M)^+$ requires 1123.4798].

[Ir(cod)(L4c)]BAr$_F$. Yield: 31 mg (88%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ 91.9 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.67 (s, 9H, CH_3, ^{t}Bu), 0.73 (m, 2H, CH_2, cod), 0.99 (m, 1H, CH_2, SCy), 1.51 (s, 9H, CH_3, ^{t}Bu), 1.71 (m, 3H, CH_2, cod, CH_2, SCy), 1.84 (s, 3H, CH_3), 1.85 (s, 3H, CH_3), 2.06 (b, 4H, CH_2, cod), 2.24 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 2.45 (m, 3H, CH_2, cod), 3.10 (b, 1H, CH=, cod), 3.73 (b, 1H, CH, SCy), 4.32 (b, 1H, CH=, cod), 5.58 (b, 2H, CH=, cod), 7.08 (m, 3H, CH=), 7.32 (m, 4H, CH=), 7.50 (m, 5H, CH=), 7.63 (t, 1H, CH=, $^3J_{H-H}$= 7.4 Hz), 7.73 (b, 8H, CH=), 7.79 (d, 1H, CH=, $^3J_{H-H}$= 8.8 Hz), 7.86 (d, 1H, CH=, $^3J_{H-H}$= 9.1 Hz), 7.92 (d, 1H, C=, $^3J_{H-H}$= 8.3 Hz), 7.99 (d, 1H, CH=, $^3J_{H-H}$= 8.1 Hz), 8.10 (d, 1H, CH=, $^3J_{H-H}$= 8.7 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 16.3 (CH_3), 16.6 (CH_3), 20.3 (CH_3), 20.5 (CH_3), 22.7 (CH_2, SCy), 24.6 (CH_2, SCy), 25.0 (CH_2, SCy), 25.5 (CH_2, SCy), 29.1 (CH_2, cod), 29.9 (CH_2, cod), 30.9 (CH_2, SCy), 30.9 (CH_3, ^{t}Bu), 31.0 (CH_3, ^{t}Bu), 32.0 (CH_2, cod), 32.8 (CH_3, ^{t}Bu), 33.1 (CH_2, cod), 34.4 (C, ^{t}Bu), 35.2 (C, ^{t}Bu), 46.0 (CH, SCy), 68.8 (CH=, cod), 75.6 (CH=, cod), 98.0 (d, CH=, cod, J_{C-P}= 17.8 Hz), 98.8 (d, CH=, cod, J_{C-P}= 14.7 Hz), 117.4-147.8 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^1J_{C-B}$ =49.9 Hz). MS HR-ESI [found 1067.4167, $C_{59}H_{67}IrO_3PS$ $(M)^+$ requires 1067.4172].

[Ir(cod)(L5a)]BAr$_F$. Yield: 34 mg (93%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ 95.6 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.74 (s, 9H, CH_3, ^{t}Bu), 1.03 (m, 6H, CH_2, S^{i}Pr), 1.32 (s, 9H, CH_3, ^{t}Bu), 1.39 (s, 9H, CH_3, ^{t}Bu), 1.47 (m, 1H, CH_2, cod), 1.56 (s, 9H, CH_3, ^{t}Bu), 1.83 (b, 3H, CH_2, cod), 2.13 (m, 2H, CH_2, cod), 2.44 (m, 2H, CH_2, cod), 3.56 (b, 1H, CH=, cod), 3.96 (m, 1H, CH, ^{i}Pr), 4.42 (b, 1H, CH=, cod), 5.61 (b, 2H, CH=, cod), 7.07 (m, 3H, CH=), 7.23 (m, 3H, CH=), 7.36 (m, 6H, CH=), 7.51 (b, 5H, CH=), 7.62 (m, 2H, CH=), 7.72 (b, 7H, CH=), 7.80 (d, 1H, CH=, $^3J_{H-H}$= 8.7 Hz), 7.87 (d, 1H, CH=, $^3J_{H-H}$= 9.1 Hz), 7.93 (d, 1H, C=, $^3J_{H-H}$= 8.3 Hz), 8.01 (d, 1H, CH=, $^3J_{H-H}$= 8.1 Hz), 8.13 (d, 1H, CH=, $^3J_{H-H}$= 8.7 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 21.4 (CH_3, S^{i}Pr), 22.4 (CH_3, S^{i}Pr), 28.9 (CH_2, cod), 29.3 (CH_2, cod), 29.7 (CH_2, cod), 30.8 (CH_3, ^{t}Bu), 31.3 (CH_3, ^{t}Bu), 31.4 (CH_3, ^{t}Bu), 31.5 (CH_2, cod), 32.6 (CH_3, ^{t}Bu), 34.8 (C, ^{t}Bu), 34.9 (C, ^{t}Bu), 35.0 (C, ^{t}Bu), 35.9 (C, ^{t}Bu), 37.7 (CH, S^{i}Pr), 69.1 (CH=,

cod), 75.9 (CH=, cod), 98.1 (d, CH=, cod, J_{C-P}= 19.8 Hz), 99.3 (d, CH=, cod, J_{C-P}= 13.7 Hz), 115.4-149.3 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^1J_{C-B}$ =50.5 Hz). MS HR-ESI [found 1083.4482, $C_{59}H_{75}IrO_3PS$ $(M)^+$ requires 1083.4485].

[Ir(cod)(L5c)]BAr_F. Yield: 32 mg (91%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ 92.1 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.67 (s, 9H, CH_3, ^{t}Bu), 1.00 (m, 6H, CH_2, S^{i}Pr), 1.44 (m, 2H, CH_2, cod), 1.51 (s, 9H, CH_3, ^{t}Bu), 1.74 (m, 2H, CH_2, cod), 1.84 (s, 3H, CH_3), 1.85 (s, 3H, CH_3), 2.03 (b, 2H, CH_2, cod), 2.24 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 2.40 (m, 2H, CH_2, cod), 3.10 (b, 1H, CH=, cod), 3.93 (m, 1H, CH, ^{i}Pr), 4.34 (b, 1H, CH=, cod), 5.55 (b, 2H, CH=, cod), 7.04 (m, 4H, CH=), 7.35 (m, 4H, CH=), 7.51 (m, 5H, CH=), 7.64 (t, 1H, CH=, $^3J_{H-H}$= 7.4 Hz), 7.72 (b, 7H, CH=), 7.78 (d, 1H, CH=, $^3J_{H-H}$= 8.7 Hz), 7.87 (d, 1H, CH=, $^3J_{H-H}$= 9.0 Hz), 7.93 (d, 1H, C=, $^3J_{H-H}$= 8.2 Hz), 8.00 (d, 1H, CH=, $^3J_{H-H}$= 8.1 Hz), 8.12 (d, 1H, CH=, $^3J_{H-H}$= 8.7 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 16.3 (CH_3), 16.6 (CH_3), 20.3 (CH_3), 20.5 (CH_3), 22.5 (CH_3, S^{i}Pr), 22.7 (CH_3, S^{i}Pr), 29.2 (CH_2, cod), 29.8 (CH_2, cod), 31.0 (CH_3, ^{t}Bu), 31.6 (CH_2, cod), 32.8 (CH_3, ^{t}Bu), 33.0 (CH_2, cod), 34.4 (C, ^{t}Bu), 35.2 (C, ^{t}Bu), 37.7 (CH, S^{i}Pr), 69.1 (CH=, cod), 75.9 (CH=, cod), 97.9 (d, CH=, cod, J_{C-P}= 17.7 Hz), 98.9 (d, CH=, cod, J_{C-P}= 14.3 Hz), 117.4-147.7 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^1J_{C-B}$ =50.0 Hz). MS HR-ESI [found 1027.3854, $C_{55}H_{63}IrO_3PS$ $(M)^+$ requires 1027.3859].

[Ir(cod)(L6a)]BAr_F. Yield: 33 mg (88%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ 96.5 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.68 (s, 9H, CH_3, ^{t}Bu), 1.31 (s, 9H, CH_3, ^{t}Bu) , 1.39 (s, 9H, CH_3, ^{t}Bu), 1.70 (s, 9H, CH_3, ^{t}Bu), 1.74 (b, 3H, CH_2, cod), 1.87 (b, 2H, CH_2, cod), 2.35 (b, 3H, CH_2, cod), 3.44 (b, 1H, CH=, cod), 4.43 (b, 1H, CH=, cod), 4.77 (b, 1H, CH=, cod), 5.30 (b, 1H, CH=, cod), 7.16 (m, 6H, CH=), 7.35 (m, 5H, CH=), 7.63 (m, 1H, CH=), 7.70 (m, 7H, CH=), 7.90 (d, 2H, CH=, $^3J_{H-H}$= 8.8 Hz), 8.09 (m, 2H, CH=), 8.25 (d, 1H, CH=, $^3J_{H-H}$= 8.9 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 28.3 (CH_2, cod), 29.3 (CH_2, cod), 30.8 (CH_3, ^{t}Bu), 31.0 (CH_2, cod), 31.3 (CH_3, ^{t}Bu), 31.4 (CH_3, ^{t}Bu), 31.6 (CH_2, cod), 32.9 (CH_3, ^{t}Bu), 34.8 (C, ^{t}Bu), 34.9 (C, ^{t}Bu), 35.0 (C, ^{t}Bu), 36.4 (C, ^{t}Bu), 69.1 (CH=, cod), 77.0 (CH=, cod), 100.8 (CH=, cod), 101.7 (CH=, cod), 117.4-149.5 (aromatic carbons), 161.9 (q, C-B, BAr_F, $^1J_{C-B}$ =49.3 Hz). MS HR-ESI [found 1117.4325, $C_{62}H_{69}IrO_3PS$ $(M)^+$ requires 1117.4329].

3.2.4.4. Procedure for the preparation of hydroxyl-thioether compounds 4

^{n}BuLi (0.4 mL of 2.5 M in hexane, 1.09 mmol) was added dropwise to a stirring solution of **2**[7] (0.30 g, 0.99 mmol) in THF at 0 ˚C under inert atmosphere. Neat iodocyclohexane (0.14 mL, 1.09 mmol, 1.1 equiv.) was added, the solution was allowed to warm to 55 ˚C and monitored by TLC (dichloromethane/petroleum ether 1:1). After 16 h the reaction mixture was quenched with HCl (2 M, 5 mL) and extracted with dichloromethane, washed with brine and dried over $MgSO_4$. Purification by flash column chromatrography (DCM/petrolium ether 1:1) yielded solid **4** (241 mg, 0.63 mmol, 63% yield). ^{1}H NMR ($CDCl_3$), δ: 0.87 (m, 2H, CH_2, SCy), 1.23 (m, 2H, CH_2, SCy), 1.61 (m, 2H, CH_2, SCy), 1.90 (m, 2H, CH_2, SCy), 3.24 (m, 1H, CH, SCy), 4.79 (s, 1H, OH), 6.96 (d, 1H, CH=, $^3J_{H-H}$= 8.6 Hz), 7.14 (d, 1H, CH=, $^3J_{H-H}$= 8.6 Hz), 7.29 (m, 4H, CH=), 7.45 (t, 1H, CH=, $^3J_{H-H}$= 7.5 Hz), 7.72 (d, 1H, CH=, $^3J_{H-H}$= 8.6 Hz), 7.93 (m, 4H, CH=). ^{13}C NMR

($CDCl_3$), δ: 25.5 (CH_2, SCy), 26.0 (CH_2, SCy), 26.1 (CH_2, SCy), 32.9 (CH_2, SCy), 33.4 (CH_2, SCy), 44.8 (CH, SCy), 117.5-130.2 (aromatic carbons).

3.2.4.5. Procedure for the preparation of hydroxyl-thioether compounds 9

Compound **7** was prepared via protection and the subsequently thioether formation of previously reported compound **6**.[4] To a dried schlenk with stir-bar and addition funnel was added NaH (60% dispersion in mineral oil, 840 mg, 21 mmol, 3 equiv.) and THF (30 mL). The reaction was cooled to 0˚C. Compound **6** (2.4 g, 7 mmol) was added as one portion. The reaction mixture was allowed to stir overnight at RT. After completion, the reaction mixture was quenched with saturated aq. NH4Cl, extracted with Et_2O, and washed with brine. The organic layer was dried with $MgSO_4$ and the solvent was removed via rotator evaporation. Purification by recristalitzation in hexane yielded solid **7** (2.3 g, 5.9 mmol, 85% yield). ^{1}H NMR ($CDCl_3$), δ: 3.20 (s, 3H, CH_3), 5.11 (m, 2H, CH_2), 7.03 (d, 1H, CH=, $^2J_{H-H}$= 8.8 Hz), 7.26 (m, 3H, CH=), 7.37 (m, 1H, CH=), 7.49 (m, 1H, CH=), 7.61 (d, 1H, CH=, $^2J_{H-H}$= 9.1 Hz), 7.84 (s, 2H, CH=), 7.92 (m, 2H, CH=), 8.01 (d, 1H, CH=, $^2J_{H-H}$= 9.1 Hz). ^{13}C NMR ($CDCl_3$), δ: 55.8 (CH_3), 95.4 (CH_2), 117.6-150.7 (aromatic carbons).

To a solution of the protected compound **7** (1.4 g, 3.7 mmol) in THF (10 mL) was added a hexane solution of *n*-BuLi (2.3 mL, 1.56 M, 3.7 mmol, 1 equiv.) at –70 °C, and then the reaction mixture was stirred for 1 h. A solution of phenyl disulfide (480 mg, 2.2 mmol, 0.6 equiv.) in THF (10 mL) was slowly added to the reaction mixture at this temperature and then the reaction mixture was stirred at –55 °C for 72 h. The reaction mixture was quenched by saturated $NH_4Cl_{(aq)}$, diluted with CH_2Cl_2, and washed once with water and once with brine. The combined aqueous solutions were extracted with CH_2Cl_2, and the combined organic solutions were dried over $MgSO_4$ and concentrated under reduced pressure to afford compound **8** (650 mg, 1.5 mmol, 42% yield). Next step was carried out without further purification. To compound **8** (650 mg, 1.5 mmol) was added MeOH (6.4 mL) and THF (6.4 mL). Amberlyst 15 resin (1 g) was then added, and reaction was allowed to reflux at 65 ˚C overnight. After completation, the resin was filtered off and the organic layer concentrated to reduce solvent amount. The residue was purified by silica gel chromatography (4:1 petrolium ether/dichloromethane) to yield the compound **9** as a white solid (480 mg, 1.3 mmol, 79% yield). ^{1}H NMR ($CDCl_3$), δ: 4.81 (br, OH), 7.08 (d, 1H, CH=, $^2J_{H-H}$= 8.5 Hz), 7.35 (m, 12H, CH=), 7.86 (m, 3H, CH=), 7.96 (d, 1H, CH=, $^2J_{H-H}$= 11.3 Hz). ^{13}C NMR ($CDCl_3$), δ: 116.8-151.0 (aromatic carbons).

3.2.4.6. 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. It was then 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**-**S5**,[8] **S6**,[9] **S7**,[8] **S8,**[10] **S9-10**,[11] **S11**,[12] **S12**,[13] **S13**,[14] **S14**,[8] **S15**[15] and **S16**[16] were determined using the conditions previously described.

3.2.5. Acknowledgments

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3.2.6. REFERENCES

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UNIVERSITAT ROVIRA I VIRGILI
SUSTAINABLE AND COST-EFFECTIVE DEVELOPMENT OF CHIRAL METAL-CATALYSTS FOR C-H AND C-X BOND FORMING REACTIONS
Carlota Borràs Noguera

3.3. A readily assembled carbohydrate derived phosphite-thioether/selenoether ligand library for a broad range of M-catalyzed asymmetric hydrogenation

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

Abstract: *A large family of phosphite-thioether/selenoether ligands has been easily prepared from accessible L-(+)-tartaric acid and D-(+)-mannitol and applied in the M-catalyzed asymmetric hydrogenation. Its highly modular architecture has been crucial to maximize the catalytic performance. Improving most approaches reported to date, this ligand family presents a broad substrate scope. By carefully selecting the ligand parameters high enantioselectivities (ee's up to 99%) have therefore been achieved in a broad range of both, functionalized and unfunctionalyzed substrates (45 compounds in total). Interestingly, both enantiomers of the hydrogenation products can be usually achieved by changing the ligand parameters.*

3.3.1. Introduction

In the present era of green chemistry, where sustainable chemical production are a "must" the transition metal-catalyzed asymmetric hydrogenation of alkenes, with its very low catalyst loading and no byproducts, has become one of the most reliable toolkit for the preparation of enantiomerically pure compounds. In contrast, to the reduction of carbonyl-based compounds, the enantioselective reduction of C=C bonds relies mainly on transition-metal-catalysts.[1] The extensive research dedicated to this process can give the erroneous impression that asymmetric hydrogenation is a mature area. However, most of the catalysts still rarely tolerate a broad range of substrates, and each type of substrate (functionalized and unfunctionalyzed) requires a particular ligand to optimize enantiopurity. Consequently, the identification of "privileged" ligands[2] remains a central task in this chemistry. For the asymmetric hydrogenation of alkenes with a good coordinating group close to the C=C bond, Rh- and Ru-compounds bearing diphosphine ligands are the catalysts of choice.[1] Nowadays, the substrate scope has been substantially expanded and it uses has been largely accepted as illustrated with the development of commercially processes, such as, the Parkinson's drug L-DOPA[3], the broad spectrum antibiotic levofloxacin,[4] sitagliptin[5] and the pesticide (S)-metolachlor[6]. As a complement, for alkenes carrying no neighboring coordinating groups, the so-called minimally functionalized olefins, as shown in previous chapters Ir-P,N compounds have been developed into efficient catalysts.[7] However, its hydrogenation has not reached the same level of development as the hydrogenation of functionalized olefins and its synthetic utility remains limited. Most Ir-catalysts are still sensitive to the olefin geometry as well as to the number and

nature of substituents. Many important substrates still provide suboptimal results with known catalysts.

Here we wish to give a new push to the search of a family of ligands that can efficiently hydrogenate both functionalized and unfunctionalyzed alkenes. In addition to provide excellent results for a broad range of both substrate types, such privileged ligands must be readily prepared form simple starting reagents and easy to handle (solid, robust and air stable). Our group has expertise in preparing easy to handle ligand families from readily available staring materials.[8] We and other have shown the useful of carbohydrates for preparing ligands as a source of cheap and readily available materials. Their polyfunctional structure and well established chemistry facilitates its modular reactivity in terms of electronic and sterical effects. We have also shown the benefits of having biaryl phosphite moieties in the ligand for asymmetric hydrogenation.[9] The reason for their good performance is the flexibility of the biaryl phosphite groups that allows the chiral pocket of the catalyst to accommodate to the steric demand of the substrate. Moreover, their easy preparation from alcohols and their higher stability towards air and other oxidizing agents than other commonly used phosphines make phosphite ligands very attractive. All these features facilitate to prepare large series of chiral ligands that can be screened in the search of the optimal ligand for each type of substrate.

In this chapter we therefore present the synthesis of a highly modular and readily accessible phosphite-thioether/selenoether ligand library, for application in the M-catalyzed asymmetric hydrogenation of both, functionalized and unfunctionalyzed olefins. These new ligands are easily prepared on a large scale from L-tartaric acid and D-mannitol and their advantages properties derive from the sugar core, the biaryl phosphite moieties, and the thioether/selenoether moieties. Their modular nature greatly expedites the evaluation of several ligand parameters, which is deemed crucial for the iterative optimization of the most promising candidates. Consequently, the catalytic performance of the ligands depicted in Figure 3.3.1 has been studied by systematically varying electronic and steric effects of the thioether group (Ligands **L7**-**L13**), the substituents and the introduction of a new stereogenic centre in the alkyl backbone chain next to the phosphite moiety (ligands **L7**, **L13**, **L14**-**L15** and **L17**-**L24**), the substituents and the introduction of a new stereogenic centre in the alkyl backbone chain next to the thioether moiety (ligands **L7**, **L8**, **L16** and **L25**), the substituents and configurations in the biaryl phosphite moiety (**a**-**g**); and finally the replacement of the thioether group by a selenoether moiety.

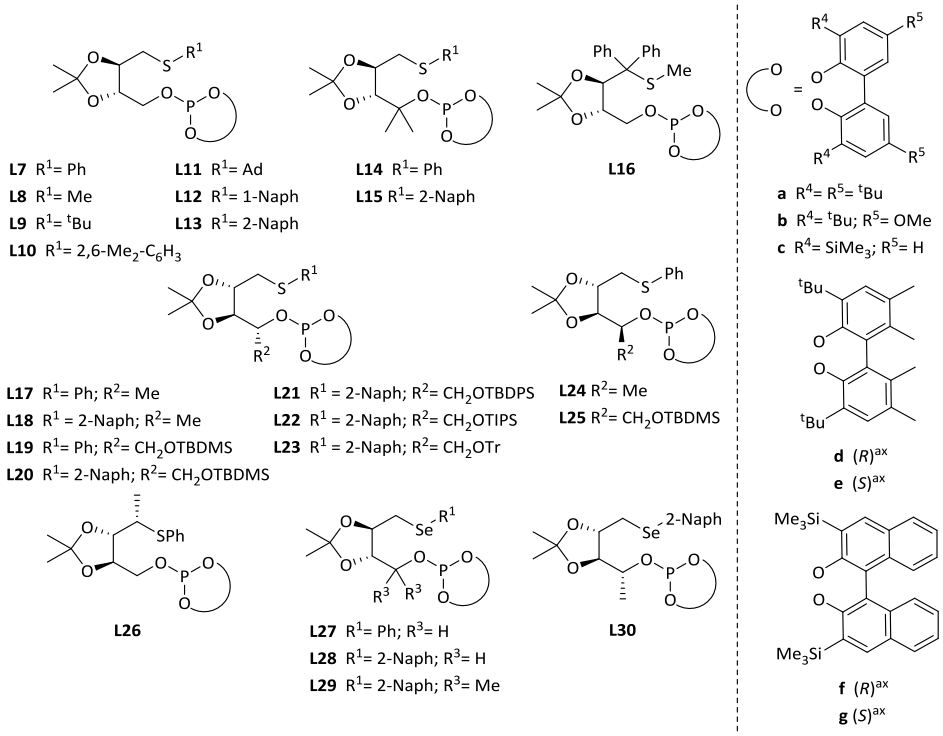


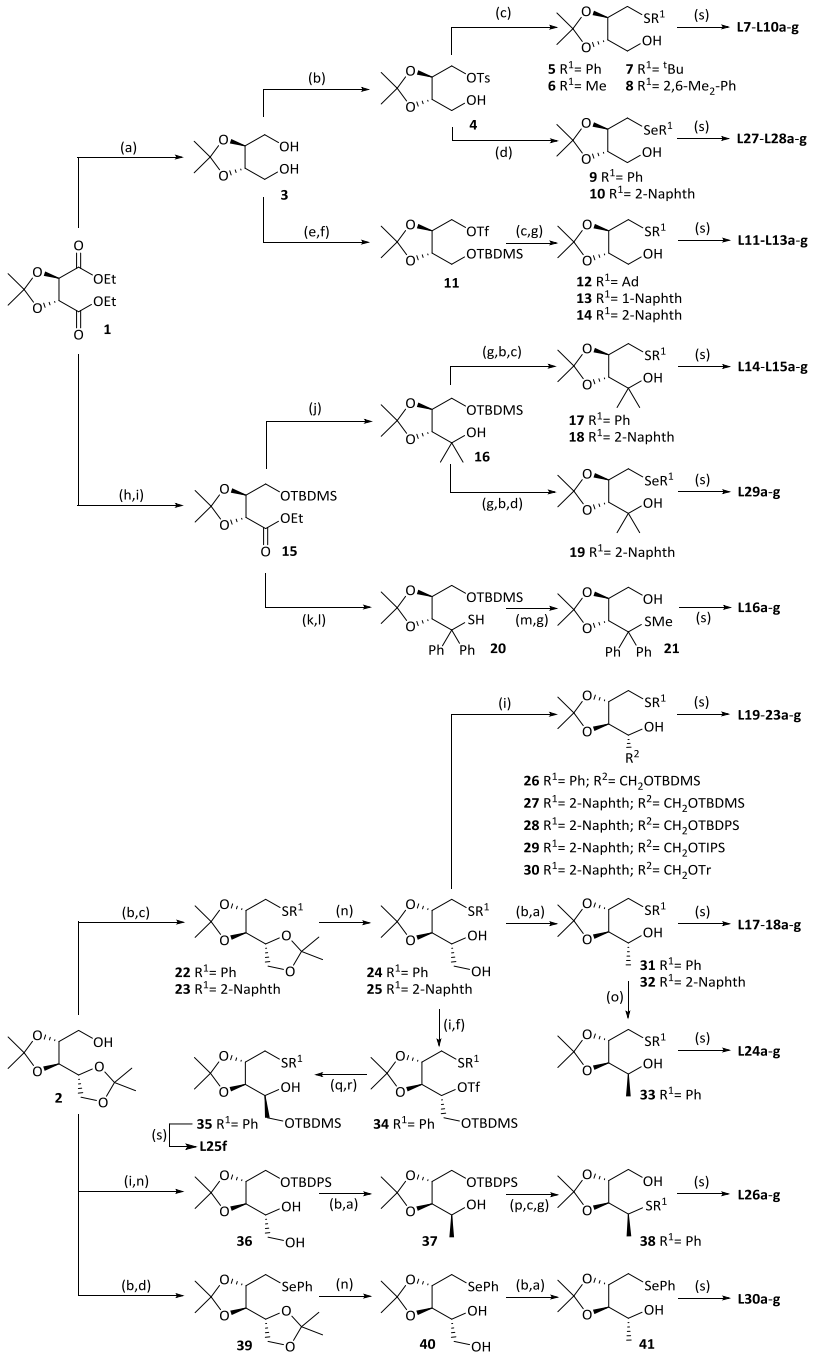
Figure 3.3.1. Sugar-based phosphite-thioether/selenoether ligand library **L7**-**L30a**-**g**.

3.3.2. Results and discussion

3.3.2.1. Synthesis of ligands

Ligands **L7**-**L30a**-**g** have been synthesized from the readily accessible hydroxyl-thioether/selenoether compounds **5**-**10**, **12**-**14**, **17**-**19**, **21**, **26**-**33**, **35**, **38** and **41** (Scheme 3.3.1). These compounds were chosen as intermediates for the synthesis of ligands because they easily allow incorporation of the desired diversity in the ligand structure. They were easily prepared on a multigram scale by highly effective methods from compounds **1** and **2**, which are obtained from inexpensive natural L-(+)-tartaric acid and D-(+)-mannitol.

Thus, hydroxyl-thioether/selenoether compounds **5**-**10** have been obtained from compound **1** in only three steps. The first step is the reduction of intermediate **1** with $LiAlH_4$ to afford diol **3** (Scheme 3.3.1, step a). The second step consists on the selective monotosylation of **3** (Scheme 3.3.1, step b). Subsequent reaction with the corresponding NaSR or Se_2R_2 (R=Ph, Me, ^{t}Bu, 2,6-$Me_2C_6H_3$) in the presence of $NaBH_4$ provided the desired hydroxyl-thioether/selenoether compounds **5**-**10** (Scheme 3.3.1, step c). However, this last step proceeded with poor yields when bulky thioether substituents were used. Therefore, for the preparation of corresponding hydroxyl-thioethers **12**-**14 a**n alternative synthetic route was developed.



Scheme 3.3.1. Synthesis of phosphite-thioether/selenoether ligands **L7**-**L29a**-**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) DBU,AcOH, toluene; r) K_2CO_3, MeOH; s) $ClP(OR)_2$; $(OR)_2$ = **a**-**g**, Py, toluene.

Compound **3** was first transformed to the triflate compound **11** via monoprotection of **3** with 1 equiv. of TBDMSCl and NaH followed by reaction with triflic anhydride (Scheme 3.3.1, steps e, f). Subsequent reaction with the desired NaSR (R= Ad, 1-Naphth and 2-Naphth) followed by the deprotection of the tert-butyldimethylsilyl group with TBAF gave access to the hydroxyl-thioether compounds **12**-**14** (Scheme 3.3.1, steps c, g).

For the preparation of hydroxyl-thioether/selenoether compounds **17**-**19** and **21**, which differs from **5**-**14**, in the substituent on the carbon atom adjacent to the alcohol group, compound **1** was first transformed to intermediate **15** by reaction with $NaBH_4$ followed by protection of the alcohol group using 1equiv. of TBDMSCl (Scheme 3.3.1, steps h, i). Treatment of compound **15** with MeLi provided compound **16** (Scheme 3.3.1, step j). Then, the hydroxyl-thioether/selenoether intermediates **17**-**19** were obtained from standard deprotection of compound **16**, followed by a treatment of the alcohol with *p*-toluenesulfonyl chloride and pyridine to afford the tosylate compound and subsequent reaction with the corresponding NaSR or Se_2R_2 in the presence of $NaBH_4$ gave access to intermediates **17**-**19** (Scheme 3.3.1, steps g, b, d). For the preparation of thioether-hydroxyl compound **21,** intermediate **15** was treated with PhMgBr and then, Laweson's reagent was used to transform the alcohol moiety to the thiol moiety achieving compound **20** (Scheme 3.3.1, step k, l). Methylation of **20** with MeI followed by deprotection of the silyl group gave access to desired hydroxyl thioether **21** (Scheme 3.3.1, steps m, g).

For the preparation of compounds **26**-**33** and **35**, which contain a substituent next to the alcohol group that generates a new chiral center, intermediate **2** was treated with 1 equivalent of *p*-toluenesulfonyl chloride and subsequent substitution reaction with the appropriated nucleophile afford thioether/selenoether compounds **22**-**23** (Scheme 3.3.1, step b, c). Then, standard acid-catalyzed acetal deprotection with AcOH provided corresponding compounds **24**-**25** (Scheme 3.3.1, step n). From this point the synthesis followed different pathways depending on the ligand to be prepared.

Thus, for synthesis of hydroxyl-thioethers **26**-**30**, intermediates **24**-**25** were treated with 1 equiv. of the corresponding silyl chlorides or trityl chloride (Scheme 3.3.1, step i). For the synthesis of hydroxyl-thioethers **31**-**32**, compounds **24**-**25** have been transformed to the corresponding tosylated compounds followed by reaction with $LiAlH_4$ (Scheme 3.3.1, steps b, a). For the synthesis of compound **33**, which differs from **31** in the configuration of the carbon next to the alcohol group, the methyl group was inverted using an standard Mitsunobu procedure (Scheme 3.3.1, step o). Similarly, for the preparation of compound **35** the configuration of the carbon next to the alcohol group was inverted using the methodology described by Quan et al.[10] (Scheme 3.3.1, steps f,q,r).

Hydroxyl-thiother compound **38** has also been obtained from intermediate **2**. The first step is the protection of the alcohol moiety of compound **2** using *tert*-butyl(chloro)diphenylsilyl chloride in presence of imidazole and DMF. Subsequent

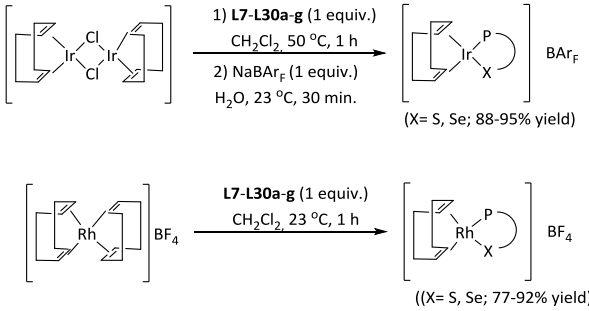
standard acid-catalyzed acetal deprotection provided compound **36** (Scheme 3.3.1, step I, n). After tosylation of the primary alcohol followed by reduction of the tosylated product provided intermediate **37** (Scheme 3.3.1, steps b, a). Mesylation of **37** followed by reaction with NaSPh and subsequent deprotection of protecting group using TBAF provided compound **38** (Scheme 3.3.1, step p, c and g). Finally, hydroxyl-selenoether compound **41** has been prepared following the same synthetic route than the one used for the preparation of compound **31**, changing the nucleophile from NaSPh to Ph_2Se_2.

The last step of the ligand synthesis is common for all of them. Hence, treating the corresponding hydroxyl-thioether/selenoether (**5**-**10**, **12**-**14**, **17**-**19**, **21**, **26**-**33**, **35**, **38** and **41**) with *in situ* generated phosphochloridite ($ClP(OR)_2$; $(OR)_2$ = **a**-**g**) in presence of pyridine provided access to the desired ligands (Scheme 3.3.1, step s). All the ligands were purified on neutral alumina under an argon atmosphere and isolated in moderated-to-good yields as white solids. Advantageously, ligands **L7**-**L30a**-**g** were stable in air so further storage and manipulation were carried out in air. 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 3.3.4). 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 diasteroisomers were not detected by low-temperature ^{31}P NMR.

3.3.2.2. Synthesis of Ir and Rh-catalysts precursors

The Ir-catalysts precursors were prepared by refluxing a dichloromethane solution of the appropriate ligand (**L7**-**L30a**-**g**) 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 3.3.2). All complexes were isolated after extraction as air-stable orange solids and were used without further purification. For the synthesis of the corresponding Rh-catalyst precursors $[Rh(cod)(\mathbf{L})]BF_4$, $[Rh(cod)_2]BF_4$ was reacted with one equivalent of the appropriate ligand and the complexes were isolated in pure form as yellow powders by adding cold hexane (Scheme 3.3.2).

All complexes were characterized by HRSM-ESI, ^{31}P NMR, ^{1}H NMR and ^{13}C NMR. 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 or the BF_4 anion from molecular species. NMR spectra showed the expected pattern for these complexes.



Scheme 3.3.2. Synthesis of Ir- and Rh-catalyst precursors [Ir(cod)(**L7**-**L30a**-**g**)]BAr_F.

3.3.2.3. Asymmetric Hydrogenation of minimally functionalized olefins

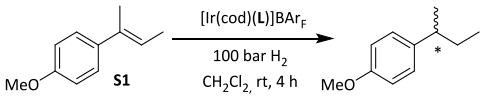
3.3.2.3.1. Hydrogenation of trisubstituted olefins

The potential of phosphite-thioether/selenoether ligands (**L7**-**L30a**-**g**) has been first investigated by applying them in the hydrogenation of the model substrate **S1**, in this way we can compare the results with the ones described in the bibliography.[7k] The results are shown in the Table 3.3.1. They indicate that enantioselectivity is mainly affected by the thioether/selenoether substituents, the substituents and configurations of the alkyl backbone chain next to both the phosphite and the S/Se groups and finally the configuration of the biaryl phosphite moiety. The best result was obtained with ligand **L25f** (ee's up to 87%).

With ligands **L7a**-**g** we first studied the effect of the substituent/configuration of the biaryl phosphite moiety on the catalytic performance (entries 1-7). We found a minor impact on enantioselectivity of the substituents; however, a chiral biaryl phosphite moiety with an (*R*)-configuration is required to achieve the highest enantioselectivities. Comparing ligands **L7**-**L13** we also found that the presence of aromatic thioether substituents has a positive effect on enantioselectivitiy rather than alkyl substituents (i.e. entries 4 vs 9, 12 and 17).The results using ligands **L14** and **L15** indicated that the presence of two methyl substituents in the carbon next to the phosphite moiety had a negative effect on enantioselectivity (entries 24, 25 vs 4 and 5). Similarly, the use of ligands **L16** and **L26**, with substituents in the carbon next to the thioether group, also had a detrimental effect on enantioselectivity (entries 29, 30 and 47-49). Interestingly, the results using ligands **L17** and **L24** indicated that there is a cooperative effect between the configuration of the carbon next to the phosphite group and the ligand backbone that results in a matched combination for ligands **L24** (i.e. entry 44 vs 32). We also studied the effect of the substitution pattern of the chiral carbon next to the phosphite moiety with ligands **L18** and **L20**-**L23**. The results indicated that the presence of a CH_2OTBDMS group has a positive effect on enantioselectivity (i.e. ee's increased from 53% with ligand **L18a** to 73% with **L20a**). This finding led us to synthesize ligand **L25f**, which contains the optimal combination of ligand parameters (phenyl group as a thioether substituent, with the presence of a CH_2TBDMS group in the carbon next to the phosphite moiety with *S* configuration and

chiral biaryl phosphite moiety **f**). As expected this ligand provided the highest enantioselectivity of the series (ee's up to 87%, entry 46). Finally, we also found that the replacement of a thioether moiety by a selenoether group has little effect on enantioselectivity (entries 1, 6-7 vs 50-58).

Table 3.3.1. Results for the Ir-catalyzed hydrogenation of **S1** using the phosphite-thioether ligand library **L7**-**L30a**-**g**.[a]



Entry	Ligand	% Conv[b]	% ee[b]	Entry	Ligand	% Conv[b]	% ee[b]
1	**L7a**	99	6 (*R*)	31	**L17a**	100	58 (*S*)
2	**L7b**	100	5 (*R*)	32	**L17f**	100	58 (*R*)
3	**L7c**	100	6 (*R*)	33	**L17g**	100	44 (*S*)
4	**L7d**	100	66 (*R*)	34	**L18a**	100	53 (*S*)
5	**L7e**	99	29 (*S*)	35	**L18f**	100	61 (*R*)
6	**L7f**	92	53 (*R*)	36	**L18g**	100	41 (*S*)
7	**L7g**	88	40 (*S*)	37	**L19a**	100	72 (*S*)
8	**L8a**	100	19 (*R*)	38	**L20a**	100	73 (*S*)
9	**L8f**	100	38 (*R*)	39	**L20g**	100	44 (*S*)
10	**L8g**	100	45 (*S*)	40	**L21g**	100	60 (*S*)
11	**L9a**	100	0	41	**L22g**	100	50 (*S*)
12	**L9d**	100	33 (*R*)	42	**L22g**	100	64 (*S*)
13	**L9e**	99	10 (*S*)	43	**L23a**	96	47 (*R*)
14	**L10a**	95	25 (*S*)	44	**L24f**	95	70 (*R*)
15	**L10d**	100	69 (*R*)	45	**L24g**	92	47 (*S*)
16	**L10e**	100	70 (*S*)	46	**L25f**	100	87 (*R*)
17	**L11d**	100	21 (*R*)	47	**L26a**	100	3 (*S*)
18	**L11e**	99	11 (*R*)	48	**L26f**	100	24 (*R*)
19	**L12d**	100	50 (*R*)	49	**L26g**	100	28 (*S*)
20	**L12e**	98	31 (*S*)	50	**L27a**	100	5 (*S*)
21	**L13d**	100	60 (*R*)	51	**L27f**	100	52 (*R*)
22	**L13e**	100	35 (*S*)	52	**L27g**	100	47 (*S*)
23	**L14a**	100	25 (*S*)	53	**L28f**	100	44 (*R*)
24	**L14d**	100	27 (*R*)	54	**L28g**	100	43 (*S*)
25	**L14e**	100	36 (*S*)	55	**L29f**	100	37 (*R*)
26	**L15a**	98	19 (*S*)	56	**L29g**	100	51 (*S*)
27	**L15f**	100	32 (*R*)	57	**L30f**	100	70 (*R*)
28	**L15g**	100	31 (*R*)	58	**L30g**	100	7 (*R*)
29	**L16f**	100	13 (*R*)	59[c]	**L20a**	98	72 (*S*)
30	**L16g**	100	10 (*R*)	60[c]	**L25f**	92	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. [c] Reaction carried out at 0.5 mol% of Ir-catalyst precursor.

We also performed the reaction at low catalyst loading (0.5 mol%) using Ir-**L20a** and Ir-**L25f** and enantioselectivities were maintained (entries 59-60).

We next studied the asymmetric hydrogenation of other (*E*)- and (*Z*)-trisubstituted olefins (**S2**-**S18**), including examples containing neighboring polar groups, with ligands **L7**-**L29a**-**g**. Selected results are shown in Table 3.3.2. We found that the correct choice of the ligand is crucial to reach the highest levels of enantioselectivity for each substrate.

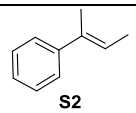
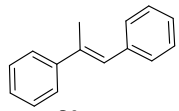
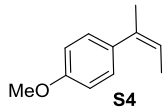
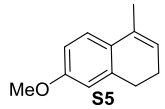
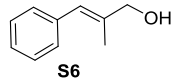
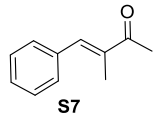
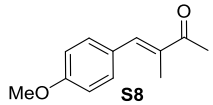
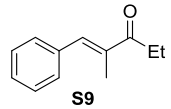
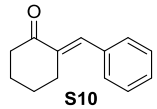
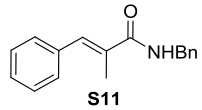
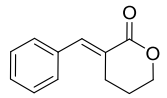
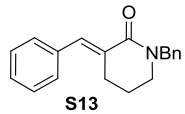
We first studied the reduction of substrates with (*E*)-geometry (**S2**-**S3**), that differ from **S1** in the substituents in both the aryl ring and the substituents *trans* to the aryl group (entries 1 and 2). Enantioselectivities followed the same trends as those observed for substrate **S1**. Enantioselectivities were therefore best with ligand **L25f** (ee's up to 93%). Then, we studied the hydrogenation of (*Z*)-trisubstituted substrates (**S4**-**S5**, entries 3 and 4), which are usually hydrogenated less enantioselectively than the corresponding (*E*)-isomers. The reduction of these substrates proceeded with moderate-to-low enantiocontrol (ee's up to 56%). In contrast to the reduction of previous *E*-substrates, the best enantioselectivities were attained with ligand **L23g**.

We next studied the reduction of a range of trisubstituted olefins containing several types of neighboring poorly coordinative groups (**S6**-**S18**). The hydrogenation of this type of substrates is especially relevant, because they can be further functionalized and could therefore led to important intermediates for the synthesis of more complex chiral molecules.

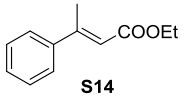
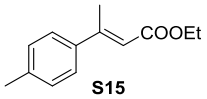
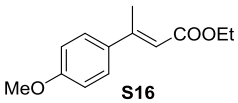
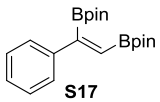
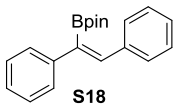
We found that enantioselectivities up to 85% (entry 5) could be achieved in the reduction of allylic alcohol **S6** using Ir-**L29g** catalytic system. A range of α,β-unsaturated ketones (**S7**-**S10**) were also hydrogenated with good enantioselectivities (ee's ranging from 83% to 87%; entries 6-9). Interestingly, the enantioselectivities are highly independent of the nature of the alkyl substituent and the electronic nature of the substrate phenyl ring. This represents an important finding for 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.[11]

α,β-Unsaturated amide **S11**, lactone **S12** and lactame **S13** represent other challenging substrate classes that has been overlooked, despite these motifs are present in several natural products and/or they can be easily transformed into other useful compounds.[12] We were pleased to find out that the reduction of these substrates proceeded with good-to-high enantiocontrol (ee's ranging from 85%-95%, entries 10-12). Interestingly, we could also efficiently hydrogenate a range of α,β-unsaturated esters (**S14**-**S16**; ee's ranging from 96% to 97%, entries 13-15). These results are noteworthy because the resulting chiral carboxylic ester derivatives are present in many relevant products. Finally, we tested our ligand library in the hydrogenation of alkenylboronic esters **S17** and **S18**, since it provides easy access to chiral borane compounds, which are valuable organic intermediates for further functionalization.[7j,9b,13] Full conversions and good-to-high enantioselectivities (up to 87% ee) were achieved.

Table 3.3.2. Results for the hydrogenation of trisubstituted olefins **S2**-**S18** using [Ir(cod)(**L7**-**L30a-g**)]BAr_F catalyst precursors.[a]

Entry	Substrate	Ligand	% Conv[b]	% ee[b]
1	 **S2**	**L25f**	100	69% (*R*)
2	 **S3**	**L25f**	100	76% (*R*)
3	 **S4**	**L23g**	100	56% (*R*)
4	 **S5**	**L23g**	100	21% (*R*)
5	 **S6**	**L29g**	100	85% (*R*)
6	 **S7**	**L30f**	100	84% (*R*)
7	 **S8**	**L30f**	100	87% (*R*)
8	 **S9**	**L30f**	100	83% (*R*)
9	 **S10**	**L30f**	100	85% (*R*)
10	 **S11**	**L24g**	100	85% (*S*)
11	 **S12**	**L30f**	85	94% (*R*)
12	 **S13**	**L24g**	43	95% (*S*)

(Continuation)

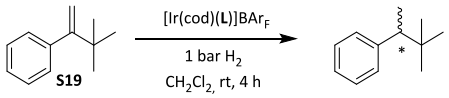
Entry	Substrate	Ligand	% Conv[b]	% ee[b]
13	 **S14**	**L30g**	100	96% (*S*)
14	 **S15**	**L30g**	100	97% (*S*)
15	 **S16**	**L30g**	100	97% (*S*)
16	 **S17**	**L13d**	100	77% (*S*)
17	 **S18**	**L27f**	100	87% (-)

[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.

3.3.2.3.2. Ir-catalyzed hydrogenation of disubstituted olefins

We next screened ligands **L7**-**L30a**-**g** in the asymmetric reduction of much more challenging substrates – the terminal olefins. As already mentioned in Chapter 3.1, disubstituted substrates has not been efficiently hydrogenated until very recently.[14] In a first set of experiments, we studied the potential of phosphite-thioether/selenoether ligands **L7**-**L30a**-**g** in the Ir-catalyzed hydrogenation of 3,3-dimethyl-2-phenyl-1-butene **S19** as a model 1,1-disubstituted substrate (Table 3.3.3). In contrast to trisubstituted olefins, the use of selenoether-based ligands led to lower enantioselectivities than their thioether analogues (i.e. entries 27-28 vs 55-56). We also found that the presence of chiral biaryl phosphite groups is needed for high enantioselectivity. However, in contrast to trisubstituted olefins, both configurations of these biaryl groups led to excellent enantioselectivities, which gives access to both enantiomers of the hydrogenated product (i.e. entries 21 and 22). Regarding the remaining ligand parameters (the nature of thioether substituents and the substituent/configuration of the alkyl backbone chain next to both phosphite and thioether groups) we found little effect on enantioselectivity. In summary, we have been therefore able to fine-tune the ligand parameters to produce both enantiomers of the hydrogenated product using ligands **L13e** and **L26g** (ee's up to 98% in the *R*-enantiomer) and **L13d** and **L16f** (ee's up to 99% in the *S*-enantiomer) at low hydrogen pressures (1 bar).

Table 3.3.3. Results for the Ir-catalyzed hydrogenation of **S19** using the phosphite-thioether ligand library **L7**-**L30a**-**g**.[a]



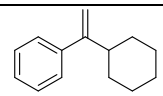
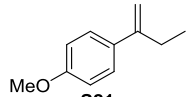
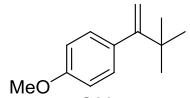
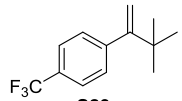
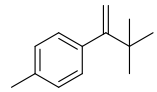
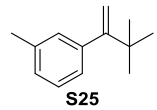
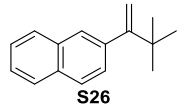
Entry	Ligand	% Conv[b]	% ee[b]	Entry	Ligand	% Conv[b]	% ee[b]
1	**L7a**	94	14 (*S*)	31	**L17a**	100	92 (*R*)
2	**L7b**	97	16 (*S*)	32	**L17f**	92	90 (*S*)
3	**L7c**	75	19 (*S*)	33	**L17g**	100	93 (*R*)
4	**L7d**	100	94 (*S*)	34	**L18a**	100	81 (*R*)
5	**L7e**	65	93 (*R*)	35	**L18f**	100	93 (*S*)
6	**L7f**	100	95 (*S*)	36	**L18g**	100	93 (*R*)
7	**L7g**	60	88 (*R*)	37	**L19a**	100	96 (*R*)
8	**L8a**	100	20 (*S*)	38	**L20a**	100	93 (*R*)
9	**L88f**	100	95 (*S*)	39	**L20g**	100	93 (*R*)
10	**L8g**	100	96 (*R*)	40	**L21g**	100	93 (*R*)
11	**L9a**	55	23 (*S*)	41	**L22g**	100	95 (*R*)
12	**L9d**	100	90 (*S*)	42	**L22g**	100	91 (*R*)
13	**L9e**	96	88 (*R*)	43	**L23a**	100	84 (*S*)
14	**L10a**	100	39 (*R*)	44	**L24f**	100	92 (*S*)
15	**L10d**	100	92 (*S*)	45	**L24g**	100	86 (*R*)
16	**L10e**	100	93 (*R*)	46	**L25f**	100	96 (*S*)
17	**L11d**	100	90 (*S*)	47	**L26a**	100	30 (*R*)
18	**L11e**	100	89 (*R*)	48	**L26f**	100	90 (*S*)
19	**L12d**	100	91 (*S*)	49	**L26g**	100	98 (*R*)
20	**L12e**	100	93 (*R*)	50	**L27a**	100	15 (*R*)
21	**L13d**	100	96 (*S*)	51	**L27f**	100	91 (*S*)
22	**L13e**	100	98 (*R*)	52	**L27g**	100	85 (*R*)
23	**L14a**	100	6 (*R*)	53	**L28f**	100	82 (*S*)
24	**L14d**	100	94 (*S*)	54	**L28g**	100	62 (*R*)
25	**L14e**	100	96 (*R*)	55	**L29f**	100	53 (*S*)
26	**L15a**	100	10 (*R*)	56	**L29g**	100	45 (*R*)
27	**L15f**	100	95 (*S*)	57	**L30f**	100	36 (*S*)
28	**L15g**	100	94 (*R*)	58	**L30g**	100	66 (*R*)
29	**L16f**	100	99 (*S*)	59[c]	**L13e**	91	98 (*R*)
30	**L16g**	100	33 (*R*)	60[c]	**L16f**	88	99 (*S*)

[a] Reactions carried out using 0.5 mmol of **S19** 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.

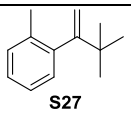
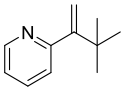
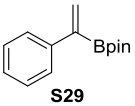
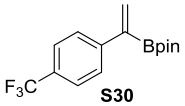
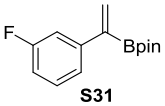
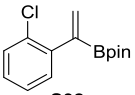
We then investigated the asymmetric hydrogenation of other terminal disubstituted olefins (Table 3.3.4). The results for several α-alkylstyrenes (**S19**-**S21**) indicated that enantioselectivity is affected by the nature of the alkyl chain (ee's ranging from 68% to 99%). This could be due to the competition between direct hydrogenation and isomerization. This is supported by the fact that the hydrogenation of substrate **S17** with a *tert*-butyl group, which cannot isomerize, provides the highest enantioselectivity. We next studied several α-*tert*-butylstyrene type substrates (**S22**-

S27, entries 3-8) to evaluate how the electronic and steric properties of the aryl group of the substrate affected the catalytic performance (entries 3-8). Positively, the results indicate that the substitution pattern and the electronic nature of the substituents have no effect in enantioselectivity (ee's ranging 97% to 99%), albeit the presence of *ortho* substituents at the aryl group has a negative effect on activity (**S27**, entry 8). It is noteworthy that replacing phenyl group by heteroaromatic group the excellent activities and enantioselectivities were maintained (ee's up to 98%; entry 9). This is of great importance because *N*-containing heterocycles are present in many relevant compounds such us pharmaceuticals and natural products. Finally, our ligands have also been tested in the hydrogenation of the aryl-boronic esters **S29-S32,** with enantioselectivities as high as 88% ee (entries 10-13).[7j,9b] In summary, the results obtained in the hydrogenation of 1,1-disubstituted olefins are comparable to the best ones reported in the literature.

Table 3.3.4. Results for the hydrogenation of disubstituted olefins **S20**-**S32** using [Ir(cod)(**L7**-**L30a**-**g**)]BAr_F catalyst precursors.[a]

Entry	Substrate	Ligand	% Conv[b]	% ee[c]
1	 **S20**	**L30g**	100	78% (*R*)
		L16f	100	59% (*S*)
2	 **S21**	**L30g**	100	68% (*R*)
		L16f	100	42% (*S*)
3	 **S22**	**L13e**	100	98% (*R*)
		L16f	100	98% (*S*)
4	 **S23**	**L13e**	100	99% (*R*)
		L16f	100	99% (*S*)
5	 **S24**	**L13e**	100	97% (*R*)
		L16f	100	99% (*S*)
6	 **S25**	**L13e**	100	99% (*R*)
		L16f	100	99% (*S*)
7	 **S26**	**L13e**	100	97% (*R*)
		L16f	100	98% (*S*)

(*Continuation*)

Entry	Substrate	Ligand	% Conv[b]	% ee[c]
8	 **S27**	**L13e** **L16f**	41 29	97% (*R*) 99% (*S*)
9	 **S28**	**L13e** **L16f**	99 100	96% (*R*) 98% (*S*)
10	 **S29**	**L28f** **L16g**	100 100	80% (*R*) 86% (*S*)
11	 **S30**	**L28f** **L16g**	100 100	81% (*R*) 82% (*S*)
12	 **S31**	**L28f** **L16g**	100 100	79% (*R*) 86% (*S*)
13	 **S32**	**L28f** **L16g**	100 100	81% (*R*) 88% (*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] Reaction carried out at 0.5 mol% of Ir-catalyst precursor

3.3.2.4. Asymmetric hydrogenation of functionalized olefins

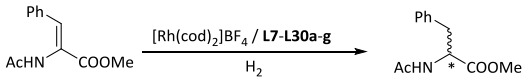
3.3.2.4.1. Rh-catalyzed hydrogenation of α-dehydroamino acid derivatives **S33** and **S34**

Encouraged by the high enantioselectivities achieved in the reduction of minimally functionalized olefins, we decided to apply our ligands in the Rh-catalyzed hydrogenation of functionalized olefins in order to further evaluate their versatility. Initially, we studied if there is any effect on the catalytic outcome of using the isolated precatalysts or the in situ formed catalyst precursors (by adding the corresponding ligands to $[Rh(cod)_2]BF_4$). The results indicated that there is no need to synthesize and isolate the precatalysts prior to use (see Supporting Information). The next reactions were therefore performed at room temperature in dichloromethane using 1 mol % of the corresponding in situ prepared catalyst precursors.

Initially, we studied the Rh-catalyzed hydrogenation of the model substrate **S33** to evaluate the potential of the **L7**-**L30a**-**g** ligand library (Table 3.3.5). Results again indicated that enantioselectivity is affected by different ligand parameters, being the most crucial ones the thioether/selenoether substituents, the different substituents and configurations of the alkyl backbone chain next to both, phosphite moiety and S/Se group and finally the configuration of the biaryl moiety. However, the effect of these parameters on enantioselectivity was different from previous minimally

functionalized olefins. In this case, the introduction of two methyl substituents at the carbon adjacent to the phosphite moiety (ligands **L14** and **L15**; entries 24 and 27 vs 4 and 21) enhanced enantioselectivity considerably.

Table 3.3.5. Selected results for the Rh-catalyzed hydrogenation of **S33** using the phosphite-thioether ligand library **L7**-**L30a**-**g**.[a]



S33

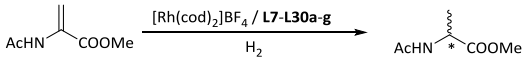
Entry	Ligand	% Conv[b]	% ee[b]	Entry	Ligand	% Conv[b]	% ee[b]
1	**L7a**	99	48 (*R*)	31	**L17a**	100	60 (*S*)
2	**L7b**	100	40 (*R*)	32	**L17f**	100	84 (*R*)
3	**L7c**	100	30 (*R*)	33	**L17g**	100	93 (*S*)
4	**L7d**	100	68 (*R*)	34	**L18a**	100	59 (*S*)
5	**L7e**	100	21 (*S*)	35	**L18f**	100	89 (*R*)
6	**L7f**	100	78 (*R*)	36	**L18g**	100	96 (*S*)
7	**L7g**	100	64 (*S*)	37	**L19a**	100	55 (*S*)
8	**L8a**	92	21 (*R*)	38	**L20a**	100	58 (*S*)
9	**L88f**	100	42 (*R*)	39	**L20g**	100	95 (*S*)
10	**L8g**	100	19 (*S*)	40	**L21g**	100	96 (*S*)
11	**L9a**	100	9 (*R*)	41	**L22g**	100	98 (*S*)
12	**L9d**	100	55 (*R*)	42	**L22g**	100	95 (*S*)
13	**L9e**	100	35 (*S*)	43	**L23a**	100	16 (*S*)
14	**L10a**	82	8 (*S*)	44	**L24f**	100	95 (*R*)
15	**L10d**	96	28 (*S*)	45	**L24g**	100	70 (*S*)
16	**L10e**	95	11 (*R*)	46	**L25f**	100	96 (*R*)
17	**L11d**	100	59 (*R*)	47	**L26a**	100	13 (*S*)
18	**L11e**	100	51 (*S*)	48	**L26f**	100	34 (*R*)
19	**L12d**	100	54 (*R*)	49	**L26g**	100	63 (*S*)
20	**L12e**	100	18 (*S*)	50	**L27a**	100	39 (*R*)
21	**L13d**	100	83 (*R*)	51	**L27f**	100	75 (*R*)
22	**L13e**	100	16 (*S*)	52	**L27g**	100	64 (*S*)
23	**L14a**	100	36 (*R*)	53	**L28f**	100	81 (*R*)
24	**L14d**	100	96 (*R*)	54	**L28g**	100	23 (*S*)
25	**L14e**	100	34 (*S*)	55	**L29f**	100	90 (*R*)
26	**L15a**	100	29 (*R*)	56	**L29g**	100	48 (*S*)
27	**L15f**	100	91 (*R*)	57	**L30f**	100	85 (*R*)
28	**L15g**	100	34 (*S*)	58	**L30g**	100	92 (*S*)
29	**L16f**	100	61 (*R*)	59[c]	**L22g**	100	99 (*S*)
30	**L16g**	100	29 (*S*)	60[c]	**L24f**	100	98 (*R*)

[a] Reactions conditions: $[Rh(cod)_2]BF_4$ (1 mol%), ligand (1 mol%), **S33** (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. [c] Reaction carried out at 5 ˚C for 20 h.

Another important feature is that there is a cooperative effect between the configurations of the carbon adjacent to the phosphite group and that of the phosphite moiety, which results in a matched combination for ligands **L17**-**L23g** and

L24-**L25f**. Interestingly, each of these ligand combinations led to opposite enantiomers of the hydrogenated product. Thus, by correctly choosing the ligand parameters, we were able to achieve full conversion and both enantiomers of the hydrogenation product in high enantioselectivity (ee's up to 98%) using Rh-**L22g** and Rh-**L25f** catalytic systems (entries 41 and 46). This result clearly shows the efficiency of using highly modular scaffolds for the ligand design. Enantioselectivities were further improved to 99% ee by lowering the reaction temperature (entries 59 and 60).

Table 3.3.6. Selected results for the Rh-catalyzed hydrogenation of **S34** using the phosphite-thioether ligand library **L7**-**L30a**-**g**.[a]



S34

Entry	Ligand	% Conv[b]	% ee[b]	Entry	Ligand	% Conv[b]	% ee[b]
1	**L7a**	100	37 (*R*)	31	**L17a**	100	18 (*R*)
2	**L7b**	100	15 (*R*)	32	**L17f**	100	43 (*R*)
3	**L7c**	100	19 (*S*)	33	**L17g**	100	56 (*S*)
4	**L7d**	100	45 (*R*)	34	**L18a**	100	22 (*R*)
5	**L7e**	100	15 (*R*)	35	**L18f**	100	39 (*R*)
6	**L7f**	100	55 (*R*)	36	**L18g**	100	60 (*S*)
7	**L7g**	100	11 (*R*)	37	**L19a**	100	19 (*R*)
8	**L8a**	100	13 (*R*)	38	**L20a**	100	21 (*R*)
9	**L88f**	100	21 (*R*)	39	**L20g**	100	56 (*S*)
10	**L8g**	100	2 (*S*)	40	**L21g**	100	58 (*S*)
11	**L9a**	100	9 (*S*)	41	**L22g**	100	57 (*S*)
12	**L9d**	100	50 (*S*)	42	**L22g**	100	56 (*S*)
13	**L9e**	100	17 (*R*)	43	**L23a**	100	38 (*R*)
14	**L10a**	100	43 (*S*)	44	**L24f**	100	49 (*R*)
15	**L10d**	100	53 (*S*)	45	**L24g**	100	56 (*S*)
16	**L10e**	100	18 (*R*)	46	**L25f**	100	48 (*R*)
17	**L11d**	100	43 (*S*)	47	**L26a**	100	28 (*R*)
18	**L11e**	100	18 (*R*)	48	**L26f**	100	60 (*R*)
19	**L12d**	100	29 (*R*)	49	**L26g**	100	49 (*S*)
20	**L12e**	100	19 (*R*)	50	**L27a**	100	24 (*R*)
21	**L13d**	99	17 (*R*)	51	**L27f**	100	58 (*R*)
22	**L13e**	100	48 (*R*)	52	**L27g**	100	18 (*R*)
23	**L14a**	100	58 (*R*)	53	**L28f**	100	41 (*R*)
24	**L14d**	100	45 (*R*)	54	**L28g**	100	19 (*R*)
25	**L14e**	100	81 (*S*)	55	**L29f**	100	50 (*R*)
26	**L15a**	100	42 (*R*)	56	**L29g**	100	86 (*S*)
27	**L15f**	100	54 (*R*)	57	**L30f**	100	44 (*R*)
28	**L15g**	100	80 (*S*)	58	**L30g**	100	62 (*S*)
29	**L16f**	100	26 (*R*)	59[c]	**L29g**	100	91 (*S*)
30	**L16g**	100	14 (*S*)	60[d]	**L29g**	100	92 (*S*)

[a] Reactions conditions: $[Rh(cod)_2]BF_4$ (1 mol%), ligand (1 mol%), **S34** (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. [c] Reaction carried out at 10 °C for 20 h. [d] Reaction carried out at 5 °C for 20 h.

Next, we screened ligands **L7**-**L30a**-**g** in the asymmetric reduction of methyl 2-acetamidoacrylate **S34**, which differs from previous substrate in the lack of the phenyl group (Table 3.3.6). The effect of the ligand parameters is similar to that observed for the related substrate **S33**, except that the replacement of the thioether by a selenoether moiety has a positive effect of enantioselectivity. Thus, the highest enantioselectivity (up to 86% ee) was achieved using phosphite-selenoether ligand **L29g** (entry 56). Again enantioselectivity could be further improved (up to 92% ee) by lowering the reaction temperature (entry 60).

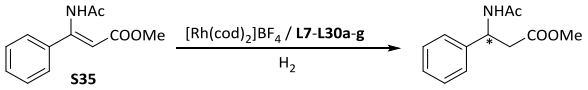
3.3.2.4.2. Rh-catalyzed asymmetric hydrogenation of β-dehydroamino acid derivatives **S35**-**S40**

Encourage by the high enantioselectivities achieved in the α-dehydroamino acid derivatives, we then moved to investigate the effect of the different ligands **L7-L30a-g** in the hydrogenation of a more challenging functionalized substrates – the β-dehydroamino acid derivatives with (Z)-geometry.[15] The hydrogenation of this sort of substrates provides much lower enantioselectivities than their (*E*)-analogues, which represents a drawback because their hydrogenation products are common motifs in biologically active compounds.[16]

We first screened ligands **L7**-**L30a**-**g** in the Rh-catalyzed hydrogenation of model (*Z*)-substrate **S35** (Table 3.3.7). The sense of the enantioselectivity is controlled by the configuration of the biaryl phosphite moiety. So, ligands containing (*R*)-biaryl phosphite moiety (**f**) led to (*S*)-hydrogenated products (entry 1) and vice versa, ligands containing (*S*)-biaryl phosphite moiety (**g**) led to (*R*)-hydrogenated products (entry 2). Although, slightly higher enantioselectivities are achieved with ligands which contain (*S*)-biaryl phosphite moieties. We also found that the introduction of an stereocenter in the carbon next to the phosphite moiety (**L17**-**L25**) increases substantially the enantioselectivity values (entries 7-13). In summary, both enantiomers of the hydrogenation product are accessible with similar good enantioselectivities (ee's up to 87%) using Rh-**L17g,** Rh-**L24g** and Rh-**L25f** catalytic systems (entries 8, 12 and 13).

Then, we evaluated the applicability of ligands **L24g** and **L25f** in a range of β-dehydroamino acid derivatives (**S36**-**S40**). The results are found in Table 3.3.8. As expected, the enantioselectivity is strongly affected by the nature of the β-dehydroamino acid substituents and of the ester substituent. Thus, as expected enantioselectivity is negatively affected when either using less sterically hindered β-dehydroamino acid substituents (entries 1-3) or increasing the size of ester substituent (entries 3, 5 and 6).

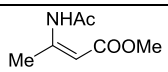
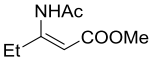
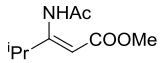
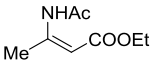
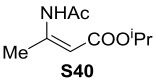
Table 3.3.7. Selected results for the Rh-catalyzed hydrogenation of **S35** using the phosphite-thioether ligand library **L7**-**L30a**-**g**.[a]



Entry	Ligand	% Conv[b]	% ee[b]
1	**L7f**	60	70 (*S*)
2	**L7g**	55	79 (*R*)
3	**L8f**	65	29 (*S*)
4	**L8g**	45	63 (*R*)
5	**L14f**	100	75 (*S*)
6	**L14g**	100	20 (*R*)
7	**L17f**	100	70 (*S*)
8	**L17g**	100	86 (*R*)
9	**L18g**	100	60 (*R*)
10	**L20g**	100	74 (*R*)
11	**L24f**	100	80 (*S*)
12	**L24g**	100	86 (*R*)
13	**L25f**	100	87 (*S*)
14	**L26f**	100	39 (*S*)
15	**L26g**	100	49 (*R*)
16	**L29f**	100	76 (*S*)
17	**L29g**	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.

Table 3.3.8. Asymmetric hydrogenation of β-dehydroamino acid esters **S36**-**S40** using Rh-**L24g** and Rh-**L25f** catalysts precursor.[a]

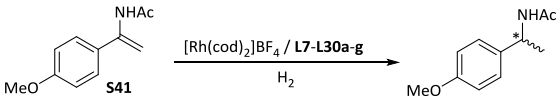
Entry	Substrate	Ligand	% Conv[b]	% ee[b]
1	 **S36**	**L24g**	61	47% (*R*)
2	 **S37**	**L24g**	92	63% (*R*)
3		**L24g**	100	70% (*S*)
4	**S38**	**L25f**	100	72% (*R*)
5	 **S39**	**L24g**	75	32% (*R*)
6	 **S40**	**L24g**	21	14% (*S*)

[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.

3.3.2.4.3. Asymmetric hydrogenation of α-enamides **S41**-**S45**

Finally, we investigated the effect of the different ligands **L7-L30a-g** in the hydrogenation of α-enamides **S41**-**S45**. The hydrogenated products obtained from the reduction of this type of substrates give optically active secondary amines, which are useful building blocks for the synthesis of fine chemicals.[17]

Table 3.3.9. Selected results for the Rh-catalyzed hydrogenation of **S41** using the phosphite-thioether ligand library **L7**-**L30a**-**g**.[a]



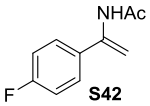
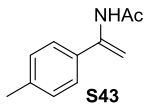
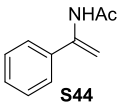
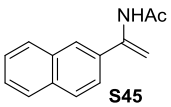
Entry	Ligand	% Conv[b]	% ee[b]	Entry	Ligand	% Conv[b]	% ee[b]
1	**L7a**	100	32 (*R*)	30	**L16g**	100	58 (*S*)
2	**L7b**	100	30 (*R*)	31	**L17a**	100	70 (*S*)
3	**L7c**	100	31 (*R*)	32	**L17f**	100	75 (*R*)
4	**L7d**	100	54 (*R*)	33	**L17g**	100	63 (*S*)
5	**L7e**	100	31 (*S*)	34	**L18a**	100	70 (*S*)
6	**L7f**	100	51 (*R*)	35	**L18f**	100	67 (*R*)
7	**L7g**	100	40 (*S*)	36	**L18g**	100	72 (*S*)
8	**L8a**	100	15 (*R*)	37	**L19a**	100	87 (*S*)
9	**L88f**	100	19 (*R*)	38	**L20a**	100	86 (*S*)
10	**L8g**	100	12 (*S*)	39	**L20g**	100	90 (*S*)
11	**L9a**	100	33 (*S*)	40	**L21g**	100	92 (*S*)
12	**L9d**	100	14 (*R*)	41	**L22g**	100	89 (*S*)
13	**L9e**	100	29 (*S*)	42	**L22g**	100	91 (*S*)
14	**L10a**	100	19 (*S*)	43	**L23a**	100	59 (*R*)
15	**L10d**	100	8 (*R*)	44	**L24f**	100	81 (*R*)
16	**L10e**	100	19 (*S*)	45	**L24g**	100	46 (*S*)
17	**L11d**	100	52 (*R*)	46	**L26a**	100	14 (*R*)
18	**L11e**	100	30 (*S*)	47	**L26f**	100	27 (*R*)
19	**L12d**	100	59 (*R*)	48	**L26g**	100	35 (*S*)
20	**L12e**	100	29 (*S*)	49	**L27a**	100	35 (*R*)
21	**L13d**	100	25 (*R*)	50	**L27f**	100	54 (*R*)
22	**L13e**	100	19 (*S*)	51	**L27g**	100	43 (*S*)
23	**L14a**	100	13 (*R*)	52	**L28f**	100	48 (*R*)
24	**L14d**	100	84 (*R*)	53	**L28g**	100	36 (*S*)
25	**L14e**	100	11 (*S*)	54	**L29f**	100	80 (*R*)
26	**L15a**	100	46 (*R*)	55	**L29g**	100	29 (*S*)
27	**L15f**	100	84 (*R*)	56	**L30f**	100	79 (*R*)
28	**L15g**	100	13 (*S*)	57	**L30g**	100	90 (*S*)
29	**L16f**	100	46 (*R*)	58[c]	**L21g**	100	96 (*S*)

[a] Reactions conditions: $[Rh(cod)_2]BF_4$ (1 mol%), ligand (1 mol%), **S43** (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. [C] Reaction carried out at 0 ˚C for 36 h.

To study the effect of the different ligand parameters on catalytic performance, we first studied the Rh-catalyzed hydrogenation of the model substrate N-(1-(4-methoxyphenyl)vinyl)-acetamide **S41** under standard conditions (Table 3.3.9).[18] The results again indicate that effect of the different ligand parameters on enantioselectivity is different from those observed for the previous substrates. Thus, albeit the use of ligands **L17**-**L23g**, with an (*R*)-configured carbon adjacent to the phosphite group and an *R*-biaryl phosphite group, had a positive effect on enantioselectivity (i.e. entries 32 and 33 vs 6 and 7); similar high ee's were obtained with ligands **L19g**, with an (*S*)-configured carbon adjacent to the thioether group (entry 42 vs 40). Thus, in summary, by correctly choosing the ligand parameters, we were able to achieve full conversion and high enantioselectivity (ee's up to 96%; entry 58) using Rh-**L21g** catalytic system.

We then extended the use of the previous optimized system Rh-**L21g** in the hydrogenation of others α-enamides (**S42**-**S45**, Table 3.3.10). The results indicated that the catalytic performance is hardly affected by the electron nature of the aryl substituent (ee's ranging from 93% to 97%), albeit the highest enantioselectivity of the series was achieved for substrate **S42**, which contains an electronwithdrawing group in the *para* position of the aryl group (entry 1).

Table 3.3.10. Asymmetric hydrogenation of α-aryl enamides **S42**-**S45** using Rh-**L21g** catalyst precursor.[a]

Entry	Substrate	% Conv[b]	% ee[b]
1	 **S42**	100	97% (*S*)
2	 **S43**	100	93% (*S*)
3	 **S44**	100	94% (*S*)
4	 **S45**	100	96% (*S*)

[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), 36 h at 0 °C. [b] Conversion and enantiomeric excesses determined by chiral GC.

3.3.3. Conclusions

A highly modular new class of phosphite-thioether/selenoether ligand library has been applied in the Ir-catalyzed hydrogenation of minimally functionalized olefins and in the Rh-catalyzed hydrogenation of functionalized olefins. These ligands have been easily synthesized from the readily available and inexpensive L-(+)-tartaric acid and D-mannitol on a big scale. They have the advantage of the robustness of the thioether/selenoether moieties and the extra control provided by the flexibility of the chiral pocket through the presence of a biaryl phosphite group and a modular carbohydrate-derived backbone. The catalytic results indicated that enantioselectivity is highly affected by the ligand parameters as well as the substrate. In every type of substrates the effects of the parameters have a different influence on the enantioselectivity. Moderate enantioselectivities were achieved in the Ir-catalyzed hydrogenation of model (*E*)- and (*Z*)-trisubstituted olefins, but 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. For the Rh-catalyzed hydrogenation of the α- and β-dehydroamino acid esters and α-enamides good-to-excellent ee values have been achieved. To sum up, these easily prepared ligand family can be applied with high results in the hydrogenation of a wide range of substrate classes, which clearly shows their high versatility.

3.3.4. Experimental part

3.3.4.1. 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.[19] Compounds **1**,[20] **2**,[21] **3**,[22] **4**,[23] **5**,[23] 2,3-*O*-isopropylidene-1-*O*-(*tert*-butyldimethylsilyl)-L-threitol[24] and 1-deoxy-2,3-*O*-isopropylidene-1-tosyl-D-arabinitol[25] were prepared as previously described. All other reagents were used as commercially available. ^{1}H, $^{13}C\{^{1}H\}$, $^{31}P\{^{1}H\}$ NMR spectra experiments 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 done based on ^{1}H-^{1}H gCOSY and ^{1}H-^{13}C gHSQC experiments.

3.3.4.2. General procedure for the preparation of phosphite-thioether/selenoether ligands L7-L29a-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 **L19**-**23a**-**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 **L14**-**L15**, **26a**-**g**, triethylamine (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.

L7a. 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].

L7b. 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].

L7c. 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-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, $C_{31}H_{41}O_5PSSi_2$ $(M-Na)^+$ requires 635.1843].

L7d. 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). ^1H 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, $^2J_{H-H}$= 13.6 Hz, $^3J_{H-H}$= 6 Hz, CH_2-S), 2.97 (dd, 1H, $^2J_{H-H}$= 13.6 Hz, $^3J_{H-H}$= 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-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, $C_{37}H_{49}O_5PS$ $(M-Na)^+$ requires 659.2931].

L7e. 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). ^1H 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, $^2J_{H-H}$= 13.6 Hz, $^3J_{H-H}$= 6.4 Hz, CH_2-S), 2.96 (dd, 1H, $^2J_{H-H}$= 13.2 Hz, $^3J_{H-H}$= 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-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, $C_{37}H_{49}O_5PS$ $(M-Na)^+$ requires 659.2931]..

L7f. 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). ^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), 1.30 (s, 3H, CH_3), 2.77 (dd, 1H, CH_2-S, $^2J_{H-H}$ =13.2 Hz, $^3J_{H-H}$ =6.0 Hz), 2.95 (dd, 1H, CH_2-S, $^2J_{H-H}$ =13.6 Hz, $^2J_{H-H}$ =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=, $^3J_{H-H}$ =8.4 Hz), 7.34 (d, 1H, CH=, $^3J_{H-H}$ =8.4 Hz), 7.70 (d, 2H, CH=, $^3J_{H-H}$ =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-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, $C_{39}H_{45}O_5PSSi_2$ $(M-Na)^+$ requires 735.2156].

L7g. 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). ^1H 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].

L8a. 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].

L8a. 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].

L8f. 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].

L8g. 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). ^{1}H 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].

L9d. 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). ^{1}H 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].

L9e. 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). ^{1}H 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].

L10a. 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). ^{1}H 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$_2$S), 80.2 (d, *C*HCH$_2$O, $J_{C\text{-}P}$= 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-Na)$^+$ requires 743.3870].

L10d. Yield: 315 mg (47%); SiO$_2$-flash chromatography (toluene/hexane/NEt$_3$ = 5:5:0.1). ^{31}P NMR (400 MHz, C$_6$D$_6$) δ: 125.4 (s). ^{1}H NMR (C$_6$D$_6$), 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$_2$O), 3.88-3.93 (m, 1H, C*H*CH$_2$S), 4.13-4.19 (m, 1H, CH$_2$-O), 6.86-7.18 (m, 5H, CH=). ^{13}C NMR (C$_6$D$_6$), 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$_2$S), 79.5 (d, *C*HCH$_2$O, $J_{C\text{-}P}$= 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-Na)$^+$ requires 687.3244].

L10e. Yield: 297 mg (45%); SiO$_2$-flash chromatography (toluene/hexane/NEt$_3$ = 5:5:0.1). ^{31}P NMR (400 MHz, C$_6$D$_6$) δ: 128.0 (s). ^{1}H NMR (C$_6$D$_6$), 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$_2$O), 3.84-3.89 (m, 1H, C*H*CH$_2$S), 4.06-4.12 (m, 1H, CH$_2$-O), 6.84-7.11 (m, 5H, CH=). ^{13}C NMR (C$_6$D$_6$), 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$_2$S), 79.4 (d, *C*HCH$_2$O, $J_{C\text{-}P}$= 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-Na)$^+$ requires 687.3244].

L11d. Yield: 381 mg (62%); SiO$_2$-flash chromatography (toluene/hexane/NEt$_3$ = 5:5:0.1). ^{31}P NMR (400 MHz, C$_6$D$_6$) δ: 128.6 (s). ^{1}H NMR (C$_6$D$_6$), 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$_2$O), 4.05-4.10 (m, 1H, C*H*CH$_2$S), 4.39-4.45 (m, 1H, CH$_2$-O), 6.99-7.25 (m, 2H, CH=). ^{13}C NMR (C$_6$D$_6$), 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$_2$S), 81.0 (d, *C*HCH$_2$O, $J_{C\text{-}P}$= 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-Na)$^+$ requires 717.3713].

L11e. Yield: 331 mg (54%); SiO$_2$-flash chromatography (toluene/hexane/NEt$_3$ = 5:5:0.1). ^{31}P NMR (400 MHz, C$_6$D$_6$) δ: 125.8 (s). ^{1}H NMR (C$_6$D$_6$), 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].

L12d. 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].

L12e. 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].

L13d. 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_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-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].

L13e. 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, $^2J_{H-H}$= 13.6 Hz, $^3J_{H-H}$= 5.6 Hz, CH_2-S), 3.11 (dd, 1H, $^2J_{H-H}$= 13.6 Hz, $^3J_{H-H}$= 5.2 Hz, CH_2-S), 3.63-3.68 (m, 1H, CH_2-O), 3.94-3.99 (m, 1H, C*H*CH_2O), 4.04-4.09 (m, 1H, C*H*CH_2S), 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_2S), 79.6 (d, *C*HCH_2O, J_{C-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].

L14a. 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, $^2J_{H-H}$= 14.8 Hz, $^3J_{H-H}$= 7.6 Hz, CH_2-S), 3.07 (dd, 1H, $^2J_{H-H}$= 14.8 Hz, $^3J_{H-H}$= 2.4 Hz, CH_2-S), 3.88-3.91 (m, 1H, C*H*CMe_2O), 4.22-4.28 (m, 1H, C*H*CH_2S), 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_2S), 79.9 (*C*Me_2O), 84.5 (d, *C*HCMe_2O, J_{C-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].

L14d. 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, $^2J_{H-H}$= 14.8 Hz, $^3J_{H-H}$= 6.8 Hz, CH_2-S), 2.93 (dd, 1H, $^2J_{H-H}$= 14.8 Hz, $^3J_{H-H}$= 2.8 Hz, CH_2-S), 4.06 (d, 1H, $^3J_{H-H}$= 4 Hz, C*H*CMe_2O), 4.20-4.25 (m, 1H, C*H*CH_2S), 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_2S), 79.9 (d, *C*Me_2O, $J_{C\text{-}P}$= 11.4 Hz), 84.4 (*C*HCMe_2O), 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].

L14e. 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). ^{1}H 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, $^2J_{H\text{-}H}$= 14.8 Hz, $^3J_{H\text{-}H}$= 9.6 Hz, CH_2-S), 2.94 (dd, 1H, $^2J_{H\text{-}H}$= 14.8 Hz, $^3J_{H\text{-}H}$= 1.6 Hz, CH_2-S), 3.76 (d, 1H, $^3J_{H\text{-}H}$= 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, $J_{C\text{-}P}$= 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].

L15a. 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). ^{1}H 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, $^2J_{H\text{-}H}$ =14.6 Hz, $^3J_{H\text{-}H}$ =7.7 Hz), 3.21 (dd, 1H, CH_2-S, $^2J_{H\text{-}H}$ =14.5 Hz, $^3J_{H\text{-}H}$ =2.6 Hz), 3.97 (d, 1H, $CHCMe_2O$, $^3J_{H\text{-}H}$ =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].

L15f. 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). ^{1}H 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, $^4J_{H\text{-}H}$ =2.4 Hz), 2.48 (dd, 1H, CH_2-S, $^2J_{H\text{-}H}$ =14.0 Hz, $^3J_{H\text{-}H}$ =7.2 Hz), 2.63 (dd, 1H, CH_2-S, $^2J_{H\text{-}H}$ =14.4 Hz, $^3J_{H\text{-}H}$ =3.2 Hz), 3.97 (d, 1H, C*H*CMe_2O, $^3J_{H\text{-}H}$ =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=, $^3J_{H\text{-}H}$ =7.6 Hz), 7.41 (d, 1H, CH=, $^3J_{H\text{-}H}$ =8.8 Hz), 7.47-7.70 (m, 4H, CH=), 7.69 (d, 1H, CH=, $^3J_{H\text{-}H}$ =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, $SiMe_3$, $J_{C\text{-}P}$ =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, $^3J_{C\text{-}P}$ =18.4 Hz), 37.7 (CH_2-S), 77.3 (*C*HCH_2S), 80.9 (d, CMe_2-O, $^2J_{C\text{-}P}$ =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].

L15g. 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). ^{1}H 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, $^{2}J_{H-H}$ =14.4 Hz, $^{3}J_{H-H}$ =8.4 Hz), 2.96 (d, 1H, CH_2-S, $^{2}J_{H-H}$ =14.8 Hz), 3.95 (d, 1H, C*H*CMe_2O, $^{3}J_{H-H}$ =8.0 Hz), 4.15 (pt, 1H, C*H*CH_2S, $^{3}J_{H-H}$ =8.0 Hz), 6.43 (pt, 1H, CH=, $^{3}J_{H-H}$ =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_2O), 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].

L16f. 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, $CHCMe_2S$, $^{3}J_{H-H}$ =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_2S), 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].

L16g. 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, $CHCMe_2S$, $^{3}J_{H-H}$ =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_2S), 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].

L17a. 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, $^3J_{C-P}$ =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, $^2J_{C-P}$ =6.1 Hz), 78.4 (*C*HCH_2S), 82.6 (d, *C*HCHO, $^3J_{C-P}$ = 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].

L17f. 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, $^3J_{H-H}$ =6.4 Hz), 2.33 (dd, 1H, CH_2-S, $^2J_{H-H}$ =13.6 Hz, $^2J_{H-H}$ =4.3 Hz), 2.40 (dd, 1H, CH_2-S, $^2J_{H-H}$ =14.0 Hz, $^2J_{H-H}$ =3.6 Hz), 3.83 (pt, 1H, C*H*CHO, $^3J_{H-H}$ =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=, $^3J_{H-H}$ =8.8 Hz), 7.33 (d, 1H, CH=, $^3J_{H-H}$ =8.4 Hz), 7.69 (dd, 2H, CH=, $^3J_{H-H}$ =10.8 Hz, $^3J_{H-H}$ =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, $^2J_{C-P}$ = 4.6 Hz), 77.4 (*C*HCH_2S), 81.2 (d, *C*HCHO, $^3J_{C-P}$ =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].

L17g. 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, $^3J_{H-H}$ =6.8 Hz), 1.32 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 3.00 (d, 2H, CH_2-S, $^3J_{H-H}$ =5.6 Hz), 3.93 (dd, 1H, C*H*CHO, $^3J_{H-H}$ =5.6 Hz, $^3J_{H-H}$ =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=, $^3J_{H-H}$ =8.8 Hz), 7.69 (dd, 2H, CH=, $^3J_{H-H}$ =6.4 Hz, $^4J_{H-H}$ =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, $^2J_{C-P}$ = 6.9 Hz), 77.1 (*C*HCH_2S), 82.9 (d, *C*HCHO, $^3J_{C-P}$ =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].

L18a. 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, $^2J_{H-H}$ =14.4 Hz, $^3J_{H-H}$ =5.6 Hz), 3.17 (dd, 1H, CH_2-S, $^2J_{H-H}$ =14.4 Hz, $^3J_{H-H}$ =4.4 Hz), 3.97 (pt, 1H, C*H*CHO, $^3J_{H-H}$ =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=, $^4J_{H-H}$ = 2.4 Hz), 7.60 (d, 1H, CH=, $^4J_{H-H}$ = 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, $^3J_{C-P}$ =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, $^2J_{C-P}$ =4.6 Hz), 78.4 (*C*HCH_2S), 82.7 (d, *C*HCHO, $^3J_{C-P}$ = 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].

L18f. 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_2S), 82.2 (*C*HCHO), 109.5 (CMe_2), 124.9-152.0 (aromatic carbons). MS HR-ESI [found 799.2460, $C_{44}H_{49}O_5PSSi_2$ $(M\text{-}Na)^+$ requires 799.2475].

L18g. 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_2S), 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_2S), 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, $C_{44}H_{49}O_5PSSi_2$ $(M\text{-}Na)^+$ requires 799.2475].

L19a. 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_2S, 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_2S), 109.5 (CMe_2), 123.9-146.6 (aromatic carbons). MS HR-ESI [found 879.4215, $C_{50}H_{69}O_6PSSi$ $(M\text{-}Na)^+$ requires 879.4214].

L19f. 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, $^2J_{H-H}$ =14.0 Hz, $^3J_{H-H}$ =4.4 Hz), 2.37 (dd, 1H, CH_2-S, $^2J_{H-H}$ =14.4 Hz, $^3J_{H-H}$ =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_2S), 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=, $^3J_{H-H}$ =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_2S), 110.4 (CMe_2), 122.7-152.1 (aromatic carbons). MS HR-ESI [found 879.3124, $C_{46}H_{61}O_6PSSi_3$ $(M\text{-}Na)^+$ requires 879.3132].

L20a. 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].

L20g. 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].

L21g. 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). ^1H 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_2S), 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].

L22g. 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_2S), 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_2S), 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].

L23g. 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_2S), 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_2S), 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

L24a. 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 ^tBu), 1.35 (s, 3H, CH_3), 1.57 (s, 18H, CH_3, ^tBu), 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_2S), 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, ^tBu), 34.3 (C, ^tBu), 35.3 (C, ^tBu), 36.8 (CH_2-S), 71.0 (d, CH-O, $^2J_{C-P}$ =1.7 Hz), 75.5 (*C*HCH_2S), 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].

L24f. 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].

L24g. 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). ^1H 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].

L25f. Yield: 101 mg (25%). SiO_2-flash chromatography (toluene/hexane/NEt_3 = 6:4:0.1). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 144.4 (s). ^1H NMR ($CDCl_3$), δ: -0.43 (s, 3H, CH_3, OTBDMS), -0.40 (s, 3H, CH_3, OTBDMS), 0.45 (s, 9H, CH_3, $SiMe_3$), 0.54 (s, 9H, CH_3, $SiMe_3$), 0.69 (s, 9H, CH_3, ^tBu, OTBDMS), 1.41 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 2.99 (m, 1H, CH_2-O), 3.18 (m, 1H, CH_2-S), 3.30 (m, 1H, CH_2-S), 3.57 (m, 1H, CH_2-O), 4.47 (m, 3H, C*H*CHO, C*H*CH_2S, CHO), 6.85 (m, 2H, CH=), 6.97 (m, 2H, CH=), 7.10 (m, 2H, CH=), 7.22 (m, 1H, CH=), 7.32 (m, 2H, CH=), 7.69 (m, 3H, CH=), 8.08 (m, 3H, CH=). ^{13}C NMR ($CDCl_3$), δ: -6.2 (CH_3, OTBDMS), -6.1 (CH_3, OTBDMS), -1.1 (CH_3, $SiMe_3$), -0.1 (CH_3, $SiMe_3$), 0.0 (CH_3,

$SiMe_3$), 0.2 (CH_3, $SiMe_3$), 1.1 (CH_3, $SiMe_3$), 1.2 (CH_3, $SiMe_3$), 17.8 (C, ^{t}Bu, OTBDMS), 25.5 (CH_3, ^{t}Bu, OTBDMS), 27.1 (CH_3), 27.1 (CH_3), 37.2 (CH_2-S), 62.6 (CH_2-O), 74.5 (CHO), 76.0 (*C*HCH_2S), 79.3 (*C*HCHO), 109.4 (CMe_2), 122.6-157.0 (aromatic carbons). MS HR-ESI [found 879.3125, $C_{46}H_{61}O_6PSSi_3$ $(M\text{-}Na)^+$ requires 879.3132].

L26a. 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, $^2J_{H\text{-}H}$ =7.6 Hz, $^3J_{H\text{-}H}$ =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, $C_{42}H_{59}O_5PS$ $(M\text{-}Na)^+$ requires 729.3719].

L26f. 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, $^3J_{H\text{-}H}$ =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, $^3J_{H\text{-}H}$ =3.6 Hz, $^3J_{H\text{-}H}$ =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=, $^3J_{H\text{-}H}$ =8.8 Hz), 7.36 (d, 1H, CH=, $^3J_{H\text{-}H}$ =8.4 Hz), 7.66 (d, 1H, CH=, $^3J_{H\text{-}H}$ = 8.0 Hz), 7.69 (d, 1H, CH=, $^3J_{H\text{-}H}$ =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, $SiMe_3$, $J_{C\text{-}P}$ =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, $^2J_{C\text{-}P}$ =5.4 Hz), 77.8 (d, *C*HCH_2O, $^3J_{C\text{-}P}$ =3.8 Hz), 79.6 (*C*HCHS), 109.3 (CMe_2), 122.4-154.0 (aromatic carbons). MS HR-ESI [found 749.2315, $C_{40}H_{47}O_5PSSi_2$ $(M\text{-}Na)^+$ requires 749.2318].

L26g. 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). ^{1}H NMR (400 MHz, C_6D_6): δ=0.52 (s, 9H, CH_3, $SiMe_3$), 0.54 (s, 9H, CH_3, $SiMe_3$), 1.15 (d, 3H, CH_3, $^3J_{H\text{-}H}$ =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, $^3J_{H\text{-}H}$ =7.6 Hz, $^3J_{H\text{-}H}$ =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=, $^3J_{H\text{-}H}$ =8.0 Hz), 7.16 (s, 1H, CH=), 7.23-7.28 (m, 3H, CH=), 7.34 (d, 1H, CH=, $^3J_{H\text{-}H}$ =8.4 Hz), 7.69 (pt, 2H, CH=, $^3J_{H\text{-}H}$ = 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, $SiMe_3$, $J_{C\text{-}P}$ =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, $C_{40}H_{47}O_5PSSi_2$ $(M\text{-}Na)^+$ requires 749.2318].

L27a. 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). ^{1}H 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, $^2J_{H\text{-}H}$= 12.6 Hz, $^3J_{H\text{-}H}$ =6.0 Hz), 2.97 (dd, 1H, CH_2-Se, $^2J_{H\text{-}H}$ =12.6 Hz, $^3J_{H\text{-}H}$ =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=, $^{3}J_{H-H}$ =2.4 Hz), 7.36-7.44 (m, 2H, CH=), 7.58 (d, 2H, CH=, $^{4}J_{H-H}$ =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, $^{3}J_{C-P}$ =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].

L27f. 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). ^{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), 1.32 (s, 3H, CH_3), 2.79 (dd, 1H, CH_2-Se, $^{2}J_{H-H}$ =12.5 Hz, $^{3}J_{H-H}$ =6.1 Hz), 2.88 (dd, 1H, CH_2-Se, $^{2}J_{H-H}$ =12.5 Hz, $^{3}J_{H-H}$ =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=, $^{3}J_{H-H}$ =8.6 Hz), 7.27-7.33 (m, 2H, CH=), 7.35 (d, 1H, $^{3}J_{H-H}$ =8.5 Hz, CH=), 7.70 (d, 2H, CH=, $^{3}J_{H-H}$ =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].

L27g. 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). ^{1}H 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, $^{2}J_{H-H}$ =12.5 Hz, $^{3}J_{H-H}$ =6.3 Hz), 2.87 (dd, 1H, CH_2-Se, $^{2}J_{H-H}$ =12.5 Hz, $^{3}J_{H-H}$ =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, $^{3}J_{H-H}$ =8.4 Hz, CH=), 7.28-7.34 (m, 2H, CH=), 7.37 (d, 1H, $^{3}J_{H-H}$ =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, $^{2}J_{H-H}$ =5.4 Hz), 77.2 (*C*HCH_2Se), 80.9 (d, *C*HCH_2O, $^{3}J_{H-H}$ =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].

L28f. 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). ^{1}H 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, $^{2}J_{H-H}$ =12.6 Hz, $^{3}J_{H-H}$ =5.8 Hz), 2.97 (dd, 1H, CH_2-Se, $^{2}J_{H-H}$ =12.8 Hz, $^{3}J_{H-H}$ =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=, $^{3}J_{H-H}$ =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, $^{2}J_{C-P}$ =3.7 Hz), 77.8 (*C*HCH_2Se), 81.0 (d, *C*HCH_2O, $^{3}J_{C-P}$ =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].

L28g. 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). ^{1}H 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].

L29f. 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). ^{1}H 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].

L29g. 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). ^{1}H 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].

L30f. 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=, $^{3}J_{H-H}$ =8.4 Hz), 7.33 (s, 2H, CH=), 7.35 (d, 1H, CH=, $^{3}J_{H-H}$ =8.8 Hz), 7.45-7.52 (m, 2H, CH=), 7.63 (d, 1H, CH=, $^{3}J_{H-H}$ =8.4 Hz), 7.69 (d, 1H, CH=, $^{3}J_{H-H}$ =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, $^{2}J_{C-P}$ =4.6 Hz), 78.6 (*C*HCH_2Se), 83.0 (d, *C*HCHO, $^{3}J_{C-P}$ =2.2 Hz), 109.3 (CMe_2), 122.6-152.0 (aromatic carbons). MS HR-ESI [found 847.1913, $C_{44}H_{49}O_5PSeSi_2$ $(M\text{-}Na)^+$ requires 847.1914].

L30g. 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, $^{3}J_{H-H}$ =6.4 Hz), 1.33 (s, 3H, CH_3), 1.39 (s, 3H, CH_3), 3.05 (dd, 1H, CH_2-Se, $^{2}J_{H-H}$ =12.8 Hz, $^{3}J_{H-H}$ =6.0 Hz), 3.12 (dd, 1H, CH_2-Se, $^{2}J_{H-H}$ =12.8 Hz, $^{3}J_{H-H}$ =4.8 Hz), 3.96 (dd, 1H, C*H*CHO, $^{3}J_{H-H}$ =7.2 Hz, $^{3}J_{H-H}$ =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, $^{3}J_{C-P}$ =3.0 Hz), 27.1 (CH_3), 27.4 (CH_3), 31.5 (CH_2-Se), 72.8 (d, CH-O, $^{2}J_{C-P}$ = 6.8 Hz), 77.8 (*C*HCH_2Se), 83.6 (d, *C*HCHO, $^{3}J_{C-P}$ =3.8 Hz), 109.4 (CMe_2), 122.6-152.3 (aromatic carbons). MS HR-ESI [found 833.1753, $C_{43}H_{47}O_5PSeSi_2$ $(M\text{-}Na)^+$ requires 833.1757].

3.3.4.3. Typical procedure for the preparation of [Ir(cod)(L7-L30a-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)(L7a)]BAr_F. Yield: 62 mg (91%). ^{31}P NMR (400 MHz, $CDCl_3$) δ: 101.8 (s). ^{1}H 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, $^{1}J_{C-B}$= 49 Hz). MS HR-ESI [found 993.4238, $C_{49}H_{69}IrO_5PS$ $(M)^+$ requires 993.4233].

[Ir(cod)(L7b)]BAr$_F$. Yield: 62 mg (93%). ^{31}P NMR (400 MHz, $CDCl_3$) δ: 102.6 (s). ^{1}H 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)(L7c)]BAr$_F$. Yield: 59 mg (90%). ^{31}P NMR (400 MHz, $CDCl_3$) δ: 102.6 (s). ^{1}H 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_2S), 79.5 (*C*HCH_2O), 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)(L7d)]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_2S), 3.94 (m, 1H, CH_2-O), 4.01 (m, 1H, CH_2-S), 4.17 (m, 1H, C*H*CH_2O), 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_2S), 79.9 (*C*HCH_2O), 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)(L7e)]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_2S), 4.18 (m, 1H, C*H*CH_2O), 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_2S), 79.5 (*C*HCH_2O), 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, $^1J_{C-B}$= 49 Hz). MS HR-ESI [found 937.3609, $C_{45}H_{61}IrO_5PS$ $(M)^+$ requires 937.3607].

[Ir(cod)(L7f)]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, $^2J_{H-H}$ =10.8 Hz), 3.85-3.90 (m, 1H, CH_2-S), 3.98-4.10 (m, 2H, CH= cod, C*H*CH_2O), 4.34 (b, 1H, CH=, cod), 4.59 (b, 1H, C*H*CH_2S), 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-P} =3.1 Hz), 33.5 (d, CH_2, cod, J_{C-P} =5.3 Hz), 46.4 (CH_2-S), 68.9 (d, CH_2-O, $^2J_{C-P}$ =13.8 Hz), 69.3 (CH=, cod), 76.4 (*C*HCH_2S), 77.2 (*C*HCH_2O), 79.11 (CH=, cod), 102.0 (d, CH=, cod, J_{C-P} =16.1 Hz), 106.3 (d, CH=, cod, J_{C-P} =16.1 Hz), 112.0 (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 1113.2835, $C_{47}H_{57}IrO_5PSSi_2$ $(M)^+$ requires 1013.2832].

[Ir(cod)(L7g)]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, $^2J_{H-H}$ =14.0 Hz), 4.05-4.11 (m, 2H, CH_2-S, C*H*CH_2O), 4.23 (pt, 1H, C*H*CH_2S, $^3J_{H-H}$ =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, $^2J_{C-P}$ =14.5 Hz), 75.4 (CH=, cod), 77.5 (*C*HCH_2O), 79.8 (*C*HCH_2S), 103.2 (d, CH=, cod, J_{C-P} =17.5 Hz), 104.4 (d, CH=, cod, J_{C-P} =14.5 Hz), 110.4 (CMe_2), 117.4-150.3 (aromatic carbons), 161.6 (q, C-B, BAr_F, $^1J_{C-B}$ =49.7 Hz). MS HR-ESI [found 1113.2834, $C_{47}H_{57}IrO_5PSSi_2$ $(M)^+$ requires 1013.2832].

[Ir(cod)(L8a)]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_2S), 4.15 (m, 1H, CH=, cod), 4.22 (m, 1H, C*H*CH_2O), 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-P}= 12.4 Hz), 72.2 (CH=, cod), 74.8 (CH=, cod), 77.1 (*C*HCH_2S), 77.4 (*C*HCH_2O), 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, $^1J_{C-B}$= 49 Hz). MS HR-ESI [found 931.4078, $C_{44}H_{67}IrO_5PS$ $(M)^+$ requires 931.4076].

[Ir(cod)(L8f)]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, $^2J_{H-H}$ =21.2 Hz, $^3J_{H-H}$ =10.4 Hz), 4.08 (b, 1H, C*H*CH_2O), 4.22 (b, 1H, C*H*CH_2S), 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, $^2J_{C-P}$ =13.8 Hz), 70.0 (CH=, cod), 77.2 (*C*HCH_2O), 78.1 (CH=, cod), 78.8 (*C*HCH_2S), 100.5 (d, CH=, cod, J_{C-P} =17.6 Hz), 104.0 (d, CH=, cod, J_{C-P} =16.8 Hz), 110.0 (CMe_2), 117.4-150.8 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^1J_{C-B}$ =49.7 Hz). MS HR-ESI [found 951.2679, $C_{42}H_{55}IrO_5PSSi_2$ $(M)^+$ requires 951.2676].

[Ir(cod)(L8g)]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_2O), 4.16 (pt, 1H, C*H*CH_2S, $^3J_{H-H}$ =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, $^2J_{C-P}$ =12.7 Hz), 70.5 (CH=, cod), 76.2 (CH=, cod), 77.6 (*C*HCH_2O), 78.2 (*C*HCH_2S), 100.2 (d, CH=, cod, J_{C-P} =18.1 Hz), 101.8 (d, CH=, cod, J_{C-P} =13.8 Hz), 110.5 (CMe_2), 117.5-148.8 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^1J_{C-B}$ =50.4 Hz). MS HR-ESI [found 951.2678, $C_{42}H_{55}IrO_5PSSi_2$ $(M)^+$ requires 951.2676].

[Ir(cod)(L9a)]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, $^2J_{H-H}$= 15.2 Hz, $^3J_{H-H}$= 3.2 Hz, CH_2-S), 3.50-3.56 (m, 1H, CH_2-O), 3.62 (dd, 1H, $^2J_{H-H}$= 12.4 Hz, $^3J_{H-H}$= 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, $^1J_{C-B}$= 49 Hz). MS HR-ESI [found 973.4549, $C_{47}H_{33}IrO_5PS$ $(M)^+$ requires 973.4546].

[Ir(cod)(L9d)]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)(L9e)]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)(L10a)]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, $^1J_{C\text{-}B}$= 49 Hz). MS HR-ESI [found 1021.4547, $C_{51}H_{73}IrO_5PS$ $(M)^+$ requires 1021.4546].

[Ir(cod)(L10d)]BAr_F. Yield: 63 mg (93%). ^{31}P NMR (400 MHz, $CDCl_3$) δ: 93.6 (s). ^{1}H 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)(L10e)]BAr_F. Yield: 60 mg (89%). ^{31}P NMR (400 MHz, $CDCl_3$) δ: 97.0 (s). ^{1}H 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)(L11d)]BAr_F. Yield: 64 mg (93%). ^{31}P NMR (400 MHz, $CDCl_3$) δ: 92.9 (s). ^{1}H 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)(L11e)]BAr_F. Yield: 62 mg (92%). ^{31}P NMR (400 MHz, $CDCl_3$) δ: 98.5 (s). ^{1}H 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-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, $^1J_{C-B}$= 49 Hz). MS HR-ESI [found 995.4391, $C_{49}H_{71}IrO_5PS$ $(M)^+$ requires 995.4389].

[Ir(cod)(L12d)]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, $^1J_{C-B}$= 49 Hz). MS HR-ESI [found 987.3765, $C_{49}H_{63}IrO_5PS$ $(M)^+$ requires 987.3763].

[Ir(cod)(L12e)]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, $^1J_{C-B}$= 49 Hz). MS HR-ESI [found 987.3763, $C_{49}H_{63}IrO_5PS$ $(M)^+$ requires 987.3763].

[Ir(cod)(L13d)]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-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)(L13e)]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, $J_{C\text{-}P}$= 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, $^1J_{C\text{-}B}$= 49 Hz). MS HR-ESI [found 987.3764, $C_{49}H_{63}IrO_5PS$ $(M)^+$ requires 987.3763].

[Ir(cod)(L14a)]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, $J_{C\text{-}P}$= 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, $^1J_{C\text{-}B}$= 49 Hz). MS HR-ESI [found 1021.4547, $C_{57}H_{73}IrO_5PS$ $(M)^+$ requires 1021.4546].

[Ir(cod)(L14d)]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, $^3J_{H\text{-}H}$= 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, $J_{C\text{-}P}$= 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, $^1J_{C\text{-}B}$= 49 Hz). MS HR-ESI [found 965.3923, $C_{47}H_{65}IrO_5PS$ $(M)^+$ requires 965.3920].

[Ir(cod)(L14e)]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)(L15f)]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)(L15g)]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_2, $^2J_{C\text{-}P}$ =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)(L16f)]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, $^2J_{C-P}$ =10.7 Hz), 71.8 (CH=, cod), 74.8 (CPh_2-S), 75.0 (d, *C*HCH_2O, $^3J_{C-P}$ =4.6 Hz), 78.0 (CH=, cod), 83.9 (*C*$HCPh_2S$), 102.1 (d, CH=, cod, J_{C-P} =15.3 Hz), 105.8 (d, CH=, cod, J_{C-P} =16.0 Hz), 112.7 (CMe_2), 117.4-151.0 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^1J_{C-B}$ =49.7 Hz). MS HR-ESI [found 1103.3304, $C_{54}H_{63}IrO_5PSSi_2$ $(M)^+$ requires 1103.3302].

[Ir(cod)(L16g)]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_2O, $^3J_{H-H}$ =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_2S, $^3J_{H-H}$ =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, $^2J_{C-P}$ =5.3 Hz), 72.8 (CH=, cod), 74.0 (CPh_2-S), 75.2 (d, *C*HCH_2O, $^3J_{C-P}$ =3.8 Hz), 75.7 (*C*$HCPh_2S$), 79.0 (CH=, cod), 99.9 (d, CH=, cod, J_{C-P} =16.8 Hz), 103.8 (d, CH=, cod, J_{C-P} =14.5 Hz), 109.6 (CMe_2), 117.4-150.5 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^1J_{C-B}$ =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)(L17a)]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, $^3J_{H-H}$ =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, $^3J_{H-H}$ =8.4 Hz), 3.71 (d, 1H, CH_2-S, $^2J_{H-H}$ =12.8 Hz), 4.00 (dd, 1H, CH_2-S, $^2J_{H-H}$ =12.4 Hz, $^3J_{H-H}$ =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_2S), 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_2S), 81.4 (CH-O), 83.9 (*C*HCHO), 102.4 (d, CH=, cod, J_{C-P} =16.1 Hz), 104.3 (d, CH=, cod, J_{C-P} =17.5 Hz), 112.0 (CMe_2), 118.0-140.7 (aromatic carbons), 162.1 (q, C-B, BAr_F, $^1J_{C-B}$ =49.9 Hz). MS HR-ESI [found 1007.4390, $C_{50}H_{71}IrO_5PS$ $(M)^+$ requires 1007.4389].

[Ir(cod)(L17f)]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, $^3J_{H-H}$ =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, $^2J_{H-H}$ =14.4 Hz, $^3J_{H-H}$ =7.6 Hz), 4.26 (m, 2H, CH-O, C*H*CH_2S), 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-P} =2.7 Hz), 30.7 (d, CH_2, cod, J_{C-P} =2.6 Hz), 34.8 (d, CH_2, cod, J_{C-P} =5.0

Hz), 48.4 (CH_2-S), 69.7 (CH=, cod), 77.0 (CH=, cod), 80.2 (*C*HCH_2S), 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)(L17g)]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, $^3J_{H\text{-}H}$ =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, $J_{C\text{-}P}$ =2.3 Hz), 32.1 (d, CH_2, cod, $J_{C\text{-}P}$ =4.8 Hz), 33.2 (d, CH_2, cod, $J_{C\text{-}P}$ =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, $^2J_{C\text{-}P}$ =14.5 Hz), 82.9 (d, *C*HCHO, $^3J_{C\text{-}P}$ =6.1 Hz), 102.2 (d, CH=, cod, $J_{C\text{-}P}$ =16.0 Hz), 105.5 (d, CH=, cod, $J_{C\text{-}P}$ =16.0 Hz), 112.5 (CMe_2), 117.4-150.8 (aromatic carbons), 162.1 (q, C-B, BAr_F, $^1J_{C\text{-}B}$ =41.8 Hz). MS HR-ESI [found 1027.2992, $C_{48}H_{59}IrO_5PSSi_2$ $(M)^+$ requires 1027.2989].

[Ir(cod)(L18a)]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, $^3J_{H\text{-}H}$ =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, $^3J_{H\text{-}H}$ =8.8 Hz), 3.83 (dd, 1H, CH_2-S, $^2J_{H\text{-}H}$ =13.2 Hz, $^3J_{H\text{-}H}$ =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, $J_{C\text{-}P}$ =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, $J_{C\text{-}P}$ =2.1 Hz), 32.2(CH_3, ^{t}Bu), 33.8 (d, CH_2, cod, $J_{C\text{-}P}$ =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, $^2J_{C\text{-}P}$ =14.5 Hz), 83.6 (d, *C*HCHO, $^3J_{C\text{-}P}$ =6.0 Hz), 102.1 (d, CH=, cod, $J_{C\text{-}P}$ =15.3 Hz), 103.9 (d, CH=, cod, $J_{C\text{-}P}$ =16.8 Hz), 111.9 (CMe_2), 120.8-150.7 (aromatic carbons), 162.1 (q, C-B, BAr_F, $^1J_{C\text{-}B}$ =49.3 Hz). MS HR-ESI [found 1057.4547, $C_{54}H_{73}IrO_5PS$ $(M)^+$ requires 1057.4546].

[Ir(cod)(L18f)]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, $^3J_{H\text{-}H}$ =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, $^2J_{H\text{-}H}$ =14.4 Hz, $^3J_{H\text{-}H}$ =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)(L18g)]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, $^3J_{H-H}$ =7.2 Hz), 4.02 (dd, 1H, CH_2-S, $^2J_{H-H}$ =11.6 Hz, $^3J_{H-H}$ =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, $^2J_{C-P}$ =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 1077.3147, $C_{52}H_{61}IrO_5PSSi_2$ $(M)^+$ requires 1077.3145].

[Ir(cod)(L19a)]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, $^2J_{H-H}$ =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, $^2J_{H-H}$ =11.6 Hz), 3.73 (dd, 1H, CH_2-S, $^2J_{H-H}$ =12.8 Hz, $^3J_{H-H}$ =2.8 Hz), 3.87 (dd, 1H, CH_2-S, $^2J_{H-H}$ =13.2 Hz, $^3J_{H-H}$ =6.4 Hz), 4.11 (b, 1H, CH=, cod), 4.23 (pt, 1H, C*H*CHO, $^3J_{H-H}$ =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, $^3J_{C-P}$ =5.3 Hz), 77.0 (CH=, cod), 77.2 (*C*HCH_2S), 83.1 (d, CH-O, $^2J_{C-P}$ =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, $^1J_{C-B}$ =50.5 Hz). MS HR-ESI [found 1137.5207, $C_{56}H_{85}IrO_6PSSi$ $(M)^+$ requires 1137.5203].

[Ir(cod)(L20a)]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)(L20g)]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, $^{2}J_{H-H}$ =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, $^{2}J_{H-H}$ =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, $^{2}J_{H-H}$ =11.2 Hz, $^{3}J_{H-H}$ =3.2 Hz), 4.30 (m, 2H, CH-O, CH=, cod), 4.44 (pt, 1H, C*H*CHO, $^{3}J_{H-H}$ =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-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, $^{3}J_{C-P}$ =5.3 Hz), 76.6 (*C*HCH_2S), 79.2 (CH=, cod), 82.5 (d, CH-O, $^{2}J_{C-P}$ =14.5 Hz), 102.6 (d, CH=, cod, J_{C-P} =17.6 Hz), 105.5 (d, CH=, cod, J_{C-P} =15.3 Hz), 112.4 (CMe_2), 117.4-151.6 (aromatic carbons), 162.2 (q, C-B, BAr_F, $^{1}J_{C-B}$ =63.4 Hz). MS HR-ESI [found 1207.3964, $C_{58}H_{75}IrO_6PSSi_3$ $(M)^+$ requires 1207.3959].

[Ir(cod)(L21f)]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, $^{2}J_{H-H}$ =12.0 Hz), 3.37 (d, 1H, CH_2-OTBDPS, $^{2}J_{H-H}$ =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, $^{2}J_{H-H}$ =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, $^{2}J_{C-P}$ =14.6 Hz), 102.6 (d, CH=, cod, J_{C-P} =16.0 Hz), 105.6 (d, CH=, cod, J_{C-P} =16.0 Hz), 112.4 (CMe_2), 117.4-151.0 (aromatic carbons), 161.8 (q, C-B,

BAr_F, $^1J_{C-B}$ =49.7 Hz). MS HR-ESI [found 1331.4276, $C_{68}H_{79}IrO_6PSSi_3$ $(M)^+$ requires 1331.4272].

[Ir(cod)(L22g)]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, $^2J_{H-H}$ =11.2 Hz), 3.30 (d, 1H, CH_2-OTIPS, $^2J_{H-H}$ =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, $^2J_{H-H}$ =10.8 Hz, $^3J_{H-H}$ =2.8 Hz), 4.30-4.38 (m, 2H, CH-O, CH=, cod), 4.57 (pt, 1H, C*H*CHO, $^3J_{H-H}$ =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, $^2J_{C-P}$ =14.5 Hz), 102.5 (d, CH=, cod, J_{C-P} =16.8 Hz), 105.3 (d, CH=, cod, J_{C-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)(L23g)]BAr_F. Yield: 73 mg (90%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ= 99.5 (s). ^{1}H 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)(L24a)]BAr_F. Yield: 62 mg (91%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ= 105.2 (s). ^{1}H 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$_2$S), 79.1 (CH-O), 102.5 (d, CH=, cod, $J_{C\text{-}P}$ =15.8 Hz), 103.4 (d, CH=, cod, $J_{C\text{-}P}$ =16.5 Hz), 110.3 (CMe_2), 117.7-150.4 (aromatic carbons), 162.0 (q, C-B, BAr_F, $^1J_{C\text{-}B}$ =50.2 Hz). MS HR-ESI [found 1007.4392, $C_{50}H_{71}IrO_5PS$ $(M)^+$ requires 1007.4389].

[Ir(cod)(L24f)]BAr$_F$. Yield: 64 mg (92%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ= 103.8 (s). ^{1}H 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, $^3J_{H\text{-}H}$ =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, $^2J_{H\text{-}H}$ =14.4 Hz), 4.03 (dd, 1H, CH_2-S, $^2J_{H\text{-}H}$ =14.0 Hz, $^3J_{H\text{-}H}$ =6.8 Hz), 4.07-4.13 (m, 1H, C*H*CH$_2$S), 4.22 (pt, 1H, CH-O, $^3J_{H\text{-}H}$ =5.2 Hz), 4.30 (pt, 1H, C*H*CHO, $^3J_{H\text{-}H}$ =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, $^3J_{C\text{-}P}$ =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, $J_{C\text{-}P}$ =5.3 Hz), 49.2 (CH_2-S), 69.1 (CH=, cod), 75.3 (*C*HCHO), 75.7 (CH=, cod), 77.4 (*C*HCH$_2$S), 79.6 (CH-O), 102.8 (d, CH=, cod, $J_{C\text{-}P}$ =17.6 Hz), 104.2 (d, CH=, cod, $J_{C\text{-}P}$ =15.0 Hz), 110.4 (CMe_2), 117.6-150.9 (aromatic carbons), 162.0 (q, C-B, BAr_F, $^1J_{C\text{-}B}$ =49.9 Hz). MS HR-ESI [found 1027.2992, $C_{48}H_{59}IrO_5PSSi_2$ $(M)^+$ requires 1027.2989].

[Ir(cod)(L24g)]BAr$_F$. Yield: 62 mg (90%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ= 103.6 (s). ^{1}H 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, $^3J_{H\text{-}H}$ =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, $^2J_{H\text{-}H}$ =13.6 Hz), 3.89 (b, 1H, CH=, cod), 3.99 (dd, 1H, CH_2-S, $^2J_{H\text{-}H}$ =14.0 Hz, $^3J_{H\text{-}H}$ =5.6 Hz), 4.08-4.14 (m, 1H, CH=, cod), 4.36 (b, 2H, C*H*CH$_2$S, 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$_2$S), 79.4 (d, CH-O, $^2J_{C\text{-}P}$ =16.0 Hz), 80.2 (d, *C*HCHO, $^3J_{C\text{-}P}$ =9.2 Hz), 100.9 (d, CH=, cod, $J_{C\text{-}P}$ =17.6 Hz), 102.8 (d, CH=, cod, $J_{C\text{-}P}$ =15.3 Hz), 110.7 (CMe_2), 117.4-150.7 (aromatic carbons), 161.6 (q, C-B, BAr_F, $^1J_{C\text{-}B}$ =50.5 Hz). MS HR-ESI [found 1027.2993, $C_{48}H_{59}IrO_5PSSi_2$ $(M)^+$ requires 1027.2989].

[Ir(cod)(L25f)]BAr$_F$. Yield: 66 mg (89%). Major isomer (60%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ= 105.4 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ= -0.66 (s, 3H, CH_3, OTBDMS), -0.65 (s, 3H, CH_3, OTBDMS), 0.64 (s, 9H, CH_3, ^{t}Bu, OTBDMS), 0.79 (s, 9H, CH_3, $SiMe_3$), 0.92 (s, 9H, CH_3, $SiMe_3$), 1.29 (s, 3H, CH_3), 1.56 (s, 3H, CH_3), 1.68-2.51 (m, 8H, CH_2, cod), 2.68 (m, 1H, CH_2-O), 2.80 (m, 1H, CH_2-O), 2.95 (m, 1H, CH_2-S), 3.44 (m, 1H, CH_2-S), 3.80 (b, 1H, CH=, cod), 4.02 (m, 1H, C*H*CH$_2$S), 4.27 (m, 1H, C*H*CHO), 4.55 (m, 1H, CH-O), 4.96 (m, 1H, CH=, cod), 5.29 (b, 1H, CH=), 5.53 (b, 1H, CH=, cod), 6.96-8.21 (m, 15H, CH= aromatic). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= -5.8 (CH_3, OTBDMS), -5.5 (CH_3, OTBDMS), 0.0 (CH_3, $SiMe_3$), 1.4 (CH_3, $SiMe_3$), 17.9 (C, ^{t}Bu, OTBDMS), 25.9 (CH_3, ^{t}Bu, OTBDMS), 26.6 (CH_3, ^{t}Bu, OTBDMS), 29.7-36.2 (m, CH_3, ^{t}Bu, OTBDMS, CH_2, cod), 48.2 (*C*HCH$_2$S),

59.5 (CH_2-S), 61.3 (CH_2-OP), 69.5 (b, CH=, cod), 75.5 (CH-OP), 78.2 (*C*HCH_2O), 102.0 (CH=, cod), 103.8 (CH=, cod), 106.2 (m, CH=, cod), 109.6 (CMe_2), 117.4-138.9 (aromatic carbons), 161.3 (m, C-B, BAr_F). Minor isomer (40%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ= 101.9 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ= -0.05 (s, 3H, CH_3, OTBDMS), 0.07 (s, 3H, CH_3, OTBDMS), 0.51 (s, 9H, CH_3, ^{t}Bu, OTBDMS), 0.53 (s, 9H, CH_3, $SiMe_3$), 0.56 (s, 9H, CH_3, $SiMe_3$), 1.49 (s, 3H, CH_3), 1.37 (s, 3H, CH_3), 1.68-2.51 (m, 8H, CH_2, cod), 2.51 (b, 1H, CH_2-O), 3.22 (m, 1H, CH_2-S), 3.44 (m, 1H, CH_2-O), 3.53 (m, 1H, CH_2-S), 3.80 (b, 1H, CH=, cod), 4.02 (m, 1H, C*H*CH_2S), 4.40 (m, 1H, C*H*CHO), 4.65 (m, 1H, CH-O),), 4.96 (m, 2H, CH=, cod), 5.29 (b, 1H, CH=, cod), 5.62 (b, 1H, CH=, cod), 6.96-8.21 (m, 15H, CH= aromatic). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= -6.2 (CH_3, OTBDMS), -6.3 (CH_3, OTBDMS), 0.4 (CH_3, $SiMe_3$), 1.5 (CH_3, $SiMe_3$), 17.7 (C, ^{t}Bu, OTBDMS), 25.5 (CH_3, ^{t}Bu, OTBDMS), 26.8 (CH_3, ^{t}Bu, OTBDMS), 27.3 (CH_3, ^{t}Bu, OTBDMS), 29.7-36.2 (m, CH_2, cod), 44.7 (*C*HCH_2S), 53.8 (CH_2-OP), 60.9 (CH_2-S), 69.5 (b, CH=, cod), 74.1 (CH-OP), 77.5 (*C*HCH_2O), 102.2 (CH=, cod), 103.7 (CH=, cod), 106.2 (m, CH=, cod), 108.3 (CMe_2), 117.4-138.9 (aromatic carbons), 161.3 (m, C-B, BAr_F). MS HR-ESI [found 1157.3795, $C_{54}H_{73}IrO_6PSSi_3$ $(M)^+$ requires 1157.3803].

[Ir(cod)(L26f)]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, $^3J_{H\text{-}H}$ =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, $^3J_{H\text{-}H}$ =2.0, $^3J_{H\text{-}H}$ =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, $J_{C\text{-}P}$ =4.1 Hz), 32.7 (d, CH_2, cod, $J_{C\text{-}P}$ =3.5 Hz), 54.5 (CH-S), 67.2 (d, CH_2-O, $^2J_{C\text{-}P}$ =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, $^1J_{C\text{-}B}$ =49.7 Hz). MS HR-ESI [found 1027.2990, $C_{48}H_{59}IrO_5PSSi_2$ $(M)^+$ requires 1027.2989].

[Ir(cod)(L26g)]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, $^3J_{H\text{-}H}$ =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, $^3J_{H\text{-}H}$ =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, $J_{C\text{-}P}$ =3.5 Hz), 34.5 (d, CH_2, cod, $J_{C\text{-}P}$ =4.8 Hz), 56.2 (CH-S), 68.1 (d, CH_2O, $^2J_{C\text{-}P}$ =14.5 Hz), 69.3 (CH=, cod), 72.7 (d, *C*HCH_2O, $^3J_{C\text{-}P}$ =8.1 Hz), 74.8 (CH=, cod), 81.2 (*C*HCHS), 102.4 (d, CH=, cod, $J_{C\text{-}P}$ =16.8 Hz), 104.7 (d, CH=, cod, $J_{C\text{-}P}$ =15.3 Hz), 110.4 (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 1027.2992, $C_{48}H_{59}IrO_5PSSi_2$ $(M)^+$ requires 1027.2989].

[Ir(cod)(L27a)]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_2O), 79.3 (*C*HCH_2S), 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)(L27f)]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_2O), 4.41-4.46 (m, 1H, C*H*CH_2Se), 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_2O), 78.2 (*C*HCH_2S), 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)(L27g)]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_2O), 4.28 (pt, 1H, C*H*CH_2Se, $^3J_{H\text{-}H}$ =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_2O), 80.4 (*C*HCH_2S), 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)(L28f)]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_2O), 4.32 (pt, 1H, C*H*CH_2S, $^3J_{H-H}$ =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, $^2J_{C-P}$ =14.6 Hz), 76.4 (CH=, cod), 78.0 (*C*HCH_2O), 79.6 (*C*HCH_2S), 102.7 (d, CH=, cod, J_{C-P} =17.6 Hz), 103.8 (d, CH=, cod, J_{C-P} =14.5 Hz), 110.2 (CMe_2), 117.4-150.1 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^1J_{C-B}$ =49.7 Hz). MS HR-ESI [found 1111.2438, $C_{51}H_{59}IrO_5PSeSi_2$ $(M)^+$ requires 1111.2433].

[Ir(cod)(L28g)]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)(L29a)]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)(L29f)]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*$HCMe_2O$, $^3J_{C\text{-}P}$ =8.3 Hz), 93.2 (d, CMe_2O, $^2J_{C\text{-}P}$ =21.4 Hz), 99.6 (d, CH=, cod, $J_{C\text{-}P}$ =16.0 Hz), 101.9 (d, CH=, cod, $J_{C\text{-}P}$ =15.3 Hz), 111.7 (CMe_2), 116.8-150.1 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^1J_{C\text{-}B}$ =49.7 Hz). MS HR-ESI [found 1139.2749, $C_{53}H_{63}IrO_5PSeSi_2$ $(M)^+$ requires 1139.2746].

[Ir(cod)(L29g)]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, $^2J_{H\text{-}H}$ =12.4 Hz), 4.01-4.08 (m, 2H, CH_2-Se, C*H*CMe_2O), 4.47 (pt, 1H, C*H*CH_2Se, $^3J_{H\text{-}H}$ =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, $^3J_{C\text{-}P}$ =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*$HCMe_2O$), 92.3 (d, CMe_2O, $^2J_{C\text{-}P}$ =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)(L30f)]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_2Se), 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_2S), 68.0 (CH=, cod), 77.8 (CH=, cod), 80.1 (*C*HCH_2S), 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)(L30g)]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_2Se, 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_2Se), 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].

3.3.4.4. Synthesis of [Rh(cod)(L)]BF_4 catalyst precursor

Corresponding ligand (0.05 mmol) was dissolved in CH_2Cl_2 (1 mL) and [Rh(cod)$_2$]BF_4 (20.3 mg, 0.05 mmol) was added. The reaction was stirred for 10 min at room temperature. The product was precipitated by adding cold hexane (5 mL). The product was then filtered and washed with cold hexane (3x5 mL). The solid was then dried to afford the catalyst precursor as a yellow solid.

[Rh(cod)(L7f)]BF_4. Yield: 43 mg (43%).^{31}P NMR (161.9 MHz, $CDCl_3$): δ= 114.2 (d, minor isomer, $^1J_{P\text{-}Rh}$= 260.0 Hz), 117.8 (d, major isomer, $^1J_{P\text{-}Rh}$= 256.0 Hz). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 0.43 (s, 9H, CH_3, $SiMe_3$), 0.74 (s, 9H, CH_3, $SiMe_3$), 1.33 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 1.82-2.53 (b, 8H, CH_2, cod), 2.79 (m, 1H, CH_2-OP), 3.38 (m, 2H, CH_2-S, C*H*CH_2S), 3.74 (m, 2H, CH_2-OP, CH=, cod), 3.93 (m, 2H, CH_2-S, CH=, cod), 4.34 (m, 1H, C*H*CH_2OP, cod), 4.93 (b, 1H, CH=, cod), 5.17 (b, 1H, CH=, cod), 6.91-8.26 (m, 15H, CH= aromatic). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= -0.2 (CH_3, $SiMe_3$), 1.8 (CH_3, $SiMe_3$), 28.4 (CH_3), 28.7 (CH_3), 29.7 (CH_2, cod), 30.2 (CH_2, cod), 33.6 (CH_2, cod), 37.4 (CH_2, cod), 66.1 (CH_2-S), 72.1 (*C*HCH_2S), 72.4 (CH_2-OP), 78.7 (*C*HCH_2O), 83.9 (CH=, cod), 92.9 (b, CH=, cod), 112.3 (b, CH=, cod), 112.8 (CMe_2), 113.1 (b, CH=, cod), 120.5-150.7 (aromatic carbons). MS HR-ESI [found 923.2250, $C_{47}H_5O_5PRhSSi_2$ $(M)^+$ requires 923.2258].

[Rh(cod)(L7g)]BF_4. Yield: 40 mg (80%). Major isomer (60%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ= 122.0 (d, $^1J_{P\text{-}Rh}$= 258.4 Hz). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 0.56 (s, 9H, CH_3, $SiMe_3$), 0.87 (s, 9H, CH_3, $SiMe_3$), 1.18 (s, 3H, CH_3), 1.21 (s, 3H, CH_3), 1.88-2.68 (b, 8H, CH_2, cod), 3.39 (m, 1H, CH_2-OP), 3.58 (m, 2H, CH_2-S, CH_2-O), 3.83 (m, 1H, CH_2-S), 3.95 (m, 1H, CH=, cod), 4.01 (m, 1H, C*H*CH_2OP, cod), 4.22 (b, 1H, C*H*CH_2S), 4.46 (b, 1H, CH=, cod), 4.87 (b, 1H, CH=, cod), 4.95 (b, 1H, CH=, cod), 6.74-8.27 (m, 15H, CH= aromatic). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 0.0 (CH_3, $SiMe_3$), 1.1 (CH_3, $SiMe_3$), 26.0 (CH_3), 26.4 (CH_3), 28.6 (b, CH_2, cod), 29.4 (CH_2, cod), 30.7 (CH_2, cod), 34.8 (CH_2, cod), 46.4 (CH_2-S), 69.3 (CH_2-O), 74.8 (*C*HCH_2O), 77.4 (CH=, cod), 80.2 (*C*HCH_2S), 89.1 (CH=, cod), 109.7 (CMe_2), 112.2 (b, CH=, cod), 112.9 (b, CH=, cod), 120.2-151.4 (aromatic carbons). Minor isomer (40%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ= 114.5 (d, $^1J_{P\text{-}Rh}$= 266.6 Hz). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 0.58 (s, 9H, CH_3, $SiMe_3$), 0.69 (s, 9H, CH_3, $SiMe_3$), 1.29 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 1.88-2.68 (b, 8H, CH_2, cod), 3.03 (m, 1H, CH_2-S), 3.30 (m, 1H, CH_2-S), 3.39 (m, 1H, CH_2-OP), 3.58 (m, 1H, CH_2-O),), 3.95 (m, 1H, CH=, cod), 4.01 (m, 1H, C*H*CH_2OP, cod), 4.13 (b, 1H, C*H*CH_2S), 4.46 (b, 1H, CH=, cod), 5.49 (b, 1H, CH=, cod), 5.69 (b, 1H, CH=, cod), 6.74-8.27 (m, 15H, CH= aromatic). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 0.9 (CH_3, $SiMe_3$), 1.0 (CH_3, $SiMe_3$), 26.2 (CH_3), 26.8 (CH_3), 28.6 (b, CH_2, cod), 30.0

(CH_2, cod), 31.0 (CH_2, cod), 34.3 (CH_2, cod), 35.6 (CH_2-S), 69.2 (CH_2-O), 74.6 (*C*HCH_2O), 79.7 (*C*HCH_2S), 81.2 (CH=, cod), 86.4 (b, CH=, cod), 111.1 (CMe_2), 115.4 (b, CH=, cod), 115.6 (b, CH=, cod), 120.2-151.4 (aromatic carbons). MS HR-ESI [found 923.2250, $C_{47}H_5O_5PRhSSi_2$ $(M)^+$ requires 923.2258].

[Rh(cod)(L17f)]BF_4. Yield: 43 mg (84%).^{31}P NMR (161.9 MHz, $CDCl_3$): δ= 119.5 (d, $^1J_{P\text{-}Rh}$= 260.8 Hz). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 0.34 (d, 3H, CH_3, $^3J_{H\text{-}H}$ =5.8 Hz), 0.54 (s, 9H, CH_3, $SiMe_3$), 0.83 (s, 6H, CH_3, $SiMe_3$), 0.90 (s, 3H, CH_3, $SiMe_3$), 1.20 (s, 3H, CH_3), 1.24 (s, 3H, CH_3), 1.80 (b, 1H, CH_2, cod), 2.13 (m, 5H, CH_2, cod), 2.47 (m, 2H, CH_2, cod), 3.58 (b, 1H, CH=, cod), 3.69 (d, 1H, CH_2-S, $^2J_{H\text{-}H}$= 14.2 Hz), 3.88 (m, 2H, CH_2-S, C*H*CHO), 4.25 (m, 2H, $CHCH_2$-S, CHOP), 4.55 (b, 1H, CH=, cod), 4.67 (b, 1H, CH=, cod), 4.97 (b, 1H, CH=, cod), 6.94-8.28 (m, 15H, CH= aromatic). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= -0.2 (CH_3, $SiMe_3$), 1.4 (CH_3, $SiMe_3$), 18.1 (CH_3), 26.0 (CH_2, cod), 26.4 (CH_3), 26.6 (CH_3), 29.1 (CH_2, cod), 30.7 (CH_2, cod), 34.6 (CH_2, cod), 46.0 (CH_2-S), 80.2 (*C*HCH_2S), 82.1 (*C*HCHO), 82.4 (CH=, cod), 83.6 (d, CH-O, $^2J_{C\text{-}P}$ =19.8 Hz), 90.6 (d, CH=, cod, $J_{C\text{-}P}$ =8.4 Hz), 109.3 (CMe_2), 110.4 (d, CH=, cod, $J_{C\text{-}P}$= 10.0 Hz), 111.6 (d, CH=, cod, $J_{C\text{-}P}$= 12.3 Hz), 121.3-150.9 (aromatic carbons). MS HR-ESI [found 937.2406, $C_{48}H_{59P}RhO_5SSi_2$ $(M)^+$ requires 937.2414]

[Rh(cod)(L17g)]BF_4. Yield: 39 mg (77%).^{31}P NMR (161.9 MHz, $CDCl_3$): δ= 117.8 (d, $^1J_{P\text{-}Rh}$= 258.4 Hz). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 0.50 (d, 3H, CH_3, $^3J_{H\text{-}H}$ =5.0 Hz), 0.58 (s, 9H, CH_3, $SiMe_3$), 0.73 (s, 9H, CH_3, $SiMe_3$), 1.28 (s, 3H, CH_3), 1.32 (s, 3H, CH_3), 1.90 (b, 3H, CH_2, cod), 2.11 (m, 1H, CH_2, cod), 2.28 (m, 2H, CH_2, cod), 2.41 (m, 1H, CH_2, cod), 2.53 (m, 1H, CH_2, cod), 3.16 (m, 1H, CH_2-S), 3.98 (m, 3H, CH_2-S, C*H*CHO, CH=, cod), 4.30 (b, 1H, CH, cod), 4.43 (m, 2H, $CHCH_2$-S, CHOP), 5.33 (b, 2H, CH=, cod) 6.97-8.20 (m, 15H, CH= aromatic). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 0.2 (CH_3, $SiMe_3$), 0.76 (CH_3, $SiMe_3$), 18.2 (CH_3), 26.3 (CH_3), 26.6 (CH_3), 27.6 (CH_2, cod), 28.7 (CH_2, cod), 31.6 (CH_2, cod), 32.7 (CH_2, cod), 42.5 (CH_2-S), 77.3 (*C*HCH_2S), 79.2 (CH-O), 82.0 (b, CH=, cod), 82.7 (d, *C*HCHO, $^2J_{C\text{-}P}$ =6.0 Hz), 90.3 (b, CH=, cod), 111.5 (d, CH=, cod, $J_{C\text{-}P}$= 12.6 Hz), 111.8 (CMe_2), 114.2 (b, CH=, cod), 120.6-150.9 (aromatic carbons). MS HR-ESI [found 937.2408, $C_{48}H_{59P}RhO_5SSi_2$ $(M)^+$ requires 937.2414].

[Rh(cod)(L18g)]BF_4. Yield: 47 mg (88%).^{31}P NMR (161.9 MHz, $CDCl_3$): δ= 118.4 (d, $^1J_{P\text{-}Rh}$= 260.1 Hz). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 0.53 (d, 3H, CH_3, $^3J_{H\text{-}H}$ =5.0 Hz), 0.62 (s, 9H, CH_3, $SiMe_3$), 0.75 (s, 9H, CH_3, $SiMe_3$), 1.29 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 1.85 (b, 3H, CH_2, cod), 2.10 (m, 1H, CH_2, cod), 2.24 (m, 2H, CH_2, cod), 2.43 (m, 1H, CH_2, cod), 2.58 (m, 1H, CH_2, cod), 3.24 (m, 1H, CH_2-S), 4.02 (m, 2H, C*H*CHO, CH=, cod), 4.25 (m, 2H, CH_2-S, CH, cod), 4.44 (m, 1H, CHOP), 4.55 (m, 1H, $CHCH_2$-S), 5.35 (b, 2H, CH=, cod) 6.98-8.21 (m, 17H, CH= aromatic). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 0.3 (CH_3, $SiMe_3$), 0.5 (CH_3, $SiMe_3$), 19.1 (CH_3), 26.1 (CH_3), 26.7 (CH_3), 26.8 (CH_2, cod), 29.9 (CH_2, cod), 30.3 (CH_2, cod), 33.9 (CH_2, cod), 42.8 (CH_2-S), 76.8 (*C*HCH_2S), 79.0 (*C*HCHO), 79.1 (CH=, cod), 82.4 (CH-O), 93.1 (d, CH=, cod, $J_{C\text{-}P}$ =8.2 Hz), 111.6 (d, CH=, cod, $J_{C\text{-}P}$= 11.8 Hz), 112.3 (CMe_2), 114.6 (d, CH=, cod, $J_{C\text{-}P}$= 12.4 Hz), 120.0-150.0 (aromatic carbons). MS HR-ESI [found 987.2567, $C_{52}H_{61}PRhO_5SSi_2$ $(M)^+$ requires 987.2571].

[Rh(cod)(L21g)]BF_4. Yield: 53 mg (89%).^{31}P NMR (161.9 MHz, $CDCl_3$): δ= 119.9 (d, $^1J_{P\text{-}Rh}$= 261.5 Hz). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 0.59 (s, 9H, CH_3, $SiMe_3$), 0.72 (s, 9H, CH_3, $SiMe_3$), 0.84 (b, 6H, CH_3), 1.04 (s, 9H, CH_3, ^{t}Bu, OTBDMS), 1.20 (s, 3H, CH_3), 1.26 (s, 3H, CH_3), 1.79 (m, 2H, CH_2, cod), 1.95 (m, 1H, CH_2, cod), 2.12 (m, 1H, CH_2, cod), 2.27 (m, 1H, CH_2-OTBDMS), 2.37 (m, 2H, CH_2, cod), 2.49 (m, 1H, CH_2, cod), 2.69 (m, 1H, CH_2, cod), 3.16 (m, 2H, CH_2-OTBDMS and CH_2-S), 4.16 (b, 1H, CH=, cod), 4.27 (m, 3H, CH_2-S, CH= cod, CH), 4.64 (m, 2H, CH), 5.50 (m, 2H, CH=, cod), 6.91-8.21 (m, 17H, CH=, aromatic). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= -0.1 (CH_3, $SiMe_3$), 0.4 (CH_3, $SiMe_3$), 14.3 (CH_3), 18.4 (C, ^{t}Bu, OTBDMS), 22.9 (CH_3), 26.8 (CH_3, ^{t}Bu, OTBDMS), 29.7 (b, CH_2, cod), 30.4 (b, CH_2, cod), 31.9 (CH_3), 34.5 (b, CH_2, cod), 34.9 (b, CH_2, cod), 42.5 (CH_2-S), 62.2 (CH_2-OTBDMS), 75.6 (CH), 75.7 (CH), 81.1 (CH), 82.7 (CH=, cod), 94.0 (CH, cod), 112.1 (C), 112.3 (CH, cod), 114.6 (CH=, cod), 114.6-151.4 (aromatic carbons). MS HR-ESI [found 1241.3689, $C_{58}H_{75}RhO_6PSSi_3$ $(M)^+$ requires 1241.3692].

[Rh(cod)(L24f)]BF_4. Yield: 47 mg (92%). Major isomer (53%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ= 122.6 (d, $^1J_{P\text{-}Rh}$= 257.3 Hz). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 0.55 (s, 9H, CH_3, $SiMe_3$), 0.87 (s, 9H, CH_3, $SiMe_3$), 0.90 (b, 3H, CH_3), 1.20 (s, 3H, CH_3), 1.90-2.52 (b,8H, CH_2, cod), 3.67 (m, 1H, CH_2-S), 3.82 (m, H, CH_2-S, CH-OP), 4.12 (m, 1H, CH=, cod), 4.25 (m, 1H, C*H*CHO), 4.41 (m, 2H, C*H*CH_2S, CH=, cod), 4.90 (b, 1H, CH=, cod), 4.99 (b, 1H, CH=, cod), 7.01-8.25 (m, 15H, CH= aromatic). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 0.0 (CH_3, $SiMe_3$), 1.2 (CH_3, $SiMe_3$), 14.4 (CH_3), 23.0 (CH_3), 26.4 (m, CH_2, cod), 32.0 (CH_3), 34.6 (b, CH_2, cod), 46.6 (m, CH_2-S), 75.5 (*C*HCHO), 76.8 (CH-OP), 79.2 (CH=, cod), 88.9 (b, CH=, cod), 109.5 (CMe_2), 111.5 (b, CH=, cod), 112.0 (b, CH=, cod), 112.5 (b, *C*HCH_2S,), 120.9-151.0 (aromatic carbons). Minor isomer (47%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ= 113.4 (d, $^1J_{P\text{-}Rh}$= 268.3 Hz). ^{1}H NMR (400 MHz, $CDCl_3$): δ= = 0.47 (s, 9H, CH_3, $SiMe_3$), 0.82 (b, 3H, CH_3), 0.83 (s, 9H, CH_3, $SiMe_3$), 1.20 (s, 3H, CH_3), 1.33 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 1.90-2.52 (b, 8H, CH_2), 3.54 (m, 1H, CH_2-S), 3.82 (m, H, CH_2-S, CH-OP), 4.12 (m, 1H, CH=, cod), 4.25 (m, 1H, C*H*CHO), 4.41 (m, 1HCH=, cod), 4.48 (b, 1H, C*H*CH_2S), 5.48 (b, 1H, CH=, cod), 5.61 (b, 1H, CH=, cod),), 7.01-8.25 (m, 15H, CH= aromatic). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 0.1 (CH_3, $SiMe_3$), 1.1 (CH_3, $SiMe_3$), 14.6 (CH_3), 26.4 (m, CH_2, cod), 29.6 (CH_3), 30.3 (CH_2, cod), 30.7 (CH_3), 34.6 (b, CH_2, cod), 46.6 (m, CH_2-S), 76.1 (*C*HCHO), 77.3 (CH-OP), 81.5 (CH=, cod), 88.9 (b, CH=, cod), 110.1 (CMe_2), 112.5 (b, *C*HCH_2S), 120.9-151.0 (aromatic carbons). MS HR-ESI [found 937.2406, $C_{48}H_{59P}RhO_5SSi_2$ $(M)^+$ requires 937.2414].

3.3.4.5. 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, $^{2}J_{H-H}$= 13.6 Hz, $^{3}J_{H-H}$= 6.4 Hz, CH_2-S), 2.78 (dd, 1H, $^{2}J_{H-H}$= 14 Hz, $^{3}J_{H-H}$= 6 Hz, CH_2-S), 3.69 (dd, 1H, $^{2}J_{H-H}$= 11.6 Hz, $^{3}J_{H-H}$= 4 Hz, CH_2-O), 3.85 (dd, 1H, $^{2}J_{H-H}$= 15.2 Hz, $^{3}J_{H-H}$= 4.8 Hz, CH_2-O), 3.90 (dd, 1H, $^{2}J_{H-H}$= 8 Hz, $^{3}J_{H-H}$= 3.6 Hz, C*H*CH_2O), 4.08 (dd, 1H, $^{2}J_{H-H}$= 13.6 Hz, $^{3}J_{H-H}$= 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, $^{2}J_{H-H}$= 12.4 Hz, $^{3}J_{H-H}$= 7.2 Hz, CH_2-S), 2.87 (dd, 1H, $^{2}J_{H-H}$= 12.4 Hz, $^{3}J_{H-H}$= 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, $^{2}J_{H-H}$= 7.2 Hz, $^{3}J_{H-H}$= 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, $^{2}J_{H-H}$= 12 Hz, $^{3}J_{H-H}$= 8 Hz, CH_2-S), 2.89 (dd, 1H, $^{2}J_{H-H}$= 12 Hz, $^{3}J_{H-H}$= 4 Hz, CH_2-S), 3.66 (dd, 1H, $^{2}J_{H-H}$= 12 Hz, $^{3}J_{H-H}$= 4 Hz, CH_2-O), 3.83 (dd, 1H, $^{2}J_{H-H}$= 12 Hz, $^{3}J_{H-H}$= 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).

3.3.4.6. Typical procedure for the preparation of hydroxyl-selenoether compounds 9-10[26]

Powdered $NaBH_4$ (98.4 mg, 2.6 mmol) was added in portions to a solution of the corresponding $(Se\text{-}Ar)_2$[27] (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, $^{2}J_{H-H}$ =12.4 Hz, $^{3}J_{H-H}$= 6.4 Hz), 3.19 (dd, 1H, CH_2-Se, $^{2}J_{H-H}$ =12.4 Hz, $^{3}J_{H-H}$ =4.8 Hz), 3.68 (dd, 1H, CH_2-O, $^{2}J_{H-H}$ =12.0 Hz, $^{3}J_{H-H}$= 4.8 Hz), 3.85 (dd, 1H, CH_2-O, $^{2}J_{H-H}$ =12.4 Hz, $^{3}J_{H-H}$ =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, $^2J_{H-H}$ =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).

3.3.4.7. 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).

3.3.4.8. 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*CH_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 ˚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 ºC 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).

3.3.4.9. 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, $^{2}J_{H-H}$= 7.6 Hz, C*H*-CMe_2), 4.08 (dd, 1H, $^{2}J_{H-H}$= 10.8 Hz, $^{3}J_{H-H}$= 4.8 Hz, CH_2), 4.13-4.16 (m, 1H, C*H*-CH_2), 4.23 (dd, 1H, $^{2}J_{H-H}$= 10.8 Hz, $^{3}J_{H-H}$= 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, $^{2}J_{H-H}$= 12 Hz, $^{3}J_{H-H}$= 8 Hz, CH_2-S), 3.3 (dd, 1H, $^{2}J_{H-H}$= 16 Hz, $^{3}J_{H-H}$= 4 Hz, CH_2-S), 3.76 (d, 1H, $^{2}J_{H-H}$= 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, $^{2}J_{H-H}$= 13.2 Hz, $^{3}J_{H-H}$= 6.8 Hz), 3.41 (dd, 1H, CH_2-S, $^{2}J_{H-H}$= 13.6 Hz, $^{3}J_{H-H}$ =3.2 Hz), 3.80 (d, 1H, C*H*CMe_2O, $^{2}J_{H-H}$= 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$_2$S), 86.0 (*C*HCMe$_2$O), 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, $^2J_{H-H}$= 12.7 Hz, $^3J_{H-H}$= 7.2 Hz, CH_2-Se), 3.38 (dd, 1H, $^2J_{H-H}$= 16.0 Hz, $^3J_{H-H}$= 4.0 Hz, CH_2-Se), 3.77 (d, 1H, $^3J_{H-H}$= 8.0 Hz, CHCMe$_2$O), 4.28-4.22 (m, 1H, C*H*CH$_2$Se), 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$_2$Se), 86.8 (*C*HCMe$_2$O), 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).

3.3.4.10. 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 precipitates. 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, $^2J_{H-H}$= 11.2 Hz, $^3J_{H-H}$= 2.8 Hz), 3.51 (dd, 1H, CH_2-O, $^2J_{H-H}$= 11.6 Hz, $^3J_{H-H}$= 2.4 Hz), 3.65 (s, 1H, OH), 4.20 (m, 1H, C*H*CH$_2$O), 5.30 (d, 1H, CHCPh$_2$O, $^3J_{H-H}$= 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$_2$O), 78.2 (*C*HCPh$_2$O), 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 ºC. 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: 1.3 g (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, $^2J_{H-H}$= 10.0 Hz), 3.31 (dd, 1H, CH_2-O,

$^{2}J_{H-H}$= 11.2 Hz, $^{3}J_{H-H}$= 1.2 Hz), 4.12 (m, 1H, C*H*CH_2O), 5.11 (d, 1H, CHCPh_2S, $^{3}J_{H-H}$= 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=).

3.3.4.11. 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=).

3.3.4.12. 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 ºC, and the corresponding thiol (37.5 mmol) in THF (8 mL), at -15 ºC 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 ºC. 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=).

3.3.4.13. General procedure for preparation of compound 37

Selenoether-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).

3.3.4.14. General procedure for obtention of thioether 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, $^2J_{H\text{-}H}$ =13.6 Hz, $^3J_{H\text{-}H}$ =6.0 Hz), 3.33 (dd, 1H, CH_2-S, $^2J_{H\text{-}H}$ =13.6 Hz, $^3J_{H\text{-}H}$ =4.8 Hz), 3.68 (dd, 1H, CH_2-O, $^2J_{H\text{-}H}$ =10.8 Hz, $^3J_{H\text{-}H}$ =5.2 Hz), 3.72-3.76 (m, 1H, CH-O), 3.80 (dd, 1H, CH_2-O, $^2J_{H\text{-}H}$ =10.4 Hz, $^3J_{H\text{-}H}$ =3.2 Hz), 3.87 (pt, 1H, C*H*CH-O, $^3J_{H\text{-}H}$ =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, $^2J_{H\text{-}H}$ =13.6 Hz, $^3J_{H\text{-}H}$ =7.2 Hz), 3.46 (dd, 1H, CH_2-S, $^2J_{H\text{-}H}$ =14.0 Hz, $^3J_{H\text{-}H}$ =4.4 Hz), 3.65 (dd, 1H, CH_2-O, $^2J_{H\text{-}H}$ =11.6 Hz, $^3J_{H\text{-}H}$ =6.0 Hz), 3.67-3.73 (m, 1H, CH-O), 3.79 (dd, 1H, CH_2-O, $^2J_{H\text{-}H}$ =10.8 Hz, $^3J_{H\text{-}H}$ =2.8 Hz), 3.86 (pt, 1H, C*H*CHO, $^3J_{H\text{-}H}$ =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, $^2J_{H\text{-}H}$ =12.8 Hz, $^3J_{H\text{-}H}$ =6.4 Hz), 3.40 (dd, 1H, CH_2-Se, $^2J_{H\text{-}H}$ =12.4 Hz, $^3J_{H\text{-}H}$ =4.4 Hz), 3.65 (dd, 1H, CH_2-O, $^2J_{H\text{-}H}$ =10.8 Hz, $^3J_{H\text{-}H}$ =5.2 Hz), 3.70-3.73 (m, 1H, CH-O), 3.77 (dd, 1H, CH_2-O, $^2J_{H\text{-}H}$ =11.2 Hz, $^3J_{H\text{-}H}$ =3.2 Hz), 3.86 (pt, C*H*CHO, $^3J_{H\text{-}H}$ =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=, $^3J_{H\text{-}H}$ =8.4 Hz, $^4J_{H\text{-}H}$ =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=).

3.3.4.15. 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 2 h. 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=).

3.3.4.16. 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, $^2J_{H-H}$ =13.6 Hz, $^3J_{H-H}$ =7.2 Hz), 3.59 (dd, 1H, CH_2-S, $^2J_{H-H}$ =13.2 Hz, $^3J_{H-H}$ =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, $^2J_{H-H}$ =13.6 Hz, $^3J_{H-H}$ =7.2 Hz), 3.58 (dd, 1H, CH_2-S, $^2J_{H-H}$ =13.2 Hz, $^3J_{H-H}$ =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, $^2J_{H-H}$ =13.6 Hz, $^3J_{H-H}$ =7.6

Hz), 3.59 (dd, 1H, CH_2-S, $^2J_{H-H}$ =14.0 Hz, $^3J_{H-H}$ =3.2 Hz), 3.69 (b, 1H, CH-O), 3.76 (dd, 1H, CH_2-OTIPS, $^2J_{H-H}$ =10.0 Hz, $^3J_{H-H}$ =5.6 Hz), 3.84 (pt, 1H, C*H*CHO, $^3J_{H-H}$ =4.8 Hz), 3.88 (dd, 1H, CH_2-OTIPS, $^2J_{H-H}$ =10.0 Hz, $^3J_{H-H}$ =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=, $^3J_{H-H}$ =8.4 Hz), 7.77 (d, 1H, CH=, $^3J_{H-H}$ =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=).

3.3.4.17. 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=).

3.3.4.18. Synthesis of hydroxyl-thioether compound 35 with inversion of configuration[10]

A solution of compound **26** (518.2 mg, 1.3 mmol) and pyridine (0.26 mL, 3.25 mmol), in dichloromethane (5 mL) was cooled to -15 ˚C, Tf_2O (0.26 mL, 1.6 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 ethyl acetate (3 x 50 mL), dried with $MgSO_4$ and the solvents were removed at room temperature. Evaporation of the solvent provided the desired triflate **34**, which was used without further purification in the next step.

To a solution of DBU (0.4 mL, 2.6 mmol) in toluene (2 mL) was added acetic acid (0.3 mL, 5.2 mmol). The solution was then stirred at room temperature for 90 min, and compound **34** (1.3 mmol) was added. The mixture was heated for 80 ˚C, and stirring was then continued at this temperature for 4 h. After being cooled down to room temperature, the reaction mixture was diluted with toluene (5 mL). The solution was

transferred into separatory funnel, and was washed successively with aquos K_2CO_3 solution (10% w/v, 3 mL), and brine (1 mL). After organic solution was dried over $MgSO_4$, the solvent was removed to give the crude product which was purified by flash chromatography (EtOAc/PE – 1/9) to afford acetate (300 mg, 0.68 mmol) in 52% yield. ^{1}H NMR ($CDCl_3$), δ: 0.00 (s, 6H, CH_3, OTBDMS), 0.83 (s, 9H, CH_3, ^{t}Bu, OTBDMS), 1.34 (s, 3H, CH_3), 1.37 (s, 3H, CH_3), 1.93 (s, 3H, CH_3, OAc), 3.09 (m, 1H, CH_2-S), 3.19 (m, 1H, CH_2-S), 3.67 (m, 2H, CH_2-O), 3.98 (m, 1H, C*H*CH_2S), 4.08 (m, 1H, C*H*CHO), 4.95 (m, 1H, CHO), 7.14 (m, 1H, CH=), 7.23 (m, 2H, CH=), 7.33 (m, 2H, CH=). ^{13}C NMR ($CDCl_3$), δ: -5.4 (CH_3, OTBDMS), 14.2 (CH_3, ^{t}Bu, OTBDMS), 21.0 (CH_3, OAc), 25.8 (CH_3, ^{t}Bu, OTBDMS), 26.8 (CH_3), 27.3 (CH_3), 36.6 (C, ^{t}Bu, OTBDMS), 61.7 (CHO), 72.4 (CH_2-O), 75.1 (*C*HCHO,CH_2-S), 78.5 (*C*HCH_2S), 109.7 (CMe_2), 126.4-135.7 (aromatic carbons).

A solution of acetate compound (300 mg, 0.68 mmol) in methanol (2 mL), K_2CO_3 (188.4 mg, 1.4 mmol) was added. The reaction mixture was stirred for 30 min and methanol was removed in vacuum. Ethyl acetate was added to the crude and was washed with water (3 x 1 mL), organic phase was dried with $MgSO_4$ and the solvents were removed. The crude was purified by silica gel flash chromatography (EtOAc/PE – 1/5) to give desired compound **35** in 73% yield (199 mg). ^{1}H NMR ($CDCl_3$), δ: 0.00 (s, 6H, CH_3, OTBDMS), 0.83 (s, 9H, CH_3, ^{t}Bu, OTBDMS), 1.35 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 2.26 (d, 1H, OH, $^3J_{H\text{-}H}$= 6.9 Hz), 3.12 (m, 2H, CH_2-S), 3.60 (m, 3H, CH_2-O, CHO), 3.92 (m, 1H, C*H*CHO), 4.08 (m, 1H, C*H*CH_2S), 7.12 (m, 1H, CH=), 7.21 (m, 2H, CH=), 7.31 (m, 2H, CH=). ^{13}C NMR ($CDCl_3$), δ: -5.4 (CH_3, OTBDMS), -5.3 (CH_3, OTBDMS), 18.3 (C, ^{t}Bu, OTBDMS), 25.9 (CH_3, ^{t}Bu, OTBDMS), 27.0 (CH_3), 27.3 (CH_3), 36.9 (CH_2-S), 64.4 (CH_2-O), 70.4 (CHO), 75.4 (*C*HCH_2S), 80.4 (*C*HCHO), 109.6 (CMe_2), 126.3-135.9 (aromatic carbons).

3.3.4.19. Synthesis of hydroxyl-thioether compound 33 with inversion of configuration[28]

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, $^3J_{H\text{-}H}$ =6.0 Hz), 1.43 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 3.13 (dd, 1H, CH_2-S, $^2J_{H\text{-}H}$ =13.6 Hz, $^3J_{H\text{-}H}$ =5.6 Hz), 3.24 (dd, 1H, CH_2-S, $^2J_{H\text{-}H}$ =14.0 Hz, $^3J_{H\text{-}H}$ =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, $^3J_{H-H}$ =6.0 Hz), 1.40 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 2.29 (s, 1H, OH, $^3J_{H-H}$ =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, $^3J_{H-H}$ =6.0 Hz), 7.16-7.20 (m, 1H, CH=), 7.27 (t, 2H, CH=, , $^3J_{H-H}$ =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=).

3.3.4.20. Typical procedure for the synthesis of compound 36

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 (36). 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 **36** 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, $^2J_{H-H}$ =10.4 Hz, $^3J_{H-H}$ =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=).

3.3.4.21. Preparation of the compound 37

1-*O*-*tert*-Butyldiphenylsilyl-2,3-*O*-isopropylidene-5-*O*-tosyl-D-arabinitol. To a cooled solution (-15 ˚C) of compound **36** (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 (37). 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=).

3.3.4.22. Preparation of compound 38

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 **37** (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 1 h, 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 (EtOAc/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 ºC. After stirring at -15 ˚C for 10 min, the reaction was warmed to 67 ˚C and stirred for 36 h. 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 (38)

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 **38** 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=).

3.3.4.23. 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**,[12e] **S2**,[29] **S3**-**S6**,[12e] **S7**-**S10**,[30], **S11**,[11a] **S12**-**S13**,[31] **S14**,[12e] **S15**-**S16**,[11c] **S17**,[13] **S18**,[7j] **S19**,[12e] **S20**,[9b] **S21**,[12e] **S22**-**S27**,[32] **S28**,[12e] **S29**,[12b] **S30**,[33] **S31**[34] and **S32**[35] were determined using the conditions previously described.

3.3.4.24. General procedure for the Rh-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 ^{1}H NMR. 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 **S33**-**S34**,[36] **S35**-**S40**[37] and **S41**-**S45**[38] were determined using the conditions previously described.

3.3.5. Acknowledgments

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3.3.6. REFERENCES

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3.4 Application of a carbene-thioether ligand in the Ir-catalyzed hydrogenation of minimally functionalized olefins. Comparison with their analogues phosphinite and phosphite ligands

Carlota Borràs, Zahra Mazloomi, Pol de la Cruz Sánchez, Jordi Faiges, Oscar Pàmies and Montserrat Diéguez preliminary results.

Abstract: *A thioether-carbene ligand was prepared, and its iridium complex was evaluated as catalysts precursor for the asymmetric hydrogenation of various minimally functionalized olefins. Iridium thioether-phosphinite and thioether-phosphite complex analogues of iridium thioether-carbene complex have also been synthesized and tested in the reduction of minimally functionalized alkenes in comparison purposes. In general, catalyst precursor containing carbene-thioether ligand provided lower activity and enantioselectivity than their related P-analogues modified with phosphinite and phosphite groups. Enantioselectivity is highly dependent on both the ligand and the substrate parameters. It should be mentioned the good enantioselectivities achieved for several substrate types, such as trisubstituted α,β-unsaturated enones, esters and lactones, tri- and disubstituted enol phosphinates and (3,3-dimethylbut-1-en-2-yl)benzene with this very simple ligand scaffold.*

3.4.1. Introduction

As already mentioned in previous chapters, asymmetric hydrogenation is one of the most attractive tools for the preparation of optically active compounds, due to its perfect atom economy, low catalyst loading and that it can generally be performed under mild reaction conditions.[1] Unlike the Rh-catalyzed hydrogenation of the olefins with a coordination group close to the double bond, the Ir-catalyzed hydrogenation of olefins without any group of coordination, is less studied. Ir-phosphine/oxazoline PHOX ligand (Figure 3.4.1; **1**), reported by Pfaltz in 1997, was a breakthrough in the ligand design for the hydrogenation of minimally functionalized olefins.[2] Since then, several modifications in the ligand structure have been developed, either replacing the phosphine moiety by a phosphinite,[3] phosphite[4] or carbene group or the oxazoline by other nitrogen groups (such as pyridine, thiazole)[3] or other non-N donor groups, such as amides[5] or thioethers[6] moieties. These latter modifications widened the range of olefins that can be hydrogenated with excellent enantioselectivities.

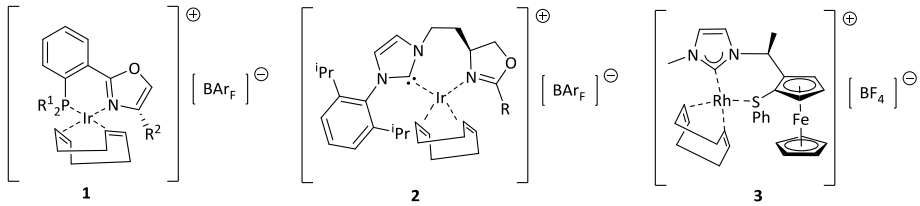


Figure 3.4.1. Selected complexes used in the hydrogenation of olefins.

In the last two decades, N-heterocyclic carbenes (NHCs) have emerged as a class of powerful ligands for promoting catalytic activity. Owing to their strong σ donor ability, air stability, and low toxicity, NHCs have been considered as practical alternatives to the more commonly used phosphines.[7],[8] Because of these unique features, exploring new classes of NHCs has been an attractive target of organometallic chemistry. In this respect, in 2001, Burgess and coworkers reported a small library of carbene-oxazoline ligands for the Ir-catalyzed hydrogenation of minimally functionalized olefins (figure 3.4.1; **2**).[9] These ligands afforded enantioselectivities up to 98% in a limited range of unfunctionalized olefins. Since then, a few more carbene-N ligands have been applied in the hydrogenation of minimally functionalized olefins with less sucess.[10] The use of NHC ligands with other heterodonor ligands is still unexplored. Regarding to bidentated sulfur-carbene ligands, to date, only one S-carbene/Rh complex has been reported by Chung and coworkers (figure 3.4.1; **3**) for the hydrogenation of functionalized olefins with poor success.[11] In order to further explore the potential of carbene-based ligands in the hydrogenation of minimally functionalized olefins using Ir-complexes, in this chapter we synthesized the simple thioether-carbene compound **L31**H·Br (Figure 3.4.2) and applied it in the hydrogenation of minimally functionalized olefins. This ligand combines the advantages of the thioether and carbene moieties. Finally, we also compare the effectiveness of this thioether-carbene ligand with its related thioether-phosphinite (**L32**) and thioether-phosphites (**L33a**–**b**).

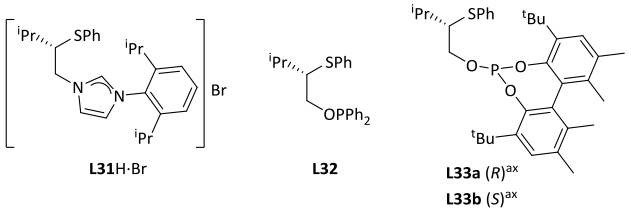


Figure 3.4.2. Thioether-carbene ligand **L31** and their analogues thioether-phosphinite/phosphites **L32**-**L33** ligands.

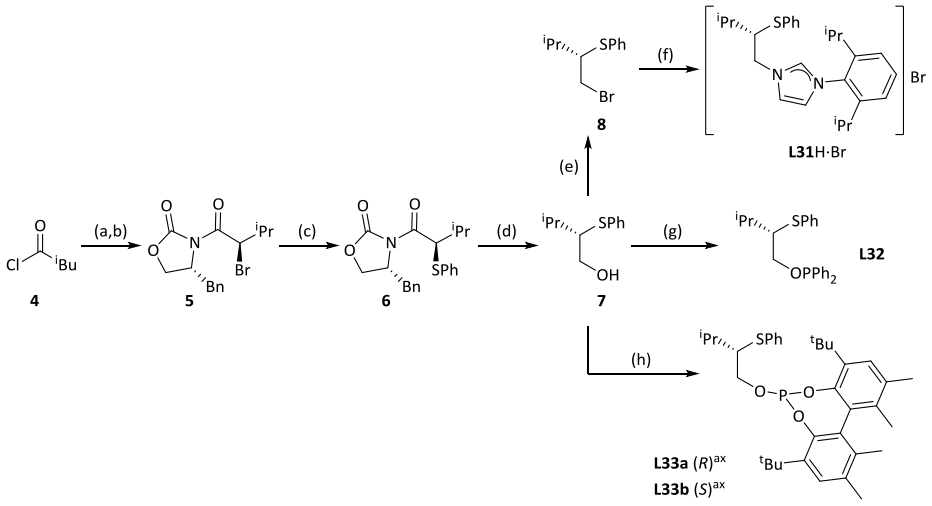
3.4.2 Results and discussion

3.4.2.1 Synthesis of thioether-NHC/P ligands L31-L33 and their corresponding Ir(I) complexes

The thioether-NHC/P ligands **L31-L33** were efficiently synthesized by the coupling of the corresponding readily accessible thioether-bromide derivative **8** or thioether-

hydroxyl derivative **7** with the either 1-(2,6-diisopropylphenyl)-1*H*-imidazole **9** (for ligand **L31**·HBr; Scheme 3.4.1, step f)[12] or chlorodiphenylphosphine (for ligand **L32**; Scheme 3.4.1, step g) or the desired phosphochloridite (for ligands **L33**; Scheme 3.4.1, step h).

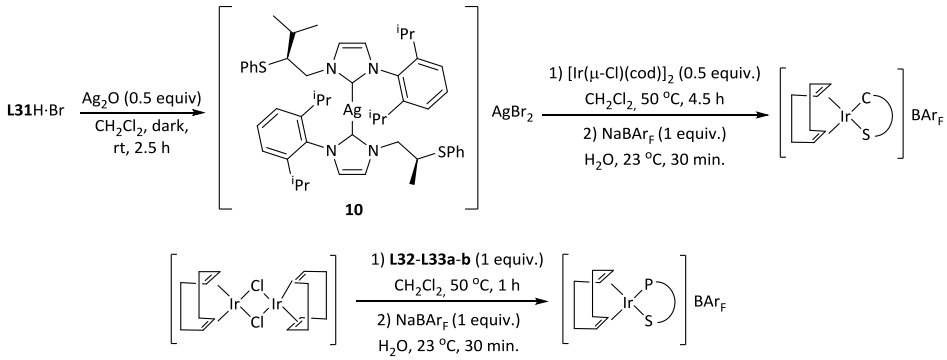
The preparation of thioether-hydroxyl/bromide derivatives **7** and **8** was carried out as depicted in Scheme 3.4.1 from commercially available starting material **4** following already reported synthetic procedures.[13] According to Evan's procedure, the (*R*)-benzyl-2-oxazolidinone were treated with *n*-butyllithium at -78 ˚C and the resulting salts were acylated with isovaleryl chloride **4** to give the corresponding *N*-acyl carboximide (Scheme 3.4.1, step a).[13b] After selective α-bromation of the *N*-acyl carboximide using *N*-bromosuccinimide (NBS) and dibutylboryl triflate in presence of *N,N*-diisopropylamine, compound **5** was achieved in excellent diastereoselectivity (dr>25:1; Scheme 3.4.1, step b).[13c] Treatment of **5** with thiophenol provides compound **6** in good yield (Scheme 3.4.1, step c)**.** Reductive cleavage of the Evan's auxiliary with lithium borohydride gave access to the corresponding thioether-hydroxyl **7** (Scheme 3.4.1, step d).[13d] Finally, treatment of alcohol **7** with tetrabromomethane and triphenylphosphine afforded the desired thioether-bromine compound **8**.[13a]



Scheme 3.4.2. Synthesis of thioether-NHC/P ligands **L31-L33**. Reaction conditions: a) Evans' auxiliary, ^{n}BuLi, THF, -78 °C, 1 h. b) DIPEA, $^{n}Bu_2OTf$, NBS, DCM, -78 °C, 1.3 h. c) Ph-SH, DBU, THF, -10 °C, 4 h. d) $LiBH_4$, H_2O, THF, 0 °C, 3 h. e) CBr_4, PPh_3, DCM, 0 °C, 6 h. f) **9**, MeCN, 1.5 days, reflux. g) $ClPPh_2$, NEt_3, toluene, 1 h. h), $ClP(OR)_2$; $(OR)_2$ = **a**-**b**, Py, toluene, 80˚C, 16 h.

The corresponding [Ir(cod)(L)]BAr_F (L=**L31**-**L33a**-**b**) complexes were prepared as previously described in the literature (Scheme 3.4.3).[7f] For the coordination of the thioether-carbene ligand **L31**, compound **L31**H·Br were first treated with Ag_2O to form the corresponding silver-carbene complex **10**. Then, transmetallation with 0.5 equivalent of [Ir(μ-Cl)cod]$_2$ followed by in situ Cl^-/BAr_F^- counterion exchange led to the desired [Ir(cod)(**L31**)]BAr_F. The thioether-P ligands **L32**-**L33** were directly coordinated to Ir by reaction with 0.5 equivalent of [Ir(μ-Cl)cod]$_2$ followed by in situ Cl^-/BAr_F^-

counterion exchange as for the preparation [Ir(cod)(**L31**)]BAr_F. All complexes were isolated after extraction and SiO_2 chromatography as air-stable orange solids. They were characterized by ^{31}P NMR, ^{1}H NMR and ^{13}C NMR. 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 molecular species. NMR spectra showed the expected pattern for these C_1-complexes.

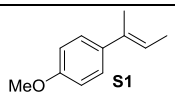
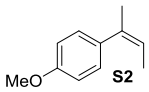
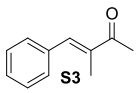
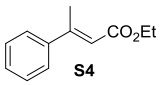
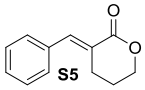
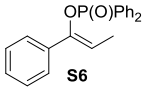
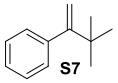
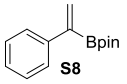
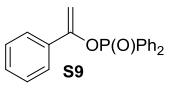
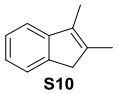


Scheme 3.4.3. Synthesis of Ir-catalyst precursors [Ir(cod)(**L31**-**L33**)]BAr_F.

3.4.2.2. Ir-catalyzed hydrogenation of minimally functionalized olefins

The newly prepared iridium complexes were evaluated in the asymmetric hydrogenation of several trisubstituted minimally functionalized olefins (substrates **S1**-**S6**), as well as in the reduction of more challenging di- and tetrasubstituted olefins (substrates **S7**-**S9** and **S10**, respectively). As shown in Table 3.4.1, catalyst precursor containing carbene-thioether ligand **L31**H·Br generally provided lower activity and enantioselectivity than their related analogues modified with phosphinite and phosphite counterparts. Exceptions to this general rule are the full conversions and high enantioselectivities (similar to those attained with the best [Ir(P-S)(cod)]BAr_F) achieved in the hydrogenation of enol phosphinates **S6** and **S9** using [Ir(**L31**)(cod)]BAr_F. The results also indicate that enantioselectivity highly depends on subtle variations of the ligand parameters as well as of the substrate parameters (substrate geometry, substitution pattern and electronic variations). Thus, while the use of catalyst precursor [Ir(**L33a**)(cod)]BAr_F provides the highest enantioselectivities of the series in the reduction of *E*-unfunctionalized olefin **S1**, α,β-unsaturated enone **S3**, enol phosphonate **S6** and tetrasubstituted olefin **S10**; the highest enantioselectivities achieved for *Z*-unfunctionalized olefin **S2**, α,β -unsaturated ester **S4**, lactone **S5** and vinyl boronate **S8** are achieved using [Ir(**L33b**)(cod)]BAr_F. However, for disubstituted olefin **S7** and enol phosphonate **S9** the highest ee's are achieved using [Ir(**L31**)(cod)]BAr_F.

Table 3.4.1. Asymmetric hydrogenation of substrates **S1**-**S10** using [Ir(cod)(**L31**-**L33a**-**b**)]BAr_F catalyst precursors.[a]

Entry	Substrate	L31	L32	L33a	L33b
1	 **S1**	42% Conv 2% (*R*)	100% Conv 48% (*S*)	100% Conv 40% (*S*)	100% Conv 30% (*S*)
2	 **S2**	-	100% Conv 21% (*R*)	100% Conv 58% (*R*)	100% Conv 31% (*R*)
3	 **S3**	10% Conv 9% (*R*)	95% Conv 82% (*S*)	80% Conv 20% (*R*)	75% Conv 60% (*S*)
4	 **S4**	20% Conv 9% (*R*)	100% Conv 31% (*S*)	90% Conv 80% (*S*)	50% Conv 50% (*S*)
5	 **S5**	20% Conv 20% (*R*)	55% Conv 28% (*R*)	90% Conv 75% (*R*)	42% Conv 33% (*S*)
6	 **S6**	100% Conv 75% (*S*)	86% Conv 85% (*S*)	25% Conv 72% (*R*)	25% Conv 9% (*S*)
7[b]	 **S7**	-	100% Conv 80% (*R*)	100% Conv 15% (*R*)	100% Conv 91% (*R*)
8[b]	 **S8**	100% Conv 10% (*R*)	100% Conv 25% (*R*)	100% Conv 44% (*S*)	100% Conv 1% (*S*)
9	 **S9**	100% Conv 91% (*S*)	100% Conv 3% (*S*)	100% Conv 94% (*S*)	100% Conv 98% (*S*)
10[c]	 **S10**	100% Conv 5% (*R*,*R*)	100% Conv 58% (*R*,*R*)	100% Conv 50% (*R*,*R*)	100% Conv 40% (*R*,*R*)

[a] Reaction conditions: substrate (0.25 mmol), [Ir(cod)(**L**)]BAr_F (2 mol%), P_{H2} (100 bar) in dichloromethane at room temperature for 4 h. [b] Reactions carried out at 1 bar of H_2. [c] Reactions carried out at 100 bar of H_2 for 24 h.

3.4.3. Conclusions

In this study, a series of thioether-carbene/phosphite/phosphite ligands were prepared, and their iridium complexes were evaluated as catalyst precursors for the asymmetric hydrogenation of various minimally functionalized olefins. In general, catalyst precursor containing carbene-thioether ligand provided lower activity and enantioselectivity than their related analogues modified with phosphinite and phosphite groups. Enantioselectivity is highly dependent on both the ligand and the substrate parameters. It should be mentioned the good enantioselectivities achieved for several substrate types, such as trisubstituted α,β-unsaturated enones, esters and

lactones, tri- and disubstituted enol phosphinates and (3,3-dimethylbut-1-en-2-yl)benzene with this very simple ligand scaffold.

3.4.4. Experimental Part

3.4.4.1. General remarks

All syntheses were performed by using standard Schlenk techniques under an argon atmosphere. Solvents were purified by standard procedures. Compounds **5**,[13b] **6**,[13d] **7**,[13d] **8**,[13a] **9**[12] and phosphorochloridites[14] were prepared as previously described. All other reagents were used as commercially available. ^{1}H, $^{13}C\{^{1}H\}$, $^{31}P\{^{1}H\}$ NMR spectra experiments 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 done based on ^{1}H-^{1}H gCOSY and ^{1}H-^{13}C gHSQC experiments.

3.4.4.2. Typical Procedure for the synthesis of thioether-imidazolium ligand L31H·Br

1-(2,6-Diisopropylphenyl)-1H-imidazole **9** (114 mg, 0.5 mmol) was charged in schlenk tube under argon, and a solution of the corresponding bromide **8** (0.4 mmol) in dry MeCN (3 mL) was added. The reaction mixture were stirred at 80˚C for 1.5 days, concentrated and purified by silica flash chromatography (dichloromethane/MeOH 20:1 to 10:1) to afford **L31**. Yield: 230 mg (42%) as dark orange oil. ^{1}H NMR (400 mHz, $CDCl_3$) δ: 0.92 (d, 3H, $^{3}J_{H-H}$= 6.8 Hz, CH_3, ^{i}Pr, Ar), 0.99 (d, 3H, $^{3}J_{H-H}$= 6.8 Hz, CH_3, ^{i}Pr, Ar), 1.01 (d, 3H, $^{3}J_{H-H}$= 6.8 Hz, CH_3, ^{i}Pr, Ar), 1.02 (d, 3H, $^{3}J_{H-H}$= 6.8 Hz, CH_3, ^{i}Pr, Ar), 1.05 (d, 3H, $^{3}J_{H-H}$= 6.8 Hz, CH_3, ^{i}Pr), 1.07 (d, 3H, $^{3}J_{H-H}$= 6.8 Hz, CH_3, ^{i}Pr), 2.12 (m, 2H, CH, ^{i}Pr, Ar), 2.32 (m, 1H, CH, ^{i}Pr), 3.80 (m, 1H, CH-S), 4.61 (dd, 1H, $^{2}J_{H-H}$ = 14.0 Hz, $^{3}J_{H-H}$= 11.3 Hz, CH_2-N), 5.37 (dd, 1H, $^{2}J_{H-H}$ = 14.0 Hz, $^{3}J_{H-H}$= 3.6 Hz, CH_2-N), 7.13 (s, 1H, NHC-H), 7.20-7.35 (m, 7H, CH=), 7.50 (m, 1H, CH=), 8.40 (s, 1H, NHC-H), 10.08 (s, 1H, NHC-H). ^{13}C NMR (100.6 mHz, $CDCl_3$) δ: 18.2 (CH_3, ^{i}Pr), 20.6 (CH_3, ^{i}Pr), 24.1 (CH_3, ^{i}Pr), 24.2 (CH_3, ^{i}Pr), 24.2 (CH_3, ^{i}Pr), 24.3 (CH_3, ^{i}Pr), 28.5 (CH, ^{i}Pr), 28.6 (CH, ^{i}Pr), 31.6 (CH, ^{i}Pr), 53.1 (CH_2-N), 58.7 (CH-S), 123.4 (CH, NHC), 124.5 (CH, NHC), 124.7-129.9 (aromatic carbons), 138.7 (CH, NHC), 145.6 (C), 145.7 (C). MS HR-ESI [found 407.2515, $C_{36}H_{35}N_2S$ $(M\text{-}Na)^+$ requires 407.2507].

3.4.4.3. Typical Procedure for the synthesis of thioether-phosphinite ligand L32

Compound **8** (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 1 h 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 ligand **L32** as a colorless oil. Yield: 118 mg (62%). ^{31}P NMR (C_6D_6), δ: 114.5 (s). ^{1}H NMR

(C_6D_6), δ: 0.91 (d, 3H, CH_3, ^iPr, $^3J_{H-H}$= 6.8 Hz), 0.98 (d, 3H, CH_3, ^iPr, $^3J_{H-H}$= 6.8 Hz), 2.20 (m, 1H, CH, ^iPr), 3.24 (m, 1H, CH-S), 4.01 (m, 2H, CH_2-N), 6.98 (m, 10H, CH=), 7.32 (m, 2H, CH=), 7.54 (m, 3H, CH=). ^{13}C NMR (C_6D_6), δ: 18.6 (CH_3, ^iPr), 21.2 (CH_3, ^iPr), 29.5 (CH, ^iPr), 58.0 (d, CH-S, J_{C-P}= 8.1 Hz), 71.1 (d, CH_2-N, J_{C-P}= 19.1 Hz), 126.0-143.2 (aromatic carbons). MS HR-ESI [found 403.1253, $C_{23}H_{25}OPS$ $(M-Na)^+$ requires 403.1261].

3.4.4.4. Typical Procedure for the synthesis of thioether-phosphite ligands L33a-b

The corresponding phosphorochloridite (1.1 mmol) produced *in situ* was dissolved in toluene (5 mL) and pyridine (3.8 mmol, 0.3 mL) was added. Compound **8** (1 mmol) was azeotropically dried with toluene (3x1 mL) and dissolved in toluene (5 mL) to which pyridine (3.8 mmol, 0.3 mL) was added. The solution was transferred slowly at 0˚C to the phosphorochloridite solution. The reaction mixture was stirred overnight at 80˚C, and the pyridine salts were removed by filtration. The evaporation of the solvent yielded a white foam, which was purified by flash chromatography in alumina (eluent: toluene/triethylamine – 100:1) to produce the corresponding ligand as a white solid.

L33a: Yield: 416 mg (72%). ^{31}P NMR (C_6D_6), δ: 128.8. ^1H NMR (C_6D_6), δ: 0.90 (d, 3H, CH_3, ^iPr, $^3J_{H-H}$= 6.8 Hz), 1.02 (d, 3H, CH_3, ^iPr, $^3J_{H-H}$= 6.8 Hz), 1.51 (s, 9H, CH_3, ^tBu), 1.51 (s, 9H, CH_3, ^tBu), 1.64 (s, 3H, CH_3), 1.67 (s, 3H, CH_3), 2.01 (s, 6H, CH_3), 2.35 (m, 1H, CH, ^iPr), 3.28 (m, 1H, CH-S), 3.68 (m, 1H, CH_2-N), 4.12 (m, 1H, CH_2-N), 6.76 (m, 1H, CH=), 6.87 (m, 2H, CH=), 7.16 (d, 2H, CH=, $^3J_{H-H}$= 5.0 Hz), 7.26 (m, 2H, CH=). MS HR-ESI [found 601.2874, $C_{35}H_{47}O_3PS$ $(M-Na)^+$ requires 601.2881].

L33b: Yield: 352 mg (61%). ^{31}P NMR (C_6D_6), δ: 127.7. ^1H NMR (C_6D_6), δ: 0.89 (d, 3H, CH_3, ^iPr, $^3J_{H-H}$= 6.8 Hz), 1.03 (d, 3H, CH_3, ^iPr, $^3J_{H-H}$= 6.8 Hz), 1.39 (s, 9H, CH_3, ^tBu), 1.52 (s, 9H, CH_3, ^tBu), 1.63 (s, 3H, CH_3), 1.75 (s, 3H, CH_3), 2.01 (s, 3H, CH_3), 2.07 (s, 3H, CH_3), 2.30 (m, 1H, CH, ^iPr), 3.18 (m, 1H, CH-S), 3.93 (m, 1H, CH_2-N), 4.26 (m, 1H, CH_2-N), 6.98 (m, 4H, CH=), 7.17 (m, 1H, CH=), 7.30 (m, 2H, CH=). MS HR-ESI [found 601.2871, $C_{35}H_{47}O_3PS$ $(M-Na)^+$ requires 601.2881].

3.4.4.4. Procedure for the preparation of [Ir(cod)(L31)]BAr_F

The corresponding ligand **L31**H·Br (0.1 mmol) and DCM (3 mL) are added into a flame dried Schlenk. Then, Ag_2O (0.05 mmol) are added and kept in the dark for 2.5 h. After that, the reaction crude is passed through a dry celite pad and evaporated affording complex **10**. Yield: 13.1 mg (29%) as a dark brown foam. ^1H NMR (400 mHz, $CDCl_3$) *δ*: 1.10 (m, 6H, CH_3 ^iPr, Ar), 1.17 (d, 3H, CH_3, ^iPr, $^3J_{H-H}$= 6.8 Hz), 1.18 (d, 3H, $^3J_{H-H}$= 6.8 Hz, CH_3 ^iPr, Ar), 1.21 (m, 6H, CH_3 ^iPr, Ar), 2.11 (m, 1H, CH ^iPr), 2.26 (m, 1H, CH ^iPr, Ar), 2.33 (m, 1H, CH ^iPr, Ar), 3.53 (m, 1H, CH-S), 4.24 (dd, 1H, $^2J_{H-H}$= 14.1 Hz, $^3J_{H-H}$= 9.2 Hz, CH_2-N), 4.56 (dd, 1H, $^2J_{H-H}$= 14.1 Hz, $^3J_{H-H}$= 5.6 Hz, CH_2-N), 7.20-7.50 (m, 8H, CH=). ^{13}C NMR (100.6 mHz, $CDCl_3$) *δ*: 24.2 (CH_3, ^iPr, Ar), 24.3 (CH_3, ^iPr, Ar), 24.4 (CH_3, ^iPr), 24.5 (CH_3, ^iPr), 24.6 (CH_3, ^iPr, Ar), 24.6 (CH_3, ^iPr, Ar), 28.3 (CH_3, ^iPr, Ar), 30.9 (CH, ^iPr), 54.3 (CH_2-N), 59.6 (CH-S), 121.5-138.4 (aromatic carbons), 145.5 (C), 145.7 (C), 146.6 (C). MS HR-ESI [found 921.3919, $C_{52}H_{70}AgN_4S$ $(M)^+$ requires 921.4093].

Precursor $[Ir(\mu\text{-}Cl)(COD)]_2$ (0.1 mmol) are added into a solution of the corresponding silver carbene **10** (0.05 mmol) in DCM (50 mL/mmol) and it is stirred for 4.5 h in the dark. Subsequently, 1.2 eq of $NaBAr_F$ and dionized water (50 mL/mmol) are added and it is stirred for 30 min. Then, it is diluted in DCM and the organic layer extracted, dried with $MgSO_4$, filtrated over celite and the solvent evaporated in vacuo. If it's necessary column chromatography can be performed for further purification (Neutral SiO_2, DCM/Hexane – 75:25). Yield: 10 mg (32%) as a bright orange solid. 1H NMR (400 mHz, $CDCl_3$) δ: 1.0 (d, 3H, $^3J_{H\text{-}H}$= 6.8 Hz, CH_3, ^{i}Pr, Ar), 1.04 (d, 3H, $^3J_{H\text{-}H}$= 6.8 Hz, CH_3, ^{i}Pr, Ar), 1.08 (d, 3H, $^3J_{H\text{-}H}$= 6.8 Hz, CH_3, ^{i}Pr, Ar), 1.10 (d, 3H, $^3J_{H\text{-}H}$= 6.8 Hz, CH_3, ^{i}Pr, Ar), 1.43(d, 3H, $^3J_{H\text{-}H}$= 6.8 Hz, CH_3, ^{i}Pr, Ar), 1.68-1.84 (b, 8H, CH_2, cod) 2.11 (m, 1H, CH, ^{i}Pr), 1.99 (m, 1H, CH, ^{i}Pr), 2.29-3.28 (m, 2H, CH_3, ^{i}Pr, Ar), 3.19 (m, 1H, CH-S), 3.63 (b, 2H, CH, cod), 3.68 (b, 1H, CH, cod), 4.12 (m, 1H, CH, cod) 4.55 (dd, 1H, $^2J_{H\text{-}H}$= 14.2 Hz, $^3J_{H\text{-}H}$= 6.3 Hz, CH_2-N), 4.78 (d, 1H, $^2J_{H\text{-}H}$= 14.2 Hz, CH_2-N), 6.99 (d, 1H, $^3J_{H\text{-}H}$= 1.9 Hz, NHC-H), 7.13 (d, 1H, $^3J_{H\text{-}H}$= 1.9 Hz, NHC-H), 7.28-7.76 (dd, 15H, CH=). ^{13}C NMR (100.6 mHz, $CDCl_3$) δ: 19.7 (CH_3, ^{i}Pr, Ar), 20.5 (CH_3, ^{i}Pr), 23.5 (CH_3, ^{i}Pr, Ar), 25.0 (CH_3, ^{i}Pr, Ar), 25.3 (CH_3, ^{i}Pr, Ar), 28.8 (CH, ^{i}Pr, Ar), 29.5 (CH, ^{i}Pr), 29.9 (CH_2, cod), 32.4 (CH_2, cod), 54.6 (CH_2-N), 58.0 (CH-S), 71.2 (CH, cod), 83.4 (CH, cod), 84.1 (CH, cod), 118.1-160.4 (aromatic carbons), 161.4 (q, C-B, BAr_F, $^1J_{C\text{-}B}$ =49.6 Hz), 169.7 (C). MS HR-ESI [found 705.2872, $C_{34}H_{46}N_2SIr$ $(M)^+$ requires 705.2982].

3.4.4.4. Procedure for the preparation of $[Ir(cod)(P\text{-}S)]BAr_F$ (P-S=L32-L33a-g)

The corresponding ligand (0.074 mmol) was dissolved in CH_2Cl_2 (5 mL) and $[Ir(\mu\text{-}Cl)(cod)]_2$ (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, $NaBAr_F$ (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 silica and the solvent was evaporated, resulting in the product as a red-orange solid.

$[Ir(cod)(L32)]BAr_F$: Yield: 99 mg (87%). ^{31}P NMR (C_6D_6), δ: 103.7 (s). ^{1}H NMR (C_6D_6), δ: 0.91 (d, 3H, CH_3, ^{i}Pr, $^3J_{H\text{-}H}$= 6.8 Hz), 1.01 (d, 3H, CH_3, ^{i}Pr, $^3J_{H\text{-}H}$= 6.8 Hz), 1.93 (m, 5H, CH, ^{i}Pr, CH_2, cod), 2.32 (m, 4H, CH_2, cod), 3.28 (b, 1H, CH, cod), 3.36 (m, 1H, CH-S), 3.55 (b, 1H, CH, cod), 4.28 (m, 2H, CH_2-N, CH, cod), 4.61 (m, 1H, CH_2-N), 4.98 (b, 2H, CH, cod), 7.26-7.72 (m, 27H, aromatic protons). ^{13}C NMR (C_6D_6), δ: 17.5 (CH_3, ^{i}Pr), 20.4 (CH_3, ^{i}Pr), 28.8 (d, CH_2, cod, $J_{C\text{-}P}$= 2.0 Hz), 29.0 (d, CH_2, cod, $J_{C\text{-}P}$= 2.0 Hz), 29.6 (CH_2, cod), 30.3 (CH, ^{i}Pr), 32.2 (d, CH_2, cod, $J_{C\text{-}P}$= 6.9 Hz), 59.0 (CH-S), 68.9 (CH_2-N), 73.2 (CH, cod), 73.3 (CH, cod), 99.7 (d, CH, cod, $J_{C\text{-}P}$= 11.4 Hz), 100.6 (d, CH, cod, $J_{C\text{-}P}$= 11.9 Hz), 117.4-134.8 (aromatic carbons), 161.6 (q, C-B, BAr_F, $^1J_{C\text{-}B}$ =49.9 Hz). MS HR-ESI [found 681.1921, $C_{31}H_{37}IrOPS$ $(M)^+$ requires 681.1932].

$[Ir(cod)(L33a)]BAr_F$: Yield: 110 mg (87%). ^{31}P NMR (C_6D_6), δ: 96.4 (s). ^{1}H NMR (C_6D_6), δ: 1.01 (d, 3H, CH_3, ^{i}Pr, $^3J_{H\text{-}H}$= 6.6 Hz), 1.11 (d, 3H, CH_3, ^{i}Pr, $^3J_{H\text{-}H}$= 6.6 Hz), 1.47 (s, 9H,

CH_3, ^{t}Bu), 1.65 (s, 9H, CH_3, ^{t}Bu), 1.78 (s, 3H, CH_3), 1.84 (s, 3H, CH_3), 2.05 (m, 9H, CH, ^{i}Pr, CH_2, cod), 2.29 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 3.08 (b, 1H, CH, cod), 3.29 (m, 1H, CH-S), 4.37 (b, 1H, CH, cod), 4.63 (m, 2H, CH_2-N, CH, cod), 4.98 (m, 1H, CH_2-N, CH, cod), 7.25-7.73 (m, 19H, aromatic protons). ^{13}C NMR (C_6D_6), δ: 14.5 (CH_3), 14.6 (CH_3), 17.3 (CH_3, ^{i}Pr), 18.3 (CH_3), 18.5 (CH_3), 18.9 (CH_3, ^{i}Pr), 25.7 (b, CH_2, cod), 27.0 (CH, ^{i}Pr), 27.5 (b, CH_2, cod), 29.6 (CH_3, ^{t}Bu), 30.2 (d, CH_2, cod, J_{C-P}= 3.9 Hz), 30.7 (CH_3, ^{t}Bu), 31.4 (, CH_2, cod, J_{C-P}= 3.1 Hz), 32.9 (C, ^{t}Bu), 33.2 (C, ^{t}Bu), 60.7 (CH-S), 66.9 (CH, cod), 67.8 (CH_2-N), 75.5 (CH, cod), 101.0 (d, CH, cod, J_{C-P}= 14.5 Hz), 104.3 (d, CH, cod, J_{C-P}= 14.9 Hz), 115.5-134.9 (aromatic carbons), 159.7 (q, C-B, BAr_F, $^1J_{C-B}$ =49.7 Hz). MS HR-ESI [found 879.3557, $C_{43}H_{59}IrO_3PS$ (M^+) requires 879.3552].

[Ir(cod)(L33b)]BAr_F: Yield: 102 mg (79%). ^{31}P NMR (C_6D_6), δ: 98.2 (s). ^{1}H NMR (C_6D_6), δ: 0.91 (d, 3H, CH_3, ^{i}Pr, $^3J_{H-H}$= 6.9 Hz), 1.04 (d, 3H, CH_3, ^{i}Pr, $^3J_{H-H}$= 6.8 Hz), 1.46 (s, 9H, CH_3, ^{t}Bu), 1.65 (s, 9H, CH_3, ^{t}Bu), 1.79 (s, 3H, CH_3), 1.82 (s, 3H, CH_3), 2.03 (m, 9H, CH, ^{i}Pr, CH_2, cod), 2.29 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 3.04 (b, 1H, CH, cod), 3.43 (m, 1H, CH-S), 4.36 (m, 1H, CH_2-N), 4.67 (m, 3H, CH_2-N, CH, cod), 5.11 (b, 1H, CH, cod), 7.28-7.93 (m, 19H, aromatic protons). ^{13}C NMR (C_6D_6), δ: 14.4 (CH_3), 14.6 (CH_3), 18.3 (2xCH_3, ^{i}Pr), 18.4 (2xCH_3) 25.8 (d, CH_2, cod, J_{C-P}= 2.2 Hz), 26.6 (CH, ^{i}Pr), 27.3 (b, CH_2, cod), 29.7 (CH_3, ^{t}Bu), 30.4 (d, CH_2, cod, J_{C-P}= 4.3 Hz), 30.6 (CH_3, ^{t}Bu), 31.4 (, CH_2, cod, J_{C-P}= 2.6 Hz), 32.9 (C, ^{t}Bu), 33.1 (C, ^{t}Bu), 54.8 (CH-S), 65.1 (CH, cod), 65.4 (CH_2-N), 76.9 (CH, cod), 102.9 (d, CH, cod, J_{C-P}= 14.4 Hz), 104.1 (d, CH, cod, J_{C-P}= 14.7 Hz), 115.5-142.3 (aromatic carbons), 159.8 (q, C-B, BAr_F, $^1J_{C-B}$ =49.9 Hz). MS HR-ESI [found 879.3590, $C_{43}H_{59}IrO_3PS$ (M^+) requires 879.3552].

3.4.4.5. Procedure for the preparation of compound 7

To a cooled (-10 ˚C) solution of 2,6-dimethylthiophenol (0.7 mL, 5.13 mmol) in dry THF (28 mL) was added DBU dropwise (0.8 mL, 5.13 mmol). After 20 min a white suspension was formed and a solution of **5** (1.5 g, 4.31 mmol) in THF was added. The reaction mixture was stirred at -10 ˚C for 90 min and then 2.5 h at RT. When the reaction was completed, the mixture was quenched with water and extracted with Et_2O. The organic phases were washed with water and brine. After drying over $MgSO_4$, the organic solution was concentrated in vacuo, and the crude was purified by silica flash chromatography (PE/EtOAc 9:1) to afford desired compound **7** (98 mg, 92% yield). ^{1}H NMR (400 mHz, $CDCl_3$) δ: 1.06 (d, 3H, CH_3, $^3J_{H-H}$= 6.8 Hz), 1.08 (d, 3H, CH_3, $^3J_{H-H}$= 6.8 Hz), 2.01 (m, 1H, CH, ^{i}Pr), 2.11(b, 1H, OH), 3.06 (ddd, 1H, $^3J_{H-H}$= 7.3 Hz, $^3J_{H-H}$= 6.0 Hz, $^3J_{H-H}$= 5.0 Hz, CH-S), 3.60 (dd, 1H, $^2J_{H-H}$= 12.0 Hz, $^3J_{H-H}$= 7.3 Hz, CH_2-OH), 3.74 (dd, 1H, $^2J_{H-H}$= 12.0 Hz, $^3J_{H-H}$= 5.0 Hz, CH_2-OH), 7.21-7.47 (m, 5H, CH=).

3.4.4.6. 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. It was then 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-S2**,[3l] **S3**,[3h] **S4**,[3l] **S5**,[15] **S6,**[16] **S7**,[3l] **S8**,[17] **S9**[18] and **S10**[19] were determined using the conditions previously described.

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3.4.6. REFERENCES

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3.5. Pyrrolidine-based P,O ligands from carbohydrates: Easily accessible and modular ligands for the Ir-catalyzed asymmetric hydrogenation of minimally functionalized olefins

Carlota Borràs, Pilar Elías-Rodríguez, Ana T. Carmona, Jordi Faiges, Inmaculada Robina, Oscar Pàmies and Montserrat Diéguez in manuscript to be submitted.

Abstract: *A modular pyrrolidine-based phosphine/phosphite-O/S ligand library is presented. These ligands are obtained in enantiomerically pure form, from readily available sugars. Carbohydrates are highly functionalized compounds with several stereogenic centers. Their modular nature offers a wide variety of opportunities for the derivatization and tailoring of synthetic tools in the search for the best ligand for each particular substrate. This new P-O/S ligand library have been applied on the reduction of a broad scope of minimally functionalized trisubstituted olefins with a different electron and steric characteristics and on the more challenging 1,1-disubtituted terminal olefins. 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. High enantioselectivities (ee's up to 99%) could therefore be achieved in the asymmetric hydrogenation of selected tris- and disubstituted substrates.*

3.5.1. Introduction

Enantiomerically pure compounds are relevant in pharmacy, agro-chemistry, fine chemistry and natural product chemistry. Enormous efforts are being made to improve the enantioselective routes for synthesizing these compounds. Of them, asymmetric metal-based catalysis is one of the most efficient, sustainable and straightforward.[1] Among the metal-catalyzed processes, the asymmetric hydrogenation (AH) of selected olefins has dominated both industry and academia, mainly because of its high efficiency in transferring the chiral information from the catalyst to the product, its perfect atom economy and its operational simplicity.[1a,1c-e,1g,2] This field is dominated by the Rh- and Ru-diphosphine catalysts for the hydrogenation of functionalized olefins (e.g. enamides, dehydroamino acid derivatives, …)[1,3] and the Ir-P-oxazoline catalysts for the reduction of minimally functionalized olefins (those without a highly coordinative group)[4]. Compared to the AH of functionalized olefins, the reduction of minimally functionalized olefins is underdeveloped and thus its synthetic utility is limited. Despite the advances in catalyst design with new types of heterodonor ligands, mainly P,N-, most catalysts are sensitive to the olefin geometry and the nature of the substrate. In 2011, Pfaltz and coworkers demonstrated for the first time that phosphine,O ligands (Figure 3.5.1), that coordinate to the metal through the carbonyl oxygen atom and the phosphine moiety, can also be used in the AH of minimally

functionalized olefins with enantioselectivities comparable to the most commonly used Ir-P-oxazoline catalysts. However, high enantioselectivities were obtained only for a few trisubstituted olefins.[5] The results indicated that high enantioselectivities were obtained when substituents at both the phosphine group and the O-donor moiety were bulky. After this initial success, no new developments were published with these P,O-ligands.[6]

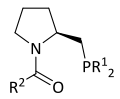


Figure 3.5.1. Proline-based P-O ligands used by Pfaltz and coworkers for the asymmetric hydrogenation of minimally functionalized trisubstituted olefins.

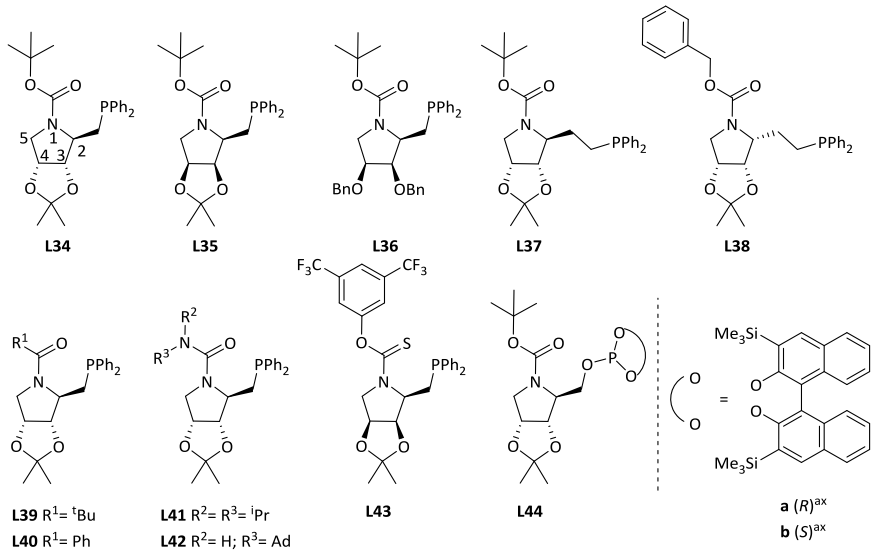


Figure 3.5.2. Pyrrolidine-based phosphine/phosphite-O/S ligand library **L34**-**L44**.

To further investigate the potential of P,O-based ligands in the Ir-catalyzed asymmetric hydrogenation of minimally functionalized olefins, we developed a modular pyrrolidine-based phosphine/phosphite-O/S ligand library (**L34**-**L44**; Figure 3.5.2). The new ligands are relevant not only because they are easily prepared in a large scale from cheap carbohydrates (D-mannose, D-ribose and D-arabinose), but also because they can be easily modulated with well-established carbohydrate chemistry. These series of ligands allowed us to study the effect on catalytic performance of (i) the configuration of the pyrrolidine moiety (with ligands **L34** and **L35**), (ii) the pyrrolidine backbone rigidity (with ligands **L35** and **L36**), (iii) the size of the chelate ring (with ligands **L37** and **L38**), (iv) the type of O-donor group (carbamate, **L34**; amide, **L39**-**L40**; and urea, **L41**-**L42**), (v) replacing the carbamate O-donor group by a

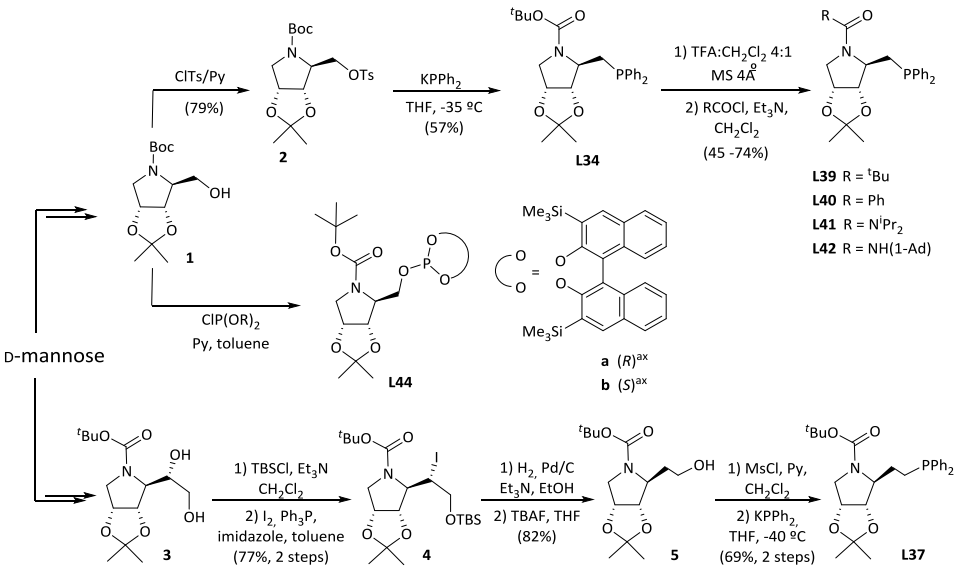
thiocarbamate moiety (ligand **L43**) and (vi) replacing the phosphine moiety by a chiral biaryl phosphite group (ligands **L44**).

3.5.2. Results and discussion

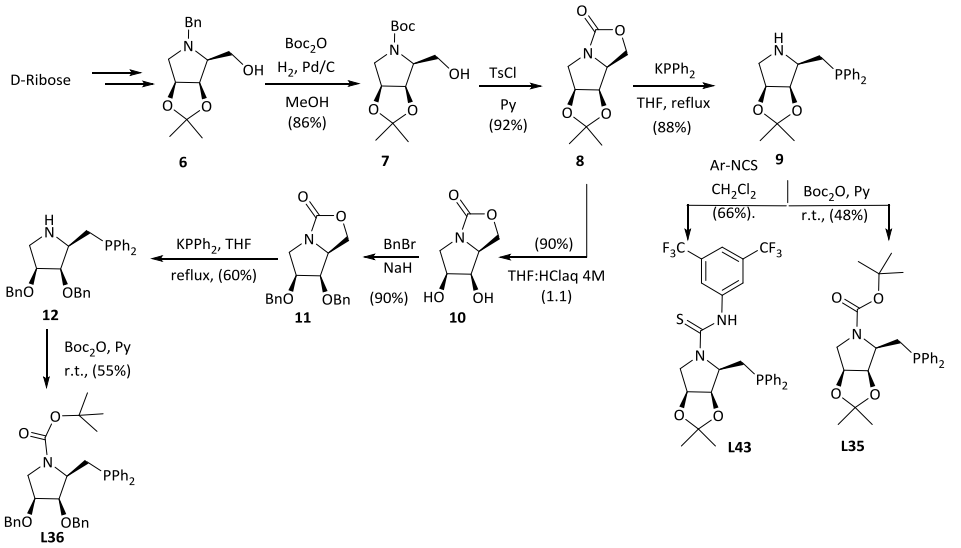
3.5.2.1. Synthesis of ligands

Schemes 3.5.1-3.5.3 show the synthetic sequences, first for those ligands derived from D-mannose, then for ligands derived from D-ribose and finally for ligands derived from D-arabinose. Starting from D-mannose (Scheme 3.5.1), the phosphine/phosphite-O ligands **L34**, **L39-L42** and **L44a**-**b** were obtained. They have the same configuration of the carbons bearing the isopropylidene group and differ on the type of the O-donor group and the type of P-functionality. Their synthesis started from pyrrolidine compound **1** which have been recently reported by our group,[7] through tosylation of alcohol **1** easily obtained from D-mannose following a modified Fleet's methodology.[8] Reaction of tosylate **2** with $KPPh_2$ in THF at -35 °C afforded amino-phosphine **L34** in 57% yield. Its structure was confirmed by ^{1}H-NMR with the disappearance of the signals corresponding to the tosyl group and the appearance of a multiplet (δ = 7.55-7.33 ppm) for 10 H corresponding to the diphenylphosphino group. In the ^{31}P-NMR spectrum the signal at -23.2 ppm is compatible with the phosphine moiety. Boc deprotection and reaction with different acyl halides in the presence of Et_3N gave compounds **L39**-**L42**, with amide and urea groups, in moderate-to-good yields. Their structures were also confirmed by NMR. Therefore, ^{31}P-NMR spectra show the expected one singlet in the region compatible with the phosphine moiety, except for **L40** that the presence of two rotamers were detected. Reaction of alcohol **1** with one equivalent of the corresponding *in situ* phosphorochloridite ($ClP(OR)_2$) gave access to carbamate-phosphite ligands **L44a-b** with the desired configuration of the biaryl phosphite group. The ^{31}P-NMR spectra shows two singlets for each compound at around 130 ppm compatible with phosphite moieties. The presence of two rotamers for each ligand, as for **L40**, were confirmed by performing the 2D-^{31}P DOSY NMR experiment that shows that the two isomers have the same diffusion coefficient. Both isomers also show the same HR-mass spectra.

Protected pyrrolidine-phosphine **L37**, with a 2,3-*trans* configuration and which differs of ligand **L34** in a longer phosphine alkyl chain, was also prepared starting from D-mannose (Scheme 3.5.1) through intermediate **3** that was recently reported by us.[7] Primary alcohol protection and iodination afforded derivative **4**, which after hydrogenation and subsequent deprotection gave alcohol **5**. Mesylation and displacement with $KPPh_2$ in THF at -40 ˚C furnished protected pyrrolidine phosphine-carbamate **L37** in 69% yield. The ^{31}P-NMR spectrum shows the expected singlet at -15.4 ppm compatible with a phosphine moiety.



Scheme 3.5.1. Synthesis of ligands **L34**, **L37**, **L39**-**L42** and **L44a**-**b** derived from D-mannose.

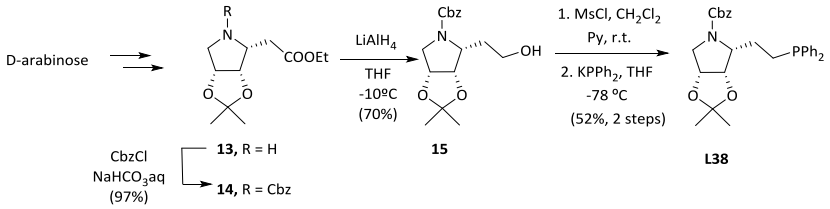


Scheme 3.5.2. Synthesis of ligands **L35**-**L36** and **L43** derived from D-ribose.

The preparation of ligands **L35**, **L36** and **L43** with different configuration of the carbons bearing isopropylidene group than **L34** and **L37** analogues, is shown in Scheme 3.5.2. Starting from D-ribose, compound **6** was prepared following reported procedure.[9] *N*-Boc protection and tosylation afforded cyclic carbamate **8** as was observed by us in similar 2,3-*cis* compounds.[10] Nucleophilic ring opening with $KPPh_2$ in THF gave the corresponding pyrrolidine-phosphine **9**. The phosphine moiety was ascertained by the signal at -20.9 ppm in the ^{31}P-NMR. Reaction with 3,5-ditrifluoromethylisothycyanate and Boc_2O/Py gave thiourea-phosphine ligand **L43** and

carbamate-phosphine ligand **L35**, respectively, in moderate yields. Deprotection of cyclic carbamate **8** with THF:HCl_{aq} 4M (1:1) followed by conventional benzylation gave the benzylated carbamate **11**. The nucleophilic ring opening of **11** using $KPPh_2$ in refluxing THF followed by *N*-Boc protection afforded **L36** in 55% yield.

Finally, protected pyrrolidine-phosphine **L38**, with a 2,3-*cis* configuration and differ from **L37** in the configuration of C-2 of the ligand backbone, was obtained from **13** which was prepared from D-arabinose (Scheme 3.5.3) following the same procedure described by us for its enantiomer.[11] Carbamate protection and reduction with $LiAlH_4$ at -10 °C gave alcohol **15** in good yield. Phosphine moiety was introduced by the above described conventional method giving **L38** in 52% yield.



Scheme 3.5.3. Synthesis of ligand **L38** derived from D-arabinose.

The formation of all ligands was confirmed by $^{31}P\{^1H\}$, ^1H and $^{13}C\{^1H\}$ NMR spectra and mass spectrometry. The spectra assignments were supported by the information obtained from ^1H-^1H and ^1H-^{13}C correlation measurements. See experimental section for purification and characterization details.

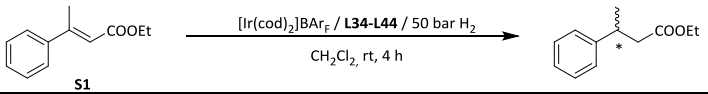
3.5.2.2. Asymmetric Ir-catalyzed hydrogenation of olefins

The library of P,O/S ligands **L34**-**L44** was evaluated in the iridium-catalyzed asymmetric hydrogenation of both, trisubstituted minimally functionalized olefins (**S1**-**S16**) and more challenging 1,1-disubstituted olefins (**S17**-**S31**). The catalyst was generated *in situ* by adding the corresponding P,O/S ligand to the catalyst precursor $[Ir(cod)_2]BAr_F$ following the procedure previously reported by Pfaltz.[5j]

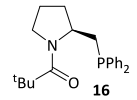
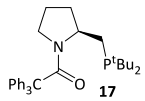
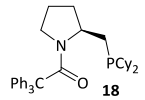
Initially, as in the previous study with proline-based P,O ligands reported by Pfaltz, we tested the potential of ligands **L34**-**L44** in the AH of ethyl (*E*)-3-phenylbut-2-enoate **S1** (Table 3.5.1). This allows a direct comparison with the Pfaltz P,O catalytic systems. Moreover, chiral carboxylic esters are versatile chiral building blocks for the preparation of fine chemicals (e.g. natural products, agrochemicals, fragrances …). The results with ligands **L34**-**L36** indicated that the catalytic outcome (activity and enantioselectivity) is very sensitive to the proper selection of the chirality and the rigidity of the pyrrolidine moiety (entries 1-3). The highest enantioselectivities were achieved using ligand **L34** (entry 1), with an *R*-configuration at C-2 and a (*3S*,*4R*)-isopropylidene group. The results with ligands **L34**, **L37** and **L38** also indicated that the chelate ring size also influences the catalytic performance. Ligands **L37**-**L38**, that form

a less stable 8-membered chelate ring, provide lower enantioselectivities than ligands **L34** and **L35** (entries 4-5 vs 1-2). This is in agreement with the hemilabile character of the carbamate group upon coordination to iridium. Moreover, the use of ligand **L37** has an extremely negative effect on activity. The results also indicated that the nature of the O-donor group affects enantioselectivity considerably (entries 1, 6-9). The presence of a carbamate (ligand **L34**) or an amido (ligands **L39** and **L40**) group are needed to achieve the highest enantioselectivities (ee's up to 98%). We also found that the replacement of either the carbamate moiety (ligand **L34**) by a thiocarbamate group (ligand **L43**) or the phosphine (ligand **L34**) by a biaryl phosphite moiety (ligands **L44**) has a detrimental effect on catalytic performance (entry 1 vs 10-12).

Table 3.5.1. Ir-catalyzed hydrogenation of substrate **S1** using Ir(cod)BAr_F/**L34**-**L44** catalyst precursors.



S1

Entry	Ligand	% Conv[b]	ee %[c]
1	**L34**	80	97 (*R*)
2	**L35**	35	68 (*R*)
3	**L36**	35	58 (*R*)
4	**L37**	<5	nd
5	**L38**	100	30 (*S*)
6	**L39**	29	97 (*R*)
7	**L40**	40	98 (*R*)
8	**L41**	60	70 (*R*)
9	**L42**	58	67 (*R*)
10	**L43**	<2	nd
11	**L44a**	50	65 (*R*)
12	**L44b**	<5	3 (*S*)
13[d]	 **16**	65	33 (*R*)
14[d]	 **17**	>99	98 (*R*)
15[d]	 **18**	>99	94 (*R*)

[a] Reactions carried out using 0.5 mmol of substrate and 2 mol% of Ir-catalyst precursor, 2 mol% of corresponding ligand at 50 bar of H_2 for 4 h. [b] Conversion determined by chiral GC or ^{1}H NMR. [c] Enantiomeric excess determined by chiral GC or HPLC. [d] Data from *Angew. Chem. Int. Ed*. **2011**, *50*, 9598

In summary, by properly selecting the ligand parameters high enantioselectivities can be achieved (ee's up to 98%) using the pyrrolidine-based phosphine-carbamate and phosphine-amido ligands **L34**, **L39** and **L40**. If we compare the results with those achieved with the proline-based analogues, we can conclude that the introduction of a more rigid bicyclic backbone had a positive effect on enantioselectivity. Enantioselectivities increases from 33% to 97% ee when using ligand **L6** instead of **16** (entry 6 vs 13). In addition, our results are comparable with the excellent enantioselectivities achieved when using the bulkier and less stable di-*tert*-butyl- or dicyclohexyl-phosphino analogues **17** and **18** developed by Pfaltz's group (see Table 1, entries 14 and 15).

To further establish the scope of the new P,O-ligands we selected a representative family of trisubstituted substrates (Figure 3.5.3). Primarily, we focused on the reduction of a variety of α,β-unsaturated carboxylic esters **S2**-**S11** using Ir/**L34** catalytic system, that have provided the best trade of between activity and enantioselectivity. Advantageously, the ee's were independent of the electronic nature of the substrate phenyl ring (**S1**-**S4**) and the steric nature of the alkyl substituent (**S1**, **S5**-**S7**). Interestingly, high enantioselectivities were also attained in the reduction of the more challenging Z-analogues (**S8**-**S9**) as well as for the challenging α-substituted carboxylic esters **S10** and **S11**. However, the pyrrolidine-based Ir-P,O catalytic systems seems to be less appropriate for the reduction of the much studied model α-methylstillbene **S12**, allylic alcohol **S14** and enone **S15**. Nevertheless, enantioselectivities up to 90% ee were achieved in the reduction of β-substituted unsaturated ketone **S16**.

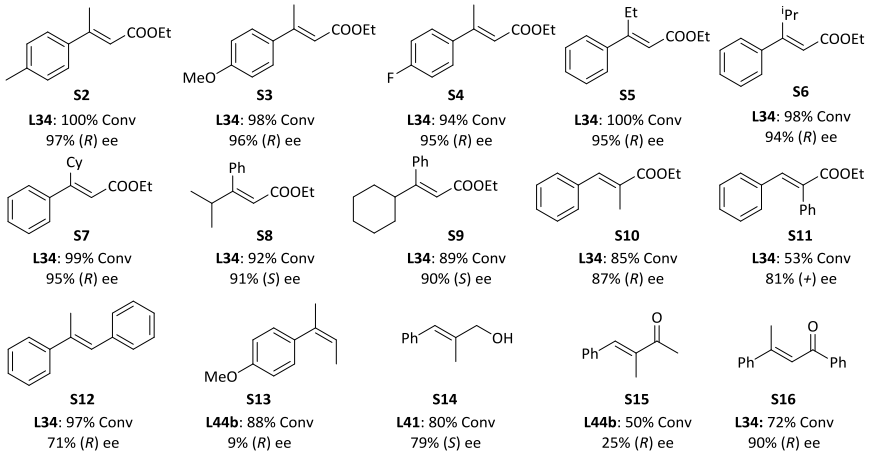
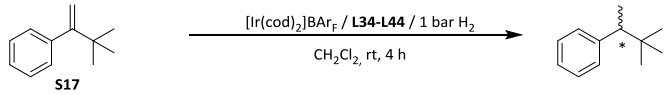


Figure 3.5.3. Selected results for the asymmetric hydrogenation of minimally functionalized trisubstituted olefins. Reaction conditions: 2 mol% of catalyst precursor, 2 mol% of **L34**, CH_2Cl_2 as solvent, 50 bar of H_2, 4 h.

Encouraged by previous results, we next screened ligands **L34**-**L44** in the asymmetric hydrogenation of more the demanding terminal olefins. Unlike trisubstituted substrates 1,1-disubstituted olefins have not been successfully hydrogenated until more recently. Only few catalysts have provided high

enantioselectivitites. This is because the catalyst has the added difficulty of controlling not only the face selectivity coordination (only two substituents compared with the three of trisubstituted olefins), but also the isomerization of the olefins to form the more stable *E*-trisubstituted substrates, which are hydrogenated to form the opposite enantiomer. As a model substrate, we have chosen the 3,3-dimethyl-2-phenyl-1-butene **S17** to assess the potential of the new ligand library. The results, which are summarized in Table 3.5.2, indicated that the effect of the different ligand parameters follow a similar general trend than in the hydrogenation of trisubstituted olefins, except for the nature of the O-donor group. The highest enantioselectivity (74% ee at only 1 bar of H_2, entry 1) was achieved with the pyrrolidine-based carbamate-phosphine ligand **L34**, while ligands **L39** and **L40** that provided also high enantioselectivity in the reduction of trisubstituted olefins were much less enantioselective (entry 6 and 7).

Table 3.5.2. Ir-catalyzed hydrogenation of substrate **S17** using Ir(cod)BAr_F/**L34**-**L44** catalyst precursors.[a]

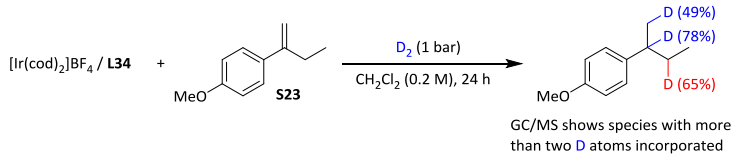


Entry	Ligand	% Conv[b]	ee %[c]
1	**L34**	80	74 (*R*)
2	**L35**	25	44 (*R*)
3	**L36**	33	42 (*R*)
4	**L37**	40	7 (*R*)
5	**L38**	100	9 (*S*)
6	**L39**	15	50 (*R*)
7	**L40**	16	12 (*R*)
8	**L41**	75	45 (*R*)
9	**L42**	35	33 (*R*)
10	**L43**	<2	nd
11	**L44a**	12	29 (*S*)
12	**L44b**	10	8 (*R*)

[a] Reactions carried out using 0.5 mmol of substrate and 2 mol% of Ir-catalyst precursor, 2mol% of corresponding ligand at 1 bar of H_2 for 4 h. [b] Conversion determined by chiral GC or ^{1}H NMR. [c] Enantiomeric excess determined by chiral GC.

We next studied the scope of the ligand library in asymmetric hydrogenation of other 1,1-disubstituted alkenes (Figure 3.5.4). Initially, we focused on the reduction of a variety of 3,3-dimethyl-2-aryl-1-butenes **S18**-**S22**, with different electronic and steric properties at the aryl moiety. As for trisubsititued α,β-unsaturated carboxylic esters, enantiomeric excesses are hardly affected by variations in the electronic and steric nature of the substrate aryl substitutent (ee's ranging from 73% to 76%). We then

studied how the nature of the alkyl chain affected enantioselectivity by comparing substrates **S17** and **S23**–**S25**. The results indicate a huge effect on the nature of the alkyl chain on enantioselectivity. Thus, high enantioselectivities are only accessible for substrates containing a *tert*-butyl group (i.e. 74% ee for **S17** vs <20% ee for substrates **S23**–**S25**). These results are in line with the presence of a competing isomerization process, which was confirmed by studying the degree of indirect incorporation of deuterium due to the isomerization process in the deuteration of **S23** (Scheme 3.5.3).



Scheme 3.5.3. Deuteration of substrate **S23**. The percentage of incorporation of deuterium atoms is shown in brackets. The results of the indirect addition of deuterium due to the isomerization process are shown in red.

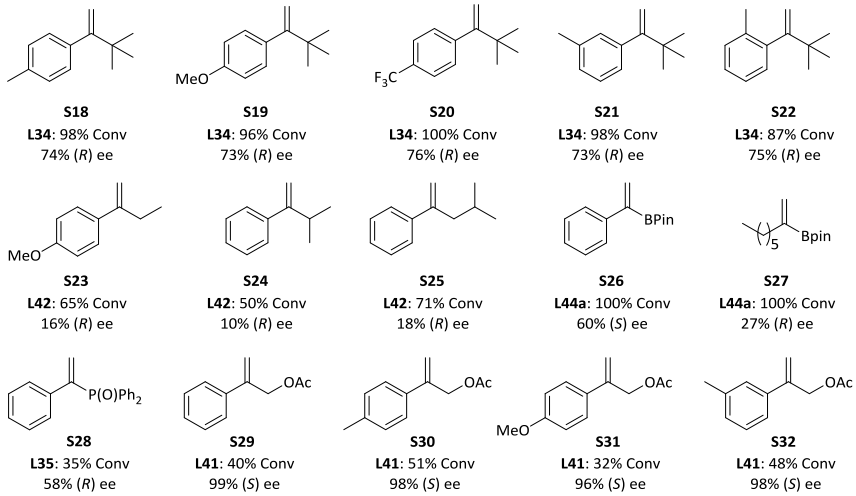


Figure 3.5.4. Selected results for the asymmetric hydrogenation of 1,1-disubstituted substrates **S18**-**S32** using $[Ir(cod)_2]$/**L34**-**L44** as catalyst precursor. Reaction conditions: 2 mol% of $[Ir(cod)_2]BAr_F$, 2 mol% of ligand, CH_2Cl_2 as solvent, 1 bar of H_2, 4 h.

Finally, we focused our attention to the hydrogenation of terminal olefins containing minimally coordinating polar groups, which would led to versatile building blocks. For this purpose, we focused in the reduction of aryl and alkyl boronic esters (**S26** and **S27**), enol phosphinate (**S28**) and allylic acetates (**S29**-**S32**). Remarkably, the pyrrolidine-based P,O ligands are well suited for the reduction of allylic acetates. Thus, high enantioselectivities (ranging from 97% to 99% ee) have been achieved for a range of differently substituted allylic acetates (**S29**-**S32**). Derivatives of the hydrogenation products of **S29**-**S32** are highly valuable. Thus, for instance, they are used in the cosmetic industry as components of fragrance mixtures (i.e., Pamplefleur) and also in

the pharmaceutical industry (i.e., intermediates for the synthesis of modulators of dopamine D3 receptors).[12]

3.5.3. Conclusions

A modular pyrrolidine-based phosphine/phosphite-O/S ligand library has been applied in the hydrogenation of minimally functionalized olefins. The new ligands are relevant not only because they are easily prepared in a large scale from cheap carbohydrates (D-mannose, D-ribose and D-arabinose), but also because they can be easily modulated with well-established carbohydrate chemistry. 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. High enantioselectivities (ee's up to 99%) could therefore be achieved in the asymmetric hydrogenation of selected tris- and disubstituted substrates.

3.5.4. Experimental Part

3.5.4.1. General remarks

All reactions were carried out using standard Schlenk techniques under an atmosphere of argon. Commercial chemicals were used as received. Solvents were dried by standard procedures and stored under argon. Phosphorochloridites were easily prepared in one step from the corresponding biphenols.[13] Compounds **1**[8], **2**[7], **3**[9], **10**[7] and **13**[11] were prepared as previous reported. Optical rotations were measured in a 1.0 cm or 1.0 dm tube with a Jasco P-2000 spectropolarimeter. Infrared spectra were recorded with Jasco FTIR-410 spectrometer. ^{1}H, $^{13}C\{^{1}H\}$ and $^{31}P\{^{1}H\}$ NMR spectra were recorded using a Bruker, AV300, AV500 and Varian Mercury-400 MHz spectrometer for solutions in $CDCl_3$, C_6D_6 and DMSO-d_6 at room temperature. Chemical shifts are relative to that of $SiMe_4$ (^{1}H and $^{13}C\{^{1}H\}$) 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. Mass spectra (CI and ESI) were recorded on Micromass AutoSpeQ and QTRAP (Applied Biosystem) and Orbitrap Elite spectrometers. NMR and mass spectra were registered in CITIUS (university of Seville) and in SRCiT (Universitat Rovira I Virgili).

(2*R*,3*S*,4*R*)-*N*-*terc*-Butoxycarbonyl-2-diphenylphosphinomethyl-3,4-*O*-isopropylidene-pyrrolidine-3,4-diol (L34)

Tosylate **2** (300 mg, 0.7 mmol) was dissolved in dry THF (9 mL) under argon and was cooled to -35 ˚C. Then $KPPh_2$ (1.7 mL, 0.9 mmol, 0.5 M in THF) was slowly added and the reaction mixture was stirred for 50 min. IRA-120H^{+} was added, stirred for several minutes and then filtered through Celite, washed with AcOEt and evaporated to dryness. Column chromatography on silica gel (Cyclohexane → AcOEt:cyclohexane, 1:5), gave **L34** (176 mg, 0.4 mmol, 57%) as a colourless oil. ^{31}P NMR (121.5 MHz,

DMSO-d_6 a 343 K, δ ppm) δ -23.2 (s). ^{1}H NMR (300 MHz, DMSO-d_6, 343 K, δ ppm, *J* Hz) δ 1.22 (s, 3H, CH_3), 1.29 (s, 12H, CH_3, ^{t}Bu, NBoc, CH_3), 2.27 (m, 2H, CH_2-OP), 3.34 (dd, 1H, CH_2-N $^2J_{H-H}$= 12.9, $^3J_{H-H}$ = 4.5), 3.66 (m, 1H, CH_2-N), 3.97 (m, 1H, CH-N), 4.73 (m, 2H, CH-O), 7.44 (m, 10H, CH=). ^{13}C NMR (75.4 MHz, DMSO-d_6, 343 K, δ ppm) δ 24.5 (CH_3), 26.4 (CH_3), 27.1 (CH_3, ^{t}Bu, NBoc), 29.1 (CH_2-OP), 50.2 (CH_2-N), 60.9 (CH-N), 78.4 (CH_3, CH-O), 83.7 (CH-O), 110.3 (C), 139.0-128.1 (aromatic carbons), 153.2 (C=O). α_D +48.4 (*c* 0.56, CH_2Cl_2). IR ν_{max} 2980, 2927, 1691 (C=O), 1162, 1055, 695 cm^{-1}.

3.5.4.2. General procedure for the prefortion of compounds L39-L42

TFA (20 mol%) was added dropwise at 0 °C to a solution of **L34** (0.2 mmol) in dry CH_2Cl_2 (3 mL) containing 4 Å molecular sieves. The mixture was stirred at r.t. for 1 h, then filtered and evaporated to dryness. The residue was dissolved in CH_2Cl_2, treated with Ambersep 900 (OH^-) resin, filtered and evaporated. A solution of NEt_3 (2.0 eq.), the corresponding carbonyl compound (1.3 eq.) and the deprotected amine was stirred at r.t. for 2-4 h. After addition of sat. aquousNH_4Cl, the mixture was extracted with CH_2Cl_2 (3x10 mL). The combined organic phases were washed brine, dried (Na_2SO_4), filtered and concentrated. Purification by column chromatography on silica gel afforded the corresponding acylated compound.

(2*R*,3*S*,4*R*)-*N*-Pivaloyl-2-diphenylphosphinomethyl-3,4-*O*-isopropylidene-pyrrolidine-3,4-diol (L39)

Compound **L39** (74% yield) was prepared according to *general procedure* from **L34** and pivaloyl chloride, followed by column chromatography on silica gel (AcOEt:cyclohexane - 1:5). ^{31}P NMR (121.5 MHz, $CDCl_3$, δ ppm) δ -24.2 (s). ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm) δ 1.14 (s, 9H, CH_3, ^{t}Bu, NBoc), 1.14 (s, 9H, CH_3, ^{t}Bu, NBoc), 1.28 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 2.18 (m, 1H, CH_2-OP), 2.44 (m, 1H, CH_2-OP), 3.51 (m, 1H, CH_2-N), 4.09 (m, 1H, CH_2-N), 4.68 (br.s, 1H, CH-N), 4.81 (m, 2H, CH-O), 7.35 (m, 6H, CH=), 7.43 (m, 2H, CH=), 7.53 (m, 2H, CH=). ^{13}C NMR (75.4 MHz, $CDCl_3$, δ ppm) δ 25.0 (CH_3), 26.7 (CH_3), 27.7 (CH_3, ^{t}Bu, NBoc), 29.7 (CH_2-OP), 38.7 (CH_3), 53.0 (CH_2-N), 63.0 (CH-N), 80.2 (CH-O), 82.3 (CH-O), 111.7 (C), 138.5-128.7 (aromatic carbons), 176.4 (C=O), α_D +198.4 (*c* 0.56, CH2Cl2). ESI-HRMS m/z found 426.2186, calc. for $C_{25}H_{33}NO_3P$ [M+H]+: 426.2193.

(2*R*,3*S*,4*R*)-*N*-Benzoyl-2-diphenylphosphinomethyl-3,4-*O*-isopropylidene-pyrrolidine-3,4-diol (L40)

Compound **L40** (72% yield) was prepared according to the general procedure from **L34** and benzoyl chloride, followed by column chromatography on silica gel (AcOEt:hexane - 1:7). Major rotamer (63%): ^{31}P NMR (121.5 MHz, $CDCl_3$, δ ppm): -24.8 (s). ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 1.28 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 2.42 (dd, 1H, CH_2-OP, $^2J_{H-H}$ = 8.4 Hz), 2.52 (ddd, 1H, CH_2-OP, $^2J_{H-H}$ = 14.1 Hz, $^3J_{H-H}$ = 5.4 Hz, $^4J_{H-H}$ = 1.8 Hz), 3.63 (m, 2H, CH_2-N), 4.88 (m, 3H, CH-N, 2x CH-O), 7.31 (m, 15H, CH=). ^{13}C NMR (75.4 MHz, $CDCl_3$, δ ppm): 25.0 (CH_3), 26.9 (CH_3), 30.5 (d, CH_2-OP, J_{C-P} = 16.1 Hz), 54.5

(CH_2-N), 61.3 (d, CH-N, J_{C-P} = 14.9 Hz), 79.7 (CH-O), 84.2 (d, CH-O, J_{C-P}= 9.7 Hz), 111.9 (C, major rotamer), 138.2-127.3 (aromatic carbons), 170.8 (C=O minor). Minor rotamer (37%): ^{31}P NMR (121.5 MHz, $CDCl_3$, δ ppm), -24.8 (s). ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 1.33 (s, 3H, CH_3), 1.51 (s, 3H, CH_3), 1.95 (m, 1H, CH_2-OP), 2.14 (m, 1H, CH_2-OP), 4.00 (m, 1H, CH_2-N), 4.14 (m, 1H, CH-N), 4.29 (d, 1H, CH_2-N, $^2J_{H-H}$ = 13.8 Hz), 4.74 (m, 1H, CH-O), 7.31 (m, 15H, CH=). ^{13}C NMR (75.4 MHz, $CDCl_3$, δ ppm): 24.8 (CH_3), 26.8 (CH_3), 31.3 (d, CH_2-OP, J_{C-P} = 17.4 Hz), 50.4 (CH_2-N), 63.2 (d, CH-N, J_{C-P}= 18.2 Hz), 78.4 (CH-O), 83.8 (d, CH-O, J_{C-P}= 10.1 Hz), 111.8 (C), 138.2-127.3 (aromatic carbons), 169.9 (C=O). α_D +85.5 (*c* 0.6, CH_2Cl_2). ESI-HRMS *m/z* found 446.1873, calc. for $C_{27}H_{29}NO_3P$ $[M+H]^+$: 446.1880.

(2*R*,3*S*,4*R*)-*N,N*-Diisopropylcarbamoyl-2-diphenylphosphinomethyl-3,4-*O*-isopropylidene-pyrrolidine-3,4-diol (L41)

Compound **L41** (45% yield) was prepared according to the general procedure from **L34** and *N*,*N*-diisopropylcarbamoyl chloride, followed by column chromatography on silica gel (AcOEt:hexane - 1:3). ^{31}P NMR (121.5 MHz, $CDCl_3$, δ ppm) δ -23.4 (s). ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm) δ 1.00 (d, 6H, CH_3, ^{i}Pr, $^3J_{H-H}$= 6.6 Hz), 1.22 (d, 6H, CH_3, ^{i}Pr, $^3J_{H-H}$= 6.6 Hz), 1.28 (s, 3H, CH_3, ^{i}Pr), 1.42 (s, 3H, CH_3, ^{i}Pr), 2.15 (ap.d, 2H, CH_2-OP, $^3J_{H-H}$= 8.1 Hz), 3.38 (ap.d, 1H, CH_2-N, $^2J_{H-H}$= 12.6 Hz), 3.51 (m, 3H, CH_2-OP, CH, ^{i}Pr), 4.18 (m, 1H, CH-N), 4.67 (m, 1H, CH-O), 4.78 (m, 1H, CH-O), 7.36 (m, 6H, CH=), 7.45 (m, 4H, CH=). ^{13}C NMR (75.4 MHz, $CDCl_3$, δ ppm) δ 20.6 (CH_3, ^{i}Pr), 22.4 (CH_3, ^{i}Pr), 25.0 (CH_3), 26.7 (CH_3, ^{i}Pr), 29.6 (d, CH_2-OP, J_{C-P}= 16.3 Hz), 47.3 (CH, ^{i}Pr), 53.3 (CH_2-N), 62.2 (d, CH-N, J_{C-P} = 17.9 Hz), 78.7 (CH-O), 84.2 (d, CH-O, J_{C-P}= 9.7 Hz), 111.5 (C), 138.1-128.6 (aromatic carbons), 161.3 (C=O). α_D -5.2 (*c* 1.3, CH_2Cl_2). ESI-HRMS *m/z* found 469.2610, calc. for $C_{27}H_{38}N_2O_3P$ $[M+H]^+$: 469.2615.

(2*R*,3*S*,4*R*)-*N*-Adamantan-1-carbamoyl-2-diphenylphosphinomethyl-3,4-*O*-isopropylidene-pyrrolidine-3,4-diol (L42)

Compound **L42** (55% yield) was prepared according to the general procedure from **L34** and 1-adamantyl isocyanate, followed by column chromatography on silica gel (AcOEt:hexane - 1:3). ^{31}P NMR (121.5 MHz, $CDCl_3$, δ ppm) δ -23.8 (s). ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm) δ 1.29 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 1.63 (s, 6H, CH_2, ad), 1.85 (s, 6H, CH_2, ad), 2.02 (s, 3H, CH, ad), 2.22 (m, 1H, CH_2-OP), 2.34 (m, 1H, CH_2-OP), 3.29 (m, 1H, CH_2-N), 3.70 (d, 1H, CH_2-N, $^2J_{H-H}$ = 12.6 Hz), 4.00 (m, 1H, CH-N), 4.78 (br.s, 2H, CH-O), 7.41 (m, 10H, CH=). ^{13}C NMR (75.4 MHz, $CDCl_3$, δ ppm) δ 25.1 (CH_3), 27.0 (CH_3), 29.7 (CH), 30.6 (d, CH_2-OP, J_{C-P} = 16.3 Hz), 36.6 (CH_2), 42.4 (CH_2), 51.4 (CH_2-N), 61.6 (d, CH-N, J_{C-P} = 16.7 Hz), 79.1 (CH-O), 85.0 (d, CH-O, J_{C-P} = 9.6 Hz), 111.9 (C), 137.8-128.7 (aromatic carbons), 155.5 (C=O). α_D +37.3 (*c* 0.75, CH_2Cl_2). ESI-HRMS *m/z* found 519.2766, calc. for $C_{31}H_{40}N_2O_3P$ $[M+H]^+$: 519.2771.

3.5.4.3. General procedure for the preparation of the pyrrolidine-phosphite ligands L44a-b

The corresponding phosphorochloridite (1.1 mmol) produced in situ was dissolved in toluene (5 mL) and pyridine (3.8 mmol, 0.3 mL) was added. The corresponding alcohol **1** (1 mmol) was azeotropically dried with toluene (3x1 mL) and dissolved in toluene (5 mL) to which pyridine (3.8 mmol, 0.3 mL) was added. The solution was transferred slowly at 0 ˚C to the solution of the phosphorochloridite. The reaction mixture was stirred overnight at 80 °C, 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:triethylamine – 100:1) to produce the corresponding ligand as a white solid.

L44a: Yield: 167.2 mg (50%). Major rotamer (63%): ^{31}P NMR (121.5 MHz, $CDCl_3$, δ ppm), 134.2 (s). ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 0.45 (s, 9H, CH_3, $SiMe_3$), , 0.52 (s, 9H, CH_3, $SiMe_3$), 1.08 (s, 3H, CH_3), 1.09 (s, 9H, CH_3, ^{t}Bu, NBoc), 1.28 (s, 3H, CH_3), 3.24 (dd, 1H, CH_2-N, $^{2}J_{H-H}$ =12.5 Hz, $^{3}J_{H-H}$ =5.2 Hz), 3.43 (m, 1H, CH), 3.55 (m, 1H, CH_2-OP), 4.07 (m, 2H, CH_2-N, CH-O), 4.39 (m, 1H, CH_2-O), 4.73 (d, 1H, CH-O, $^{3}J_{H-H}$ =5.2 Hz), 6.83 (m, 2H, CH=), 7.07 (m, 2H, CH=,), 7.18 (m, 1H, CH=), 7.27 (m, 1H, CH=), 7.65 (m, 2H, CH=), 8.04 (m, 2H, CH=). ^{13}C NMR (75.4 MHz, $CDCl_3$, δ ppm): -0.6 (CH_3, $SiMe_3$), -0.4 (CH_3, $SiMe_3$), -0.1 (CH_3, $SiMe_3$), 0.0 (CH_3, $SiMe_3$), 1.0 (CH_3, $SiMe_3$), 21.1 (C, ^{t}Bu, NBoc), 24.6 (CH_3), 26.7 (CH_3), 26.8 (CH_3), 27.9 (CH_3, ^{t}Bu, NBoc), 52.8 (CH_2-N), 63.3 (CH), 64.5 (CH_2-OP), 79.3 (CH-O), 82.5 (CH-O), 111.3 (C), 122.5 – 153.6 (aromatic carbons) 153.0 (C=O). Minor rotamer (37%): ^{31}P NMR (121.5 MHz, $CDCl_3$, δ ppm), 138.0 (s). ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 0.49 (s, 9H, CH_3, $SiMe_3$), 0.53 (s, 9H, CH_3, $SiMe_3$), 1.03 (s, 3H, CH_3), 1.28 (s, 3H, CH_3), 1.34 (s, 9H, CH_3, ^{t}Bu, NBoc), 2.79 (dd, 1H, CH_2-N, $^{2}J_{H-H}$ =12.3 Hz, $^{3}J_{H-H}$ =5.3 Hz), 3.55 (m, 1H, CH_2-N), 4.07 (m, 3H, CH_2-OP, CH), 4.23 (m, 1H, CH-O), 4.66 (d, 1H, CH-O, $^{3}J_{H-H}$ =5.3 Hz), 6.83 (m, 2H, CH=), 7.07 (m, 2H, CH=,), 7.18 (m, 1H, CH=), 7.27 (m, 1H, CH=), 7.65 (m, 2H, CH=), 8.04 (m, 2H, CH=), 8.12 (s, 1H, CH=). ^{13}C NMR (75.4 MHz, $CDCl_3$, δ ppm): NMR (C_6D_6), δ: -0.6 (CH_3, $SiMe_3$), -0.4 (CH_3, $SiMe_3$), -0.1 (CH_3, $SiMe_3$), 0.0 (CH_3, $SiMe_3$), 1.0 (CH_3, $SiMe_3$), 21.1 (C, ^{t}Bu, NBoc), 24.5 (CH_3), 26.7 (CH_3), 26.8 (CH_3), 28.0 (CH_3, ^{t}Bu, NBoc), 52.8 (CH_2-N), 63.4 (CH), 64.0 (CH_2-OP), 78.9 (CH-O), 82.0 (CH-O), 111.3 (C), 122.5 – 153.6 (aromatic carbons),153.3 (C=O). TOF-MS (ESI+): *m/z:* calcd for $C_{39}H_{50}NO_7PSi_2$: 754.2756 $[M\text{-}Na]^+$; found 754.2759.

L44b: Yield: 167.2 mg (50%). Major rotamer (61%): ^{31}P NMR (121.5 MHz, $CDCl_3$, δ ppm): 129.7 (s). ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 0.48 (m, 18H, CH_3, $SiMe_3$), 1.18 (s, 3H, CH_3), 1.32 (m, 3H, CH_3), 1.40 (s, 9H, CH_3, ^{t}Bu, NBoc), 3.53 (dd, 1H, CH_2-N, $^{2}J_{H-H}$ =11.9 Hz, $^{2}J_{H-H}$ =5.7 Hz), 3.76 (m, 2H, CH_2-OP, CH_2-N), 4.00 (m, 2H, CH_2-OP, CH), 4.54 (m, 1H, CH-O), 4.61 (m, 1H, CH-O), 6.85 (m, 2H, CH=), 7.08 (m, 2H, CH=), 7.33 (m, 2H, CH=), 7.66 (m, 2H, CH=), 8.07 (m, 2H, CH=). ^{13}C NMR (75.4 MHz, $CDCl_3$, δ ppm): -0.6 (CH_3, $SiMe_3$), -0.5 (CH_3, $SiMe_3$), -0.1 (CH_3, $SiMe_3$), 0.0 (CH_3, $SiMe_3$), 1.0 (CH_3, $SiMe_3$), 21.1 (C, ^{t}Bu, NBoc), 24.6 (CH_3), 28.0 (CH_3, ^{t}Bu, NBoc), 28.2 (CH_3), 54.2 (CH_2-N), 63.3 (CH), 64.6 (CH_2-OP), 78.9 (CH-O), 82.4 (CH-O), 111.0 (C), 124.9 – 153.7 (aromatic carbons), 153.7

(C=O). Minor rotamer (39%): ^{31}P NMR (121.5 MHz, $CDCl_3$, δ ppm), 130.6 (s). ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 0.48 (m, 18H, CH_3, $SiMe_3$), 1.12 (s, 3H, CH_3), 1.20 (m, 9H, CH_3, ^{t}Bu, NBoc), 1.32 (m, 3H, CH_3), 3.15 (m, 1H, CH_2-N), 3.25 (dd, 1H, CH_2-OP, $^2J_{H-H}$ =12.6 Hz, $^3J_{H-H}$ =5.7 Hz), 4.00 (m, 3H, CH_2-N, CH_2-OP, CH), 4.25 (m, 1H, CH-O), 4.54 (m, 1H, CH-O), 6.85 (m, 2H, CH=), 7.08 (m, 2H, CH=), 7.21 (m, 2H, CH=), 7.66 (m, 2H, CH=), 8.07 (m, 2H, CH=). ^{13}C NMR (75.4 MHz, $CDCl_3$, δ ppm): -0.6 (CH_3, $SiMe_3$), -0.5 (CH_3, $SiMe_3$), -0.1 (CH_3, $SiMe_3$), 0.0 (CH_3, $SiMe_3$), 1.0 (CH_3, $SiMe_3$), 21.1 (C, ^{t}Bu, NBoc), 24.6 (CH_3), 26.8 (CH_3, ^{t}Bu, NBoc), 28.2 (CH_3), 52.5 (CH_2-N), 63.7 (CH), 64.0 (CH_2-OP), 78.8 (CH-O), 82.6 (CH-O), 111.2 (C), 124.9 – 153.7 (aromatic carbons) 153.2 (C=O). TOF-MS (ESI+): *m/z:* calcd for $C_{39}H_{50}NO_7PSi_2$: 754.2756 $[M-Na]^+$; found 754.2761.

3.5.4.5. Procedure for the preparation of the pyrrolidine-phosphinite ligand L37

To a solution of **3** (650 mg, 2.14 mmol) in dry CH_2Cl_2 (3 mL), Et_3N (595 µL, 4.28 mmol) and TBSCl (612 mg, 2.14 mmol) were added. After stirring at r.t overnight, the reaction was quenched with sat. aq. soln. of NH_4Cl and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic phases were washed with brine, dried (Na_2SO_4), filtered and concentrated. To a solution of the crude product in dry toluene (18 mL), imidazole (466 mg, 6.85 mmol), PPh_3 (1.30 g, 4.92 mmol) and I_2 (868 mg, 3.42 mmol) were added and the mixture was refluxed for 2 h. After cooling to r.t. and diluting with AcOEt, the mixture was washed with sat. aq. $Na_2S_2O_3$, water and brine. The reaction mixture was dried (Na_2SO_4) and evaporated. Purification by column chromatography on silica gel (cyclohexane→AcOEt:cyclohexane - 1:20) afforded *N-tert*-butoxycarbonyl-1,4,5-trideoxy-6-*O*-*tert*-butyldimethylsilyl-1,4-imino-5-iodo-2,3-*O*-isopropyli-dene-D-talitol (**4**) (865 mg, 77%, 2 steps) as a colorless oil, that was used immediately in the next step. ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm) δ 0.09 (s, 6H, CH_3), 0.91 (s, 9H, CH_3, ^{t}Bu), 1.31 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 1.47 (s, 9H, CH_3), 3.81 (m, 4H), 4.11 (m, 1H), 4.62 (m, 3H).

To a solution of **4** (705 mg, 1.34 mmol) in EtOH (14 mL), Et_3N (450 µL) and Pd/C (10%, cat.) were added and the reaction hydrogenated at 1 atm for 4 h. The crude product was filtered through Celite and the solvent evaporated under vacuum. The resulting residue was purified by column chromatography on silica gel (EtOAc:cyclohexane - 1:10→AcOEt) to give dehalogenated derivative (490 mg, 82%). 1 M TBAF in THF (0.49 mL, 0.49 mmol) was added to a solution of this compound (180 mg, 1.49 mmol) in THF (6 mL) and the mixture was stirred at r.t. for 6 h and then the solvent evaporated under vacuum. Purification by column chromatography on silica gel (CH_2Cl_2:MeOH - 50:1) afforded deprotected compound (**5**) (128 mg, quant.) as a colorless oil, that was used immediately in the next step. ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm) δ 1.27 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 1.33 (m, 1H), 1.44 (s, 9H, CH_3, ^{t}Bu), 1.72 (m, 1H), 3.22 (dd, 1H, *J* = 13.2 Hz, *J* = 4.9 Hz), 3.46 (m, 3H), 3.89 (m, 1H), 4.24 (m, 1H), 4.43 (m, 1H), 4.67 (t, 1H, *J* = 5.3 Hz),

Then a solution of MsCl (55 µL, 0.71 mmol) in pyridine (1 mL) was added dropwise to a 0 ˚C solution of alcohol **5** (67.5 mg, 0.24 mmol) in CH_2Cl_2 (2 mL) and the mixture

stirred at r.t. for 2 h. Water was then added dropwise under stirring and the mixture evaporated to dryness. The residue was dissolved in CH_2Cl_2 and washed with water and brine. The organic phase was dried (Na_2SO_4), filtered and concentrated. The crude mesylate was dissolved in anhidrous THF (2 mL) and cooled to -40 ˚C. $KPPh_2$ (565 µL, 0.28 mmol, 0.5 M in THF) was slowly added and the mixture was stirred at -40˚C for 15 min. IRA-120H^+ resin was added and the mixture diluted with AcOEt, filtered through Celite and washed with AcOEt and CH_2Cl_2. Evaporation of the solvent and purification by column chromatography on silica gel (AcOEt:cyclohexane - 1:10→1:5) afforded **L37** (74mg, 69%, 2 steps). ^{31}P NMR (121.5 MHz, DMSO-*d_6*, δ ppm, mixture of rotamers) δ -15.4 (s), -16.1 (s). ^{1}H-NMR (300 MHz, DMSO-*d_6*, 363 K, δ ppm) δ 1.24 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 1.36 (s, 9H, CH_3, ^{t}Bu), 1.53 (m, 2H, CH_2-O), 2.08 (m, 2H, CH_2-CH_2O), 3.23 (dd, 1H, CH_2-N, $^3J_{H-H}$ = 4.8 Hz), 3.65 (ap.d, 1H, CH_2-N, $^2J_{H-H}$ = 12.9 Hz), 3.98 (m, 1H, CH-N), 4.48 (m, 1H, CH-O), 4.68 (t, 1H, CH-O, $^3J_{H-H}$= $^3J_{H-H}$= 5.1 Hz), 7.41 (m, 8H, CH=), 7.52 (m, 1H, CH=), 7.77 (m, 1H, CH=). ^{13}C NMR (75.4 MHz, DMSO-*d_6*, 363 K, δ ppm) δ 23.0 (d, CH_2-O, J_{C-P} = 12.1 Hz), 24.5 (CH_3), 26.3 (CH_3), 26.8 (d, CH_2-CH_2O, J_{C-P}= 17.3 Hz), 27.6 (CH_3, ^{t}Bu), 50.3 (CH_2-N), 63.7 (d, CH-N, J_{C-P}= 12.8 Hz), 78.2 (CH-O, C, ^{t}Bu), 83.1 (CH-O), 110.2 (C), 138.1-127.9 (aromatic carbons), 153.3 (C=O), α_D +14.8 (*c* 1.3, CH_2Cl_2). ESI-HRMS *m/z* found 456.2292, calc. for $C_{26}H_{35}NO_4P$ $[M+H]^+$: 456.2298.

3.5.4.4. General procedure for the preparation of the pyrrolidine-phosphine ligands L35-L36 and L43

(2*S*,3*R*,4*S*)-*N*-*terc*-Butoxycarbonyl-2-hydroxymethyl-3,4-*O*-isopropilidene pyrrolidine-3,4-diol (7)

To a solution of compound **6** (2.44 g, 9.28 mmol) in MeOH (70 mL), Boc_2O (2.02 g, 18.6 mmol) and Pd/C 10% (0.63 g) was added. The reaction mixture was hydrogenated a 1 atm for 3 h. Then filtered through Celite and washed with MeOH. The filtrate was evaporated to dryness. Purification by column chromatography on silica gel (AcOEt:cyclohexane - 1:2), gave **7** (2.18 g, 7.99 mmol, 86%) as colorless oil. ^{1}H NMR (500 MHz, DMSO-*d_6*, 363 K, δ ppm) δ 1.30 (s, 3H, CH_3), 1.42 (s, 9H, CH_3, ^{t}Bu), 1.43 (s, 3H, CH_3), 3.23 (dd, 1H, CH_2-N, $^2J_{H-H}$ = 12.0 Hz), 3.60 (dd, 1H, CH_2-N, $^2J_{H-H}$ = 12.0 Hz), 3.67 (m, 1H, CH_2-OP), 3.77 (m, 2H, CH-N, CH_2-OP), 4.05 (m, 1H, OH), 4.70 (td, 1H, CH-O, $^3J_{H-H}$ = $^3J_{H-H}$ = 6.5 Hz, $^3J_{H-H}$ = 3.5 Hz), 4.78 (m, 1H, CH-O). ^{13}C-NMR (125.7 MHz, DMSO-*d_6*, 363 K, δ ppm) δ 24.6 (CH_3), 26.0 (CH_3), 27.6 (CH_3, ^{t}Bu), 51.2 (CH_2-N), 59.3 (CH_2-OP), 61.1 (CH-N), 76.5 (CH-O), 78.8 (C, ^{t}Bu), 79.3 (CH-O), 110.9 (C), 154.1 (C=O). α_D +41.8 (*c* 1.00, CH_2Cl_2). ESI-HRMS *m/z* found 296.1465, calc. for $C_{13}H_{23}NO_5Na$ $[M+Na]^+$: 296.1468. IR ν_{max} 3419 (OH), 2979, 2935, 1675 (C=O), 1366, 1161, 856 cm^{-1}.

(6*S*,7*R*,7*aS*)-6,7-*O*-Isopropylidene-tetrahydropyrrolo [1,2-c]oxazol-3-one-6,7-diol (8)

To a solution of compound **7** (1.06 g, 3.89 mmol) in dry pyridine (15 mL) cooled to 0˚C TsCl (1.89 g, 9.74 mmol) was added. The reaction mixture was allowed to stand at r.t. for 14 h under Ar and then concentrated to dryness. Purification by column

chromatography on silica gel (AcOEt: cyclohexane - 1: 1 → 2: 1) gave **8** (713 mg, 3.58 mmol, 92%) as a white solid. NMR and IR data coincide with those of its enantiomer.[14] α_D +25.6 (*c* 0.82, CH_2Cl_2). ESI-HRMS *m/z* found 222.0735, calc. for $C_9H_{13}NO_4Na$ $[M+Na]^+$: 222.0737.

(2*R*,3*R*,4*S*)-2-Diphenylphosphinomethyl-3,4-*O*-isopropylidene-pyrrolidine-3,4-diol (9)

To a solution of **8** (147 mg, 0.74 mmol) in dry THF (5.7 mL) cooled to 0˚C $KPPh_2$ (1.8 mL, 0.89 mmol) is added dropwise. The reaction mixture was heated under Ar at reflux for 2 h, then allowed to cool to r.t. and neutralized with IRA-120H^+. The reaction mixture was filtered through Celite, washed CH_2Cl_2 and concentrated to dryness. Purification by column chromatography on silica gel (Et_2O:Acetone - 10:1, 1% Et_3N), gave **9** (226 mg, 0.66 mmol, 89%) as a colorless oil. ^{31}P NMR (121.5 MHz, $CDCl_3$, δ ppm) δ -20.9 (s). ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm) δ 1.31 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 1.95 (s.a, 1H, NH), 2.37 (dd, 1H,CH_2-P, $^3J_{H-H}$ = 8.1 Hz), 2.43 (dd, 1H, CH_2-P, $^2J_{H-H}$ = 13.2 Hz, $^3J_{H-H}$ = 6.3 Hz), 2.56 (m, 2H, CH-N, CH_2-N), 3.02 (d, 1H, CH_2-N, $^2J_{H-H}$ = 13.5 Hz), 4.57 (dd, 1H, CH-O,^{3} J_{H-H}= 5.7 Hz,^{3} J_{H-H} = 3.9 Hz), 4.63 (m, 1H, CH-O), 7.32 (m, 6H, CH=), 7.47 (m, 4H, C=). ^{13}C NMR (75.4 MHz, $CDCl_3$, δ ppm) δ 24.1 (CH_3), 26.0 (CH_3), 27.3 (d, CH_2-P, $J_{C,P}$ = 13.2 Hz), 53.2 (CH_2-N), 61.5 (d, CH-N, $J_{C,P}$ = 16.3 Hz), 81.8 (d, CH-P, $J_{C,P}$ = 4.5 Hz), 82.2 (CH-O), 110.6 (C), 138.9-128.4 (aromatic carbons). α_D +63.2 (*c* 0.57, CH_2Cl_2). ESI-HRMS *m/z* found 342.1609, calc. for $C_{20}H_{25}NO_2P$ $[M+H]^+$: 342.1617. IR ν_{max} 3296 (NH), 2970, 2927, 1431, 1075, 977, 696 cm^{-1}.

(2*R*,3*R*,4*S*)-*N*-(3,5-Bis (trifluoromethyl) phenyl)-2-diphenylphosphinomethyl-3,4-*O*-isopropylidene-pyrrolidine-1-carbothioamide-3,4-diol (L43)

To a solution of **9** (195 mg, 0.570 mmol) in dry CH_2Cl_2 (6 mL) 3,5-bis(trifluoromethyl) phenylisothiocyanate (0.26 mL, 1.5 mmol) was added. The reaction mixture was allowed to stand at r.t. for 3.5 h and then concentrated to dryness. Purification by column chromatography on silica gel (AcOEt: cyclohexane - 1:5) gave **L43** (230 mg, 0.370 mmol, 66%) as a white foam. ^{31}P NMR (121.5 MHz, $CDCl_3$, δ ppm) δ: -20.6 (s). ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm) δ: 1.40 (s, 3H, CH_3), 1.55 (s, 3H, CH_3), 2.60 (ddd, 1H, CH_2-P, $^2J_{H-H}$ = 4.5 Hz, $^3J_{H-H}$ = 2.5 Hz), 2.79 (dd, 1H, CH_2-P, $^2J_{H-H}$ = 14.0 Hz, $^3J_{H-H}$ = 9.0 Hz), 3.65 (dd, 1H, CH_2-N, $^3J_{H-H}$ = 4.5 Hz), 4.40 (m, 1H, CH-N), 4.55 (dd, 1H, CH_2-N, $^2J_{H-H}$ = 13.0 Hz, $^3J_{H-H}$ = 7.5 Hz), 4.84 (m, 1H, CH-O), 4.94 (t.a., 1H, CH-O, $^3J_{H-H}$ = $^3J_{H-H}$ = 6.5 Hz), 6.93 (d.a., 1H, NH, *J* = 2.5 Hz), 7.28 (m, 3H, CH=),7.36 (m, 3H, CH=), 7.48 (m, 4H, CH=), 7.64 (m, 3H, CH=). ^{13}C NMR (125.7 MHz, $CDCl_3$, δ ppm) δ 25.3 (CH_3), 26.6 (CH_3), 28.8 (d, CH_2-P, $J_{C,P}$ = 13.9 Hz), 54.9 (CH_2-N), 60.2 (d, CH-N, $J_{C,P}$ = 23.1 Hz), 77.1 (CH-O), 79.9 (d, CH-O, $J_{C,P}$ = 3.0 Hz), 114.0 (C), 118.9 (c, $J_{C,F}$ = 3.8 Hz, CH=), 123.2 (c, $J_{C,F}$ = 272.6, CF_3), 140.5-124.9 (aromatic carbons), 179.3 (C=S), α_D +42.4 (*c* 0.58, CH_2Cl_2). ESI-HRMS *m/z* found 613.1497, calc. for $C_{29}H_{28}F_6N_2O_2PS$ $[M+H]^+$: 613.1508. IR ν_{max} 3238 (NH), 2993, 2927, 1371, 1275 (C=S), 1126 (C-F), 695 cm^{-1}.

(2*R*,3*R*,4*S*)-*N*-*terc*-Butoxycarbonyl-2-diphenylphosphinomethyl-3,4-*O*-isopropylidene-pyrrolidine-3,4-diol (L35)

To a solution of **9** (239.3 mg, 0.70 mmol) in dry pyridine (3.5 mL) Boc_2O (382 mg, 1.75 mmol) was added and the reaction mixture was stirred at r.t. for 6.5 h. Then, the mixture was evaporated to dryness. The residue was dissolved in EtOAc and washed with water and brine. The organic phase was dried (Na_2SO_4), filtered and concentrated. Purification by column chromatography on silica gel (AcOEt:cyclohexane - 1:8) afforded **L35** (148.8 mg, 0.34 mmol, 48%) as a pale yellow oil. ^{31}P NMR (121.5 MHz, $CDCl_3$, δ ppm) δ: -20.1 (s). ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm) δ: 1.31 (s, 3H, CH_3), 1.37 (s, 9H, CH_3, ^{t}Bu, NBoc), 1.44 (s, 3H, CH_3), 2.43 (dd, 1H, CH_2-P, $^2J_{H-H}$ = 13.2 Hz, $^3J_{H-H}$ = 10.4 Hz), 2.87 (b, 1H, CH_2-P), 3.34 (dd, 1H, CH_2-N, $^2J_{H-H}$ = 13.2 Hz , $^3J_{H-H}$ = 4.5 Hz), 3.78 (m, 1H, CH_2-N), 3.98 (m, 1H, CH-N), 4.66 (m, 1H, CH-O), 4.76 (t.a., 1H, CH-O, $^3J_{H-H}$ = $^3J_{H-H}$ = 6.2 Hz), 7.32 (m, 5H, CH=), 7.45 (m, 2H, CH=), 7.55 (m, 2H, CH=). ^{13}C NMR (125.7 MHz, $CDCl_3$, δ ppm) δ: 25.4 (CH_3), 27.0 (CH_3), 28.6 (CH_3, ^{t}Bu), 29.0 (d, CH_2-P, $J_{C,P}$ = 15.1 Hz), 51.1 (CH_2-N), 58.1 (d, CH-N, $J_{C,P}$ = 24.2 Hz), 77.4 (CH-O), 80.3 (d, CH-O, $J_{C,P}$ = 21.3 Hz), 112.8 (C), 128.6-139.6 (aromatic carbons), 154.5 (C=O). α_D +61.1 (*c* 0.82, CH_2Cl_2). ESI-HRMS *m/z* found 442.2134, calc. for $C_{25}H_{33}NO_4P$ $[M+H]^+$: 442.2142.

(6*S*,7*R*,7*aS*)-6,7-Dihydroxy-tetrahydropyrrolo [1,2-*c*]-oxazol-3-one (10)

To a solution of compound **8** (170 mg, 0.850 mmol) in THF (8 mL) cooled to 0 ˚C, a solution of 4M HCl (8 mL) was added dropwise. The reaction mixture was left to stand at r.t. for 3 h. Then concentrated to dryness and the resulting crude was purified by column chromatography on silica gel (CH_2Cl_2: MeOH - 20: 1 → 10: 1) to give **10** (122 mg, 0.770 mmol, 90%) as a white solid. The NMR data and IR are consistent with those of its enantiomer.[14] α_D +28.4 (*c* 0.49, CH_2Cl_2). ESI-HRMS *m/z* found 182.0420, calc. for $C_6H_9NO_4Na$ $[M+Na]^+$: 182.0424.

(6*S*,7*R*,7*aS*)-6,7-*O*-Bis(benzyloxy)-tetrahydropyrrolo[1,2-c]oxazol-3-one (11)

To a mixture of **10** (36 mg, 0.23 mmol) and NaH (35 mg, 1.4 mmol) in dry DMF (1.8 mL) at 0 ˚C BnBr (163 µL, 1.37 mmol) was added dropwise. The reaction mixture was stirred at r.t. under Ar for 5.5 h, cooled to 0 ˚C and then Et_3N (2 mL) and MeOH (2 mL) were added. The reaction mixture is concentrated to dryness. The residue was diluted with CH_2Cl_2 and washed with H_2O and brine. The organic phase is dried (Na_2SO_4), filtered and concentrated to dryness. Purification by column chromatography on silica gel (AcOEt: cyclohexane - 1:2 → 1:1) furnished **11** (70 mg, 0.21 mmol, 90%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm) δ 3.27 (dd, 1H, CH_2-N), 3.74 (dd, 1H, CH_2-N, $^2J_{H-H}$= 11.4 Hz), 3.95 (m, 2H, CH-O, CH-N), 4.14 (td, 1H, CH-O, $^3J_{H-H}$= $^3J_{H-H}$= 5.7 Hz, $^3J_{H-H}$= 3.3 Hz), 4.31 (ap.t., 1H, CH_2-O, $^2J_{H-H}$= $^3J_{H-H}$= 8.4 Hz), 4.57-4.48 (m, 3H, CH_2Ph, CH_2Ph, CH_2-O), 4.65 (d, 1H, CH_2Ph), 4.87 (d, 1H, CH_2Ph, $^2J_{H,H}$= 12.0 Hz), 7.31 (m, 10H, CH=), ^{13}C NMR (75.4 MHz, $CDCl_3$, δ ppm) δ 49.0 (CH_2-N), 59.2 (CH-N), 63.9 (CH_2-O), 72.2 (CH_2Ph), 73.2 (CH_2Ph), 77.4 (CH-O), 80.2 (CH-O), 137.9-127.9 (aromatic carbons), 162.8 (C=O), α_D

+36.9 (*c* 0.78, CH_2Cl_2). IR ν_{max} 2922, 2894, 1749 (C=O), 1244, 766, 697 cm^{-1}. ESI-HRMS *m/z* found 362.1353, calc. for $C_{20}H_{21}NO_4Na$ $[M+Na]^+$: 362.1363.

(2*R*,3*R*,4*S*)-*N*-*tert*-Butoxycarbonyl-3,4-di-*O*-benzyl-2-diphenylphosphinomehyl-pyrrolidine-3,4-diol (L36)

To a solution of **11** (171.1 mg, 0.36 mmol) in dry THF (4 mL) cooled to 0 ˚C, $KPPh_2$ (1.8 mL, 0.89 mmol, 0.5 M in THF) was slowly added and the mixture was heated at reflux for 1.5 h. Then, IRA-120H^+ resin was added, filtered through Celite and washed with CH_2Cl_2. Evaporation of the solvent and purification by column chromatography on silica gel (CH_2Cl_2, 1% Et_3N) afforded pyrrolidine **12** (171.1 mg, 0.35 mmol, 80%). Boc_2O (194 mg, 0.89 mmol) in dry pyridine (2 mL) was subsequently added and the reaction mixture was stirred at r.t. for 6 h. Then, the mixture was evaporated to dryness. The residue was dissolved in EtOAc and washed with water and brine. The organic phase was dried (Na_2SO_4), filtered and concentrated. Purification by column chromatography on silica gel (AcOEt:cyclohexane - 1:8) afforded **L36** (114 mg, 0.20 mmol, 55%) as a pale yellow oil. ^{31}P NMR (121.5 MHz, $CDCl_3$, δ ppm) δ: -19.2 (s). ^1H NMR (500 MHz, $CDCl_3$, δ ppm) δ: 1.32 (s, 9H, CH_3, ^{t}Bu, NBoc), 2.52 (m, 1H, CH_2-P), 2.75 (m, 1H, CH_2-P), 3.29 (dd, 1H, CH_2-N, $^2J_{H-H}$ = 11.3 Hz , $^3J_{H-H}$ = 4.0 Hz), 3.62 (m, 1H, CH_2-N), 4.07 (m, 1H, CH-N), 4.16 (m, 2H, 2xCH-O), 4.67 (m, 4H, CH_2Ph), 7.37 (m, 20H, CH=). ^{13}C NMR (125.7 MHz, $CDCl_3$, δ ppm) δ: 27.7 (CH_3, ^{t}Bu, CH_2-P), 48.7 (CH_2-N), 56.1 (d, CH-N, $J_{C,P}$ = 22.4 Hz), 71.2 (CH_2Ph), 71.8 (CH_2Ph), 76.6 (CH-O), 78.4 (CH-O), 78.7 (C, ^{t}Bu), 126.9-138.1 (aromatic carbons), 153.5 (C=O. α_D +32.9 (*c* 0.78, CH_2Cl_2). ESI-HRMS *m/z* found 582.2760, calc. for $C_{36}H_{41}NO_4P$ $[M+H]^+$: 582.2768.

3.5.4.6. Procedure for the preparation of the pyrrolidine-phosphinite ligand L38.

(2*R*,3*S*,4*R*)-*N*-Benzyloxycarbonyl-2-ethoxymethyl-3,4-*O*-isopropyliden-pyrrolidine-3,4-diol (14)

To a solution of **13** (751 mg, 3.28 mmol) in EtOH:H_2O (1:1) (12 mL) $NaHCO_3$ (276 mg, 3.28 mmol) and CbzCl (0.55 mL, 3.6 mmol) were added. The reaction mixture was stand at r.t. For 3 h. Then saturated aqueous solution of $NaHCO_3$ (25 mL) was added and the aqueous phase is extracted with AcOEt (3 x 15 mL). The combined organic phases were dried ($Na_2SO_{4)}$, filtered and concentrated to dryness. Purification by column chromatography on silica gel (AcOEt: cyclohexane - 1:3) gave **14** (1.15 g, 3.16 mmol, 97%) as a colorless oil. NMR and IR data coincide with those of its enantiomer.[11c] α_D -55.2 (*c* 0.73, CH_2Cl_2). CI-HRMS *m/z* found 364.1756, calc. for $C_{19}H_{26}NO_6$ $[M+H]^+$: 364.1760.

(2*R*,3*S*,4*R*)-*N*-Benzyloxycarbonyl-2-hydroxyethyl-3,4-*O*-isopropiliden-pyrrolidine-3,4-diol (15)

To a suspension of $LiAlH_4$ (35 mg, 0.91 mmol) in dry Et_2O (3 mL) cooled at -10 ˚C, a solution of **14** (275 mg, 0.756 mmol) in dry Et_2O (5 mL) was added dropwise. The reaction mixture is allowed to stand at that temperature under an inert atmosphere

for 10 min. Saturated aqueous Na_2SO_4 solution (30 mL) is then added and stirred several minutes, diluted with water (150 mL) and partitioned with AcOEt (3x50 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated to dryness. The resulting crude is purified by column chromatography on silica gel (toluene: acetone - 5:1) to afford **15** (171 mg, 0.532 mmol, 70%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm) δ 1.34 (s, 3H, CH_3), 1.50 (s, 3H, CH_3), 1.78 (m, 1H, CH_2-O), 1.98 (m, 1H, CH_2O), 3.31 (dd, 1H, CH_2-N, $^3J_{H-H}$= 4.2 Hz), 3.63 (m, 2H, CH_2-CH_2O), 3.97 (dd, 1H, CH_2-N, $^2J_{H-H}$= 12.3 Hz, $^3J_{H-H}$= 6.9 Hz), 4.24 (m, 1H, CH-N), 4.75 (m, 2H, CH-O), 5.12 (s, 2H, CH_2Ph), 7.34 (m, 5H, CH=), ^{13}C NMR (75.4 MHz, $CDCl_3$, δ ppm) δ 25.2 (CH_3), 26.4 (CH_3), 32.4 (CH_2-O), 49.7 (CH_2-N), 57.0 (CH-N), 59.3 (CH_2-CH_2O), 67.5 (CH_2Ph), 78.3 (CH-O), 79.7 (CH-O), 113.5 (C), 136.4-128.5 (aromatic carbons), 155.4 (C=O). α_D -25.6 (*c* 0.78, CH_2Cl_2). IR ν_{max} 3472 (OH), 2948, 1677 (C=O), 1422, 1079, 696 cm^{-1}. ESI-HRMS *m/z* found 344.1466, calc. for $C_{17}H_{23}NO_5Na$ $[M+Na]^+$: 344.1468.

(2*R*,3*S*,4*R*)-*N*-Benzyloxycarbonyl-2-diphenylphosphinoethyl-3,4-*O*-isopropylidene-pyrrolidine-3,4-diol (L38)

To a solution of **15** (257 mg, 0.799 mmol) in dry CH_2Cl_2 (5 mL) cooled to 0 ˚C, a solution of MsCl (187 µL, 2.39 mmol) in dry pyridine (2.5 mL) was added. The reaction mixture was left to stand at r.t. under Ar for 2 h. Then it is cooled to 0 ˚C and H_2O (3 mL) is added dropwise, left at r.t. for 15 min and concentrated to dryness. The obtained residue was dissolved in CH_2Cl_2 (15 mL) and washed with H_2O (3 x 10 mL). The organic phase is dried (Na_2SO_4), filtered and concentrated to dryness. The resulting crude product is then dissolved in dry THF (5.8 mL) under Ar, cooled to -78 ˚C, and $KPPh_2$ (4.46 mL, 0.5 M in THF, 2.23 mmol) was added dropwise. The reaction mixture was left to stand at that temperature for 15 min under Ar. Then, a saturated aqueous solution of NH_4Cl (3 mL) was added and the solution allowed to reach r.t. The aqueous phase is extracted with CH_2Cl_2 and the combined organic phases are dried (Na_2SO_4), filtered and concentrated to dryness. Purification by column chromatography on silica gel (AcOEt: cyclohexane - 1:5) gave **L38** (201 mg, 0.42 mmol, 52%, 2 steps) as a colorless oil. ^{31}P NMR (121.5 MHz, $CDCl_3$, δ ppm) δ -15.0 (s). ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm) δ 1.33 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 1.85 (m, 1H, CH_2-OP), 2.04 (m, 2H, CH_2-CH_2OP, CH_2-OP), 2.24 (m, 1H, CH_2-CH_2OP), 3.29 (dd, 1H, CH_2-N, $^3J_{H-H}$= 4.2 Hz), 3.90 (dd, 1H, CH_2-N, $^2J_{H-H}$= 12.6 Hz, $^3J_{H-H}$= 6.9 Hz), 4.07 (m, 1H, CH-N), 4.72 (m, 2H, CH-O), 5.06 (d, 1H, CH_2Ph), 5.11 (d, 1H, CH_2Ph, $^2J_{H,H}$= 12.3 Hz), 7.31 (m, 11H, CH=), 7.43 (m, 4H, CH=). ^{13}C NMR (75.4 MHz, $CDCl_3$, δ ppm) δ 24.6 (d, CH_2-CH_2OP, $J_{C,P}$= 11.5 Hz), 25.3 (CH_3), 26.2 (d, CH_2-OP, $J_{C,P}$= 18.0 Hz), 26.6 (CH_3), 50.5 (CH_2-N), 60.9 (d, CH-N, $J_{C,P}$= 14.9 Hz), 67.0 (CH_2Ph), 77.9 (CH-O), 80.0 (CH-O), 113.1 (C), 139.2-128.0 (C-arom.), 154.8 (C=O). α_D -57.6 (*c* 0.78, CH_2Cl_2). IR ν_{max} 2985, 2929, 1698 (C=O), 1408, 1209, 695 cm^{-1}. ESI-HRMS *m/z* found 490.2134, calc. for $C_{29}H_{33}NO_4P$ $[M+H]^+$: 490.2142.

3.5.4.7. Typical Procedure for the hydrogenation of trisubstituted olefins (S1-S16)

The corresponding ligand (**L34**-**L44**) (0.01 mmol) was dissolved in CH_2Cl_2 (2 mL) and $[Ir(cod)_2]BAr_F$ (0.01 mmol, 4.0 mg) was added. Then, The trisubstituted substrate **S1**-**S13** (0.5 mmol) was added to the solution. The mixture was put in a high-pressure autoclave. The autoclave was purged four times with hydrogen. It was then pressurized at 50 bar of H_2. After 12 h, 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 the conversions were determined by ^1H NMR or chiral GC. The enantiomeric excesses of hydrogenated products from **S1**,[15] **S2-S5**,[16] **S6**,[17] **S7**,[18] **S8**,[19] **S9**,[16] **S10**,[19] **S11**,[5j] **S12**-**S14**[15] and **S15**-**S16**[20] were determined using the condition previously described.

3.5.4.28. Typical Procedure for the hydrogenation of 1,1-disubstituted olefins (S17-S32)

The corresponding ligand (**L34**-**L44**) (0.01 mmol) was dissolved in CH_2Cl_2 (2 mL) and $[Ir(cod)_2]BAr_F$ (0.01 mmol, 4.0 mg) was added. Then, the 1,1-disubtituted substrate **S17**-**S32** (0.5 mmol) was added to the solution). The mixture was put in a high-pressure autoclave, which was purged four times with hydrogen. It was then pressurized at 1 bar of H_2. After 12 h, 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 the conversions were determined by 1H NMR or chiral GC. The enantiomeric excesses of hydrogenated products from **S17**,[15] **S18**-**S22**,[21] **S23**-**S24**,[15] **S25**,[22] **S26**-**S27**,[23] **S28**[24] and **S29**[25] were determined using the condition previously described.

3.5.5. Acknowledgments

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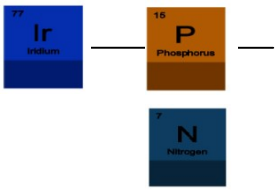
Chapter 4



ASYMMETRIC HYDROGENATION OF KETONES

UNIVERSITAT ROVIRA I VIRGILI
SUSTAINABLE AND COST-EFFECTIVE DEVELOPMENT OF CHIRAL METAL-CATALYSTS FOR C-H AND C-X BOND FORMING REACTIONS
Carlota Borràs Noguera

4.1. Synthesis of tridentated phosphite/phosphinite/phosphine-amino-oxazoline/pyridine ligands for iridium-catalyzed hydrogenation of simple ketones

Carlota Borràs, Oscar Pàmies and Montserrat Diéguez in progress

Abstract: *A new class of phosphite/phosphinite/phosphine-amino-pyridine/oxazoline ligand library (**L45**-**L48a**-**c**) has been successfully synthesized in good-to-moderated yields following a direct synthetic route. The synthesis of these ligands has been confirmed by ^{31}P, ^{1}H and ^{13}C NMR spectra. These ligands are designed for their specific application in the hydrogenation of simple ketones.*

4.1.1. Introduction

Chiral secondary alcohols are important key structural motifs in a great number of pharmaceutical products, such as aprepitant, crizotinib, duloxetine and ezetimibe (Figure 4.1.1).[1] Catalytic asymmetric hydrogenation of prochiral ketones is one of the most powerful and convenient methods to approach these enantiopure useful secondary alcohols.

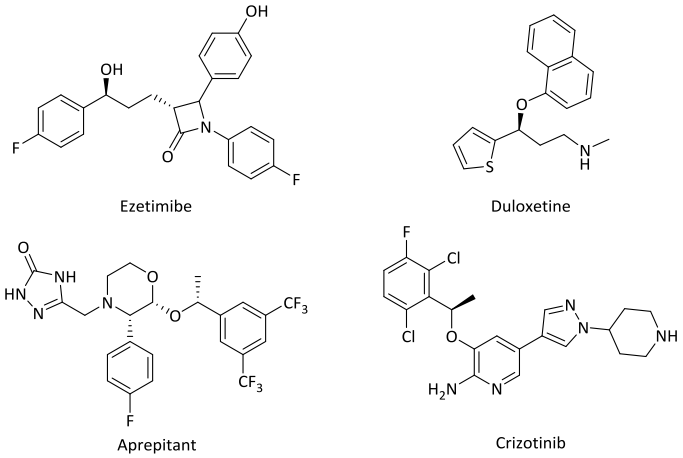


Figure 4.1.1. Chiral pharmaceuticals containing key chiral structural motifs.

Chiral iridium complexes with phosphorus nitrogen ligands are among the most commonly used catalysts in asymmetric hydrogenations.[2] Under the hydrogenation conditions of these substrates, these catalysts are easily deactivated by irreversible formation of inactive dimers or trimers.[3] To overcome this limitation several strategies have been investigated and one of the most useful methods was found in 2001 by Zhou and coworkers. It consisted on the addition of an extra coordinating group in the catalysts structure, they developed an Ir-SpiroPAP catalytic system **1** (Figure 4.1.2) obtaining excellent enantioselectivities although multistep complicated

reactions were involved to synthesize these ligands.[4] Since then, new ferrocene-based P,N,N-ligands **2**[5] and **3**[6] containing a phosphine moiety and oxazoline or pyridine group, respectively have been synthesized for the reductions of simple aromatic ketones (Figure 4.1.2). Despite the great success that has been achieved, it is still necessary to develop effective and readily available ligands especially for asymmetric hydrogenation of various simple ketones.

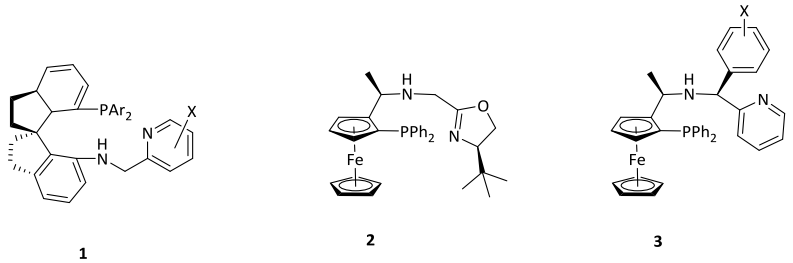


Figure 4.1.2. Examples of efficient chiral ligands for Ir-catalyzed asymmetric hydrogenation of ketones.

In order to further study the potential of the hydrogenation of prochiral ketones, in this work we synthesized a new ligand library of tridentated P,N,N ligands **L45**-**L48a**-**c** (Figure 4.1.3). Different phosphorus and nitrogen groups in the ligand structure have been synthesized. Three different phosphorus groups have been contemplated; for ligands **L45a**-**c** and **L47a**-**c**, biaryl phosphite moieties with different substituents and configurations (**a**-**c**) were included. For ligand **L46** phosphinite and N-phosphine functionality are present in the same ligand's structure. Finally a phosphine moiety is present in the structure of the ligand **L48**. Regarding to the nitrogen group, ligands with oxazoline (**L47**-**L48**) and pyridine groups (**L45**-**L46**) have been synthesized.

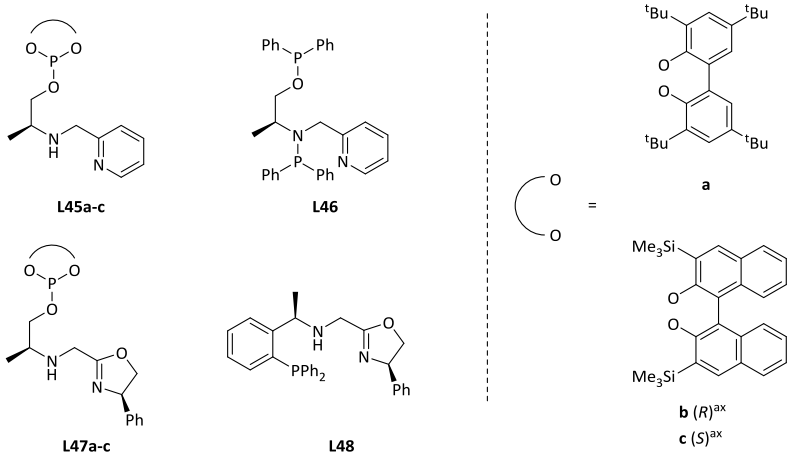


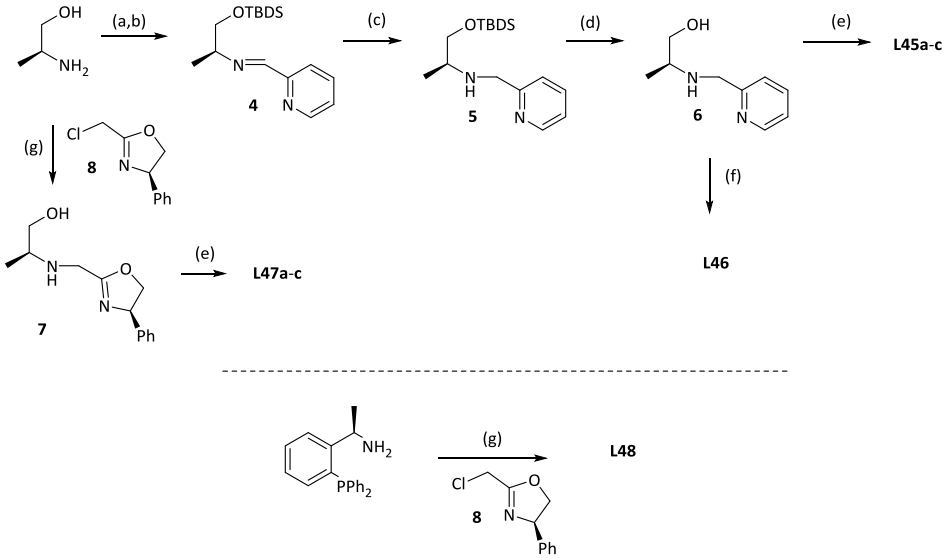
Figure 4.1.3. P,N,N-ligand library **L45**-**L48a**-**c**.

4.1.2. Results and discussion

4.1.2.1. Synthesis of ligands

The synthesis of tridentate ligands **L45**-**L48a**-**c** is straightforward (Scheme 4.1.1). Ligands **L45**-**L48a**-**c** were efficiently synthesized from the corresponding easily accessible hydroxyl compounds **6** and **7**. Compounds **6** and **7**, which are easily synthesized from inexpensive natural L-alaninol, were chosen as intermediates for the preparation of ligands because they easily allow incorporating the desired diversity in the ligand design. For the preparation of hydroxyl compound **6,** L-alaninol was protected with *tert*-butyldimethylsilane chloride in the presence of imidazole to afford the protected intermediate, which was then treated with 1 equiv of 2-pyridinecarboxaldehyde in the presence of molecular sieves 4 Å to produce the desired imine compound **4** (Scheme 4.1.1, steps a and b). Subsequent reaction with $NaBH_4$ provided direct access to the corresponding secondary amine **5**, which was treated with tetrabutylammonium fluoride to give access to desired hydroxyl-amine intermediate **6** (Scheme 4.1.1, steps c and d). For the preparation of hydroxyl-thioether compounds **7**, a new alternative route was developed. Commercially available L-alaninol was treated with previous prepared oxazoline **8**[7] and potassium carbonate to produce the desired intermediate **7** (Scheme 4.1.1, step g). The last step of the ligand synthesis is common for ligands **L45**-**L47a**-**c**. Therefore, treating the corresponding hydroxyl-amine (**6**-**7**) with 1.1 equiv of the desired in situ formed phosphorochloridite ($ClP(OR)_2$; $(OR)_2$ = **a**-**c**) in the presence of triethylamine provided easy access to the desired ligands (Scheme 4.1.1, step (e)). Ligands **L45a**-**c** were purified on neutral alumina under an argon atmosphere and isolated in moderate-to-good yields as white solids. However, ligands **L47a**-**c** decompose under column chromatography conditions and further efforts are therefore needed to purify these compounds. Ligand **L46** was prepared from the hydroxyl compound **6** by treatment with chlorodiphenylphosphine in presence of triethylamine to afford the desired ligand in moderated yield after the purification on neutral alumina under argon atmosphere.

Finally, ligand **L48** has been prepared in one step from commercially available chiral (*R*)-1-[2-(diphenylphosphino)phenyl]ethylamine by treatment with the oxazoline **8** and potassium carbonate to obtain the desired ligand **L48** without purification.



Scheme 4.1.1. Synthesis of ligands **L45**-**L48a**-**c**. Reaction conditions: a) TBDMSCl, imidazole, CH_2Cl_2; b) 2-pyridinecarboxaldehyde, molecular sieve 4 Å, toluene; c) $NaBH_4$, EtOH; d) TBAF, THF; e) $ClP(OR)_2$; $(OR)_2$ = **a**-**c**, NEt_3, toluene; f) $ClPPh_2$, NEt_3, toluene; g) K_2CO_3, **8**, CH_3CN.

The ^{1}H, ^{31}P and ^{13}C NMR spectra were as expected for these ligands (see Section 4.1.4). Expected 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.

4.1.3. Conclusions and future work

New class of phosphite/phosphinite/phosphine-amino-pyridine/oxazoline ligand library (**L45**-**L48a**-**c**) has been successfully synthesized in good to moderated yields following a direct synthetic route (75 to 25% yield). The synthesis of these ligands has been confirmed by ^{31}P, ^{1}H and ^{13}C NMR spectra. These ligands are thought to be applied in the hydrogenation of simple ketones in the future.

4.1.4. Experimental Part

4.1.4.1. General remarks

All reactions were carried out using standard Schlenk techniques under an atmosphere of argon. Commercial chemicals were used as received. Solvents were dried by standard procedures and stored under argon. Phosphorochloridites were easily prepared in one step from the corresponding biphenols.[8] Compound **8**[7] was prepared as previously reported. ^{1}H, $^{13}C\{^{1}H\}$ and $^{31}P\{^{1}H\}$ NMR spectra were recorded

using a Bruker and Varian Mercury-400 MHz spectrometer for solutions in $CDCl_3$ and C_6D_6 at room temperature. Chemical shifts are relative to that of $SiMe_4$ (^1H and $^{13}C\{^1H\}$) as internal standard or H_3PO_4 (^{31}P) as external standard. ^1H and ^{13}C assignments were made on the basis of ^1H-^1H gCOSY and ^1H-^{13}C gHSQC experiments.

4.1.4.2. Procedure for the preparation of (S,E)-N-(1-((tert-butyldimethylsilyl)oxy)propan-2-yl)-1-(pyridin-2-yl)methanimine (4)

TBSCl (8.8 g, 58 mmol) was added portionwise at 0 ˚C to a mixture of amino alcohol (4 g, 53 mmol) and 7.2 g imidazole (106 mmol) in 75 mL CH_2Cl_2. The mixture was stirred overnight at room temperature and the reaction was stopped by addition of 10 mL aqueous saturated $NaHCO_3$ solution. The aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were dried (Na_2SO_4), concentrated, and purified by column chromatography on silica gel (CH_2Cl_2/MeOH/NEt_3 = 8/2/0.1.). Yield: 8.5 g (76%). ^1H NMR (400 MHz, $CDCl_3$): δ= 0.05 (s, 6H, CH_3, OTBDMS), 0.89 (s, 9H, CH_3, ^{t}Bu, OTBDMS), 1.00 (d, 3H, CH_3, $^2J_{H-H}$= 6.5 Hz), 1.65 (b, 2H, NH_2), 2.91 (m, 1H, CH-N), 3.26 (m, 1H, CH_2-O), 3.50 (dd, 1H, CH_2-O, $^2J_{H-H}$= 9.7 Hz, $^3J_{H-H}$= 4.3 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= -5.7 (CH_3, OTBDMS), -5.3 (CH_3, OTBDMS), 18.3 (CH_3), 19.4 (C, ^{t}Bu, OTBDMS), 25.7 (CH_3, ^{t}Bu, OTBDMS), 48.5 (CH-N), 69.9 (CH_2-O).

2-Pyridinecarboxaldehyde (0.6 mL, 6.16 mmol) was added to a solution of protected compound (1.4 g, 7.39 mmol) and toluene (60 mL) in presence of molecular sieves 4 Å. The reaction mixture was stirred overnight at reflux and then it was concentrated under vacuum. The crude product was subjected to SiO_2-column chromatography (EtOAc /PE = 1/1) yielding pure compound **4** as oil. Yield: 1.7 g (83%). ^1H NMR (400 MHz, $CDCl_3$): δ= -0.07 (s, 3H, CH_3, OTBDMS), -0.02 (s, 3H, CH_3, OTBDMS), 0.79 (s, 9H, CH_3, ^{t}Bu, OTBDMS), 1.20 (d, 3H, CH_3, $^2J_{H-H}$= 6.8 Hz), 3.50 (m, 1H, CH-N), 3.64 (m, 2H, CH_2-O), 7.24 (m, 1H, CH=), 7.67 (m, 1H, CH=), 7.93 (d, 1H, CH=, $^3J_{H-H}$= 4.4 Hz), 8.33 (s, 1H, N=CH), 8.59 (m, 1H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= -5.3 (CH_3, OTBDMS), -5.2 (CH_3, OTBDMS), 18.2 (CH_3), 18.2 (C, ^{t}Bu, OTBDMS), 25.8 (CH_3, ^{t}Bu, OTBDMS), 69.9 (CH_2-O), 67.8 (CH-N), 121.4-161.4 (aromatic carbons).

4.1.4.3. General procedure for the preparation of (*S*)-1-((tert-butyldimethylsilyl)oxy)-N-(pyridin-2-ylmethyl)propan-2-amine (5)

$NaBH_4$ (276.6 mg, 7.31 mmol) was added to a solution of compound **4** (1.7 g, 7.31 mmol) and MeOH (12 mL). The reaction mixture was stirred for 2 h at room temperature and then it was concentrated under vacuum. The crude product was dissolved in EtOAc and washed with H_2O. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated. The crude product was subjected to SiO_2-column chromatography (CH_2Cl_2/MeOH/NEt_3 = 8/2/0.1) yielding pure thioether-hydroxy compound **5** Yield: 1.3 g (76%). ^1H NMR (400 MHz, $CDCl_3$): δ= 0.03 (s, 3H, CH_3, OTBDMS), 0.04 (s, 3H, CH_3, OTBDMS), 0.88 (s, 9H, CH_3, ^{t}Bu, OTBDMS), 1.03 (d, 3H, CH_3, $^2J_{H-H}$= 6.4 Hz), 2.28 (b, 1H, NH), 2.79 (m, 1H, CH-N), 3.50 (m, 2H, CH_2-O), 3.91 (m, 2H, CH_2-N), 7.12 (m, 1H, CH=), 7.31 (d, 1H, CH=, $^3J_{H-H}$= 7.8 Hz), 7.63 (m, 1H, CH=), 8.52 (d,

1H, CH=, $^{2}J_{H-H}$= 8.2 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= -5.4 (CH_3, OTBDMS), -5.3 (CH_3, OTBDMS), 16.9 (CH_3), 18.3 (C, ^{t}Bu, OTBDMS), 25.9 (CH_3, ^{t}Bu, OTBDMS), 52.7 (CH_2-N), 54.2 (CH-N), 67.5 (CH_2-O), 121.7-160.2 (aromatic carbons).

4.1.4.4. General procedure for the preparation of (*S*)-2-((pyridin-2-ylmethyl)amino)propan-1-ol (6)

Compound **5** (1.3 g, 4.6 mmol) was dissolved in THF (25 mL) to which TBAF (5 mL, 5 mmol) was added slowly. The reaction mixture was stirred at room temperature for 2 h. The THF was removed under reduced pressure. The crude product was purified by flash chromatography (CH_2Cl_2/MeOH/NEt_3 = 10/1/0.1) to produce the deprotected alcohol **6**. Yield: 654.8 mg (85%). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.16 (d, 3H, CH_3, $^{2}J_{H-H}$= 6.6 Hz), 2.98 (m, 1H, CH-N), 3.11 (b, 2H, OH, NH), 3.45 (m, 1H, CH_2-O), 3.67 (m, 1H, CH_2-O), 3.96 (d, 1H, CH_2-N, $^{2}J_{H-H}$= 14.6 Hz), 4.11 (d, 1H, $^{2}J_{H-H}$= 14.6 Hz), 7.19 (m, 1H, CH=), 7.31 (d, 1H, CH=, $^{3}J_{H-H}$= 7.8 Hz), 7.66 (m, 1H, CH=), 8.54 (m, 1H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 16.7 (CH_3), 51.7 (CH_2-N), 54.6 (CH-N), 65.2 (CH_2-O), 121.3-158.8 (aromatic carbons).

4.1.4.5. General procedure for the preparation of ((*S*)-2-((((*R*)-4-phenyl-4,5-dihydrooxazol-2-yl)methyl)amino)propan-1-ol (7)

A solution of oxazoline **8** (500 mg, 2.75 mmol) and CH_3CN (8 mL) was added to a solution of L-alaninol (0.15 mL, 2.5 mmol), K_2CO_3 (798 mg, 6.25 mmol) and CH_3CN (8 mL). The reaction mixture was stirred at 80˚C for 48 h. The CH_3CN was removed under reduced pressure. The crude product was filtered in a plug of celite to produce the compound **7**. Yield: 380.7 mg (65%). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.05 (d, 3H, CH_3, $^{2}J_{H-H}$= 6.1 Hz), 2.68 (b, 2H, OH, NH), 2.85 (m, 1H, CH-N), 3.28 (m, 1H, CH_2-O), 3.56 (m, 3H, CH_2-O, CH_2-N), 4.11 (m, 1H, CH, oxazoline), 4.63 (m, 1H, CH_2, oxazoline), 5.16 (m, 1H, CH_2, oxazoline), 7.26 (m, 10H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 17.3 (CH_3), 43.6 (CH_2-N), 54.9 (CH-N), 65.3 (CH_2-O), 69.2 (CH, oxazoline), 75.1 (CH_2, oxazoline), 126.5-168.8 (aromatic carbons).

4.1.4.6. General procedure for the preparation of ligands L45a-c and L47a-c

The corresponding phosphorochloridite (0.55 mmol) produced in situ was dissolved in toluene (5 mL), and triethylamine (0.25 mL, 2.0 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 triethylamine (0.25 mL, 2.0 mmol) was added. The alcohol solution was transferred slowly to a solution of phosphorochloridite. The reaction mixture was stirred overnight at 80 ºC, after which the triethylamine salts were removed by filtration. Evaporation of the solvent gave a white foam, which was purified by flash chromatography.

L45a. Yield: 119 mg (39%); SiO_2-flash chromatography (toluene/hexane/NEt_3 = 8:2:0.1). ^{31}P NMR (400 MHz, C_6D_6) δ: 138.1. ^{1}H NMR (400 MHz, C_6D_6) δ: 0.86 (d, 3H, CH_3, $^{2}J_{H-H}$= 6.4 Hz), 1.22 (s, 18H, CH_3, ^{t}Bu), 1.53 (s, 18H, CH_3, ^{t}Bu), 2.74 (m, 1H, CH-N),

3.78 (m, 4H, CH_2-O, CH_2-N), 6.58 (m, 1H, CH=), 7.02 (m, 2H, CH=), 7.27 (m, 2H, CH=), 7.55 (d, 2H, CH=, $^3J_{H-H}$= 2.5 Hz), 8.38 (m, 1H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 17.2 (CH_3), 30.8 (CH_3, ^{t}Bu), 30.9 (CH_3, ^{t}Bu), 31.0 (CH_3, ^{t}Bu), 31.2 (CH_3, ^{t}Bu), 34.3 (C, ^{t}Bu), 35.3 (C, ^{t}Bu), 52.6 (CH_2-N), 52.9 (CH-N), 68.4 (CH_2-O), 121.1-160.7 (aromatic carbons).

L45b. Yield: 141 mg (45%); SiO_2-flash chromatography (toluene/hexane/NEt_3 = 8:2:0.1). ^{31}P NMR (400 MHz, C_6D_6) δ: 135.2. ^{1}H NMR (400 MHz, C_6D_6) δ: 0.46 (s, 9H, CH_3, $SiMe_3$), 0.48 (s, 9H, CH_3, $SiMe_3$), 0.77 (d, 3H, CH_3, $^2J_{H-H}$= 6.5 Hz), 2.59 (m, 1H, CH-N), 3.27 (m, 1H, CH_2-O), 3.56 (q, 2H, CH_2-N, $^2J_{H-H}$= 14.7 Hz), 3.90 (m, 1H, CH_2-O), 6.51 (m, 1H, CH=), 6.83 (m, 3H, CH=), 7.14 (d, 1H, CH=, $^3J_{H-H}$= 7.8 Hz), 7.21 (d, 1H, CH=, $^3J_{H-H}$= 7.9 Hz), 7.33 (d, 1H, CH=, $^3J_{H-H}$= 8.4 Hz), 7.65 (m, 3H, CH=), 8.06 (m, 3H, CH=), 8.24 (m, 1H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= -1.0 (CH_3, $SiMe_3$), -0.3 (CH_3, $SiMe_3$), -0.2 (CH_3, $SiMe_3$), -0.2 (CH_3, $SiMe_3$), 17.0 (CH_3), 52.2 (CH_2-N), 52.7 (CH-N), 68.7 (CH_2-O), 110.8-160.4 (aromatic carbons).

L45c. Yield: 413 mg (35%); SiO_2-flash chromatography (toluene/hexane/NEt_3 = 8:2:0.1). ^{31}P NMR (400 MHz, C_6D_6) δ: 134.9. ^{1}H NMR (400 MHz, C_6D_6) δ: 0.46 (s, 9H, CH_3, $SiMe_3$), 0.48 (s, 9H, CH_3, $SiMe_3$), 0.77 (d, 3H, CH_3, $^2J_{H-H}$= 6.4 Hz), 2.67 (m, 1H, CH-N), 3.34 (m, 1H, CH_2-O), 3.65 (m, 2H, CH_2-N), 3.87 (m, 1H, CH_2-O), 6.55 (m, 1H, CH=), 6.83 (m, 3H, CH=), 6.89 (m, 1H, CH=), 7.22 (d, 1H, CH=, $^3J_{H-H}$= 4.1 Hz), 7.32 (d, 1H, CH=, $^3J_{H-H}$= 8.0 Hz), 7.66 (m, 3H, CH=), 8.07 (m, 3H, CH=), 8.31 (m, 1H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= -0.3 (CH_3, $SiMe_3$), -0.2 (CH_3, $SiMe_3$), -0.2 (CH_3, $SiMe_3$), 17.2 (CH_3), 52.5 (CH_2-N), 52.9 (CH-N), 68.5 (CH_2-O), 110.8-160.7 (aromatic carbons).

L47a. Yield: 232.2 mg (69%); no purification was carried out. ^{31}P NMR (400 MHz, C_6D_6) δ: 137.7. ^{1}H NMR (400 MHz, C_6D_6) δ: 0.84 (d, 3H, CH_3, $^2J_{H-H}$= 6.3 Hz), 1.23 (s, 18H, CH_3, ^{t}Bu), 1.54 (s, 18H, CH_3, ^{t}Bu), 2.92 (m, 1H, CH-N), 3.38 (m, 2H, CH_2-N), 3.66 (t, 1H, CH_2, oxazoline, $^2J_{H-H}$= 8.3 Hz), 3.77 (m, 2H, CH_2-O), 4.01 (m, 1H, CH_2, oxazoline), 4.89 (m, CH, oxazoline), 7.04 (m, 5H, CH=), 7.32 (m, 2H, CH=), 7.57 (d, 2H, CH=, $^3J_{H-H}$= 2.4 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 17.0 (CH_3), 30.9 (CH_3, ^{t}Bu), 31.3 (CH_3, ^{t}Bu), 34.3 (C, ^{t}Bu), 35.3 (C, ^{t}Bu), 43.8 (CH_2-N), 52.8 (CH-N), 68.4 (CH_2-O), 69.3 (CH, oxazoline), 74.3 (CH_2, oxazoline), 124.0-146.3 (aromatic carbons), 166.8 (C, oxazoline).

L47b. Yield: 193.8 mg (56%); no purification was carried out. ^{31}P NMR (400 MHz, C_6D_6) δ: 135.1. ^{1}H NMR (400 MHz, C_6D_6) δ: 0.50 (s, 18H, CH_3, $SiMe_3$), 0.75 (d, 3H, CH_3, $^2J_{H-H}$= 6.4 Hz), 2.03 (m, 1H, CH_2-N), 2.75 (m, 1H, CH-N), 3.27 (m, 2H, CH_2-N, CH_2-O), 3.61 (m, 1H, CH_2, oxazoline), 3.90 (m, 1H, CH_2-O), 4.00 (m, 1H, CH_2, oxazoline), 4.84 (m, CH, oxazoline), 6.85 (m, 2H, CH=), 7.06 (m, 7H, CH=), 7.22 (d, 1H, CH=, $^3J_{H-H}$= 8.6 Hz), 7.32 (d, 1H, CH=, $^3J_{H-H}$= 8.6 Hz), 7.66 (m, 2H, CH=), 8.09 (m, 2H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= -0.3 (CH_3, $SiMe_3$), -0.2 (CH_3, $SiMe_3$), -0.1 (CH_3, $SiMe_3$), 16.7 (CH_3), 43.7 (CH_2-N), 52.7 (CH-N), 68.6 (CH_2-O), 69.3 (CH, oxazoline), 74.2 (CH_2, oxazoline), 122.3-153.0 (aromatic carbons), 166.7 (C, oxazoline).

L47c. Yield: 154.7 mg (45%); no purification was carried out. ^{31}P NMR (400 MHz, C_6D_6) δ: 134.5. ^{1}H NMR (400 MHz, C_6D_6) δ: 0.49 (s, 18H, CH_3, $SiMe_3$), 0.75 (d, 3H, CH_3, $^2J_{H-H}$= 6.4 Hz), 1.88 (m, 1H, CH_2-N), 2.81 (m, 1H, CH-N), 3.31 (m, 2H, CH_2-N, CH_2-O), 3.63

(m, 1H, CH_2, oxazoline), 3.90 (m, 1H, CH_2-O), 3.99 (m, 1H, CH_2, oxazoline), 4.87 (m, CH, oxazoline), 6.83 (m, 2H, CH=), 7.04 (m, 7H, CH=), 7.24 (d, 1H, CH=, $^3J_{H-H}$= 8.6 Hz), 7.32 (d, 1H, CH=, $^3J_{H-H}$= 10.3 Hz), 7.66 (m, 2H, CH=), 8.09 (m, 2H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= -0.3 (CH_3, $SiMe_3$), -0.2 (CH_3, $SiMe_3$), -0.1 (CH_3, $SiMe_3$), 17.0 (CH_3), 43.7 (CH_2-N), 52.9 (CH-N), 68.4 (CH_2-O), 69.3 (CH, oxazoline), 74.2 (CH_2, oxazoline), 122.3-158.8 (aromatic carbons), 166.7 (C, oxazoline).

4.1.4.7. Procedure for the preparation of ligand L46

Hydroxyl compound **7** (0.5 mmol) and DMAP (6.7 mg, 0.055 mmol) were dissolved in toluene (1 ml), and triethylamine was added (0.09 ml, 1.2 mmol) at r.t., followed by the addition of the chlorodiphenylphosphine (1.1 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 ligand **L46** as a colorless oil. Yield: 68 mg (25%). ^{31}P NMR (400 MHz, C_6D_6) δ: 46.3 (s, P-N), 113.8 (s, P-O). ^{1}H NMR (400 MHz, C_6D_6) δ: 1.17 (d, 3H, CH_3, $^2J_{H-H}$= 6.7 Hz), 3.60 (m, 1H, CH-N), 3.80 (m, 1H, CH_2-O), 4.21 (m, 1H, CH_2-O), 4.47 (m, 2H, CH_2-N), 6.49 (m, 1H, CH=), 6.65 (d, 1H, CH=, $^3J_{H-H}$= 7.8 Hz), 6.85 (m, 1H, CH=), 7.04 (m, 12H, CH=), 7.52 (m, 8H, CH=), 8.36 (d, 1H, CH=, $^3J_{H-H}$= 4.7 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 17.8 (CH_3), 56.0 (CH-N), 56.4 (CH_2-N), 73.6 (CH_2-O), 121.2-160.3 (aromatic carbons).

4.1.4.8. Procedure for the preparation of ligand L48

A solution of oxazoline **8** (41 mg, 0.21 mmol) and CH_3CN (1.4 mL) was added to a solution of (*R*)-1-(2-(diphenylphosphino)phenyl)ethylamine (61 mL, 0.2 mmol), K_2CO_3 (69 mg, 0.5 mmol) and CH_3CN (1.4 mL). The reaction mixture was stirred at 80 ˚C for 48 h. The CH_3CN was removed under reduced pressure. The crude product was filtered in a plug of celite to produce the ligand **L48**. Yield: 70 mg (75%). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 2.07 d, 3H, CH_3, $^2J_{H-H}$= 1.3 Hz), 3.20 (m, 2H, CH_2-N), 3.95 (m, 1H, CH), 4.51 (m, 2H, CH_2, oxazoline), 5.08 (m, 1H, CH, oxazoline), 6.81 (m, 2H, CH=), 7.21 (m, 9H, CH=), 7.52 (m, 4H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 22.8 (CH_3), 53.2 (CH_2-N), 68.4 (CH), 73.6 (CH, oxazoline), 73.8 (CH_2, oxazoline), 124.3-150.8 (aromatic carbons), 166.5 (C, oxazoline).

4.1.5. Acknowledgments

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4.1.6. REFERENCES

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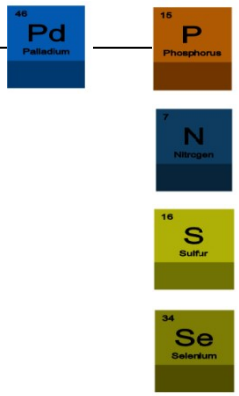
UNIVERSITAT ROVIRA I VIRGILI
SUSTAINABLE AND COST-EFFECTIVE DEVELOPMENT OF CHIRAL METAL-CATALYSTS FOR C-H AND C-X BOND FORMING REACTIONS
Carlota Borràs Noguera

Chapter 5

ASYMMETRIC Pd-CATALYZED ALLYLIC SUBSTITUTION



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SUSTAINABLE AND COST-EFFECTIVE DEVELOPMENT OF CHIRAL METAL-CATALYSTS FOR C-H AND C-X BOND FORMING REACTIONS
Carlota Borràs Noguera

5.1. Application of a high modular carbohydrate-derived phosphite-thioether/selenoether ligand library for asymmetric Pd-catalyzed allylic substitution reaction

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

***Abstract**: A readily available library of phosphite-thioether/selenoether ligands **L7-L30a-g** has been used in Pd-catalyzed allylic substitution reactions of several substrates including the more challenging monosubstituted substrates using a broad range of C-, N- and O-nucleophiles, among which are the less studied α-substituted malonates, β-diketones and benzyl alcohol. This ligand library combines the advantages of carbohydrates, the thioether/selenoether moiety with those of the phosphite group. Enantioselectivities can be tuned by correctly choosing the ligand parameters. High enantioselectivities were therefore obtained in the alkylation of a broad range of disubstituted substrates with different steric requirements using a number of C-, N- and O-nucleophiles.*

5.1.1. 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. 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 bond.[1] Most of the ligand's design rely on using either ligands with a pendant group able to interact with the nucleophile and direct its approach to the substrate;[2] or C_2 ligand scaffolds, to reduce the number of diastereoisomeric paths;[3] or a combination of strong and weak donor groups, to control the nucleophile approach due to the different *trans* influence of the donor moieties, being the last strategy the most studied.[4] All these approaches have led to the discovery of several widely used ligands (i.e. phosphine-oxazoline PHOX ligands, DACH-phenyl Trost ligand, …). Despite all these strategies and advances, the stereochemical outcome of the reaction is highly dependent on the steric demands of the substrate.

In this reaction the most predominant type of heterodonor ligands are the phosphorus-oxazoline compounds, with the prominent position of the PHOX-based ligands.[1] Some heteredonor phosphorus-thioether ligands have been proved to be potentially useful for this reaction, however, they have not been much studied.[5]This can be explained by the formation of mixtures of diastereomeric thioether complexes (because the S atom becomes an stereogenic centre when coordinated to the metal) and the difficulty of controlling their interconversion in solution.[1f]When the structure of the ligand is able to control the S-coordination, the chirality is closer to the metal

and it may be extremely beneficial. 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] Therefore, in this chapter we report the application of previous phosphite-thioether/selenoether ligand library presented in chapter 3.4 (**L7**-**L30a**-**g**; Figure 5.1.1) in this process. The high options in the variations of the ligand scaffold allowed us to systematically investigate the effect of varying: (a) the electronic and steric properties of the thioether group (ligands **L7**-**L13**); (b) the substituents and the introduction of a new stereogenic centre in the alkyl backbone chain next to the phosphite moiety (ligands **L7**, **L13**, **L14**-**L15** and **L17**-**L20**); (c) the substituents and the introduction of a new stereogenic centre in the alkyl backbone chain next to the thioether moiety (ligands **L7**, **L8**, **L16** and **L26**); (d) the substituents and configurations in the biaryl phosphite moiety (**a**-**g**); and finally (e) the replacement of the thioether group by a selenoether moiety.

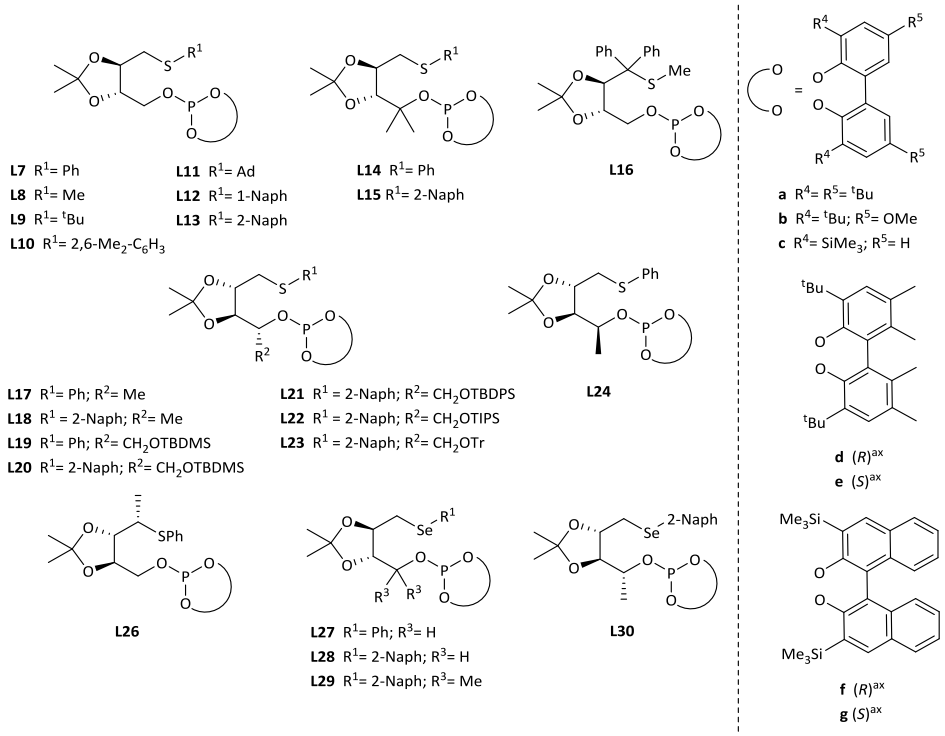


Figure 5.1.1. Sugar-based phosphite-thioether/selenoether ligand library **L7**-**L30 a**-**g**.

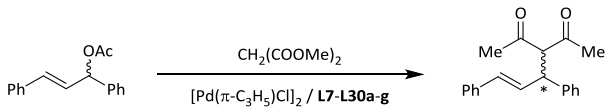
5.1.2. Results and discussion

5.1.2.1. Allylic substitution of disubstituted linear substrates

First, we tested the efficiency of the chiral phosphite-thioether/selenoether ligands **L7**-**L30a**-**g** 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) and the more challenging *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 desired nucleophile. Several C-, N- and O- nucleophiles were used under standard conditions.

Table 5.1.1. Results for the Pd-catalyzed allylic alkylation of **S1** with dimethyl malonate using the ligand library **L7**-**L30a**-**g**.[a]



S1 **1**

Entry	Ligand	%Conv (h)[b]	% ee[c]	Entry	Ligand	% Conv (h)[b]	% ee[c]
1	**L7a**	100 (3)	18 (*S*)	26	**L16g**	100 (3)	45 (*S*)
2	**L7b**	100 (3)	17 (*S*)	27	**L17a**	100 (3)	70 (*S*)
3	**L7c**	100 (3)	17 (*S*)	28	**L17f**	100 (3)	35 (*R*)
4	**L7d**	100 (3)	34 (*R*)	29	**L17g**	100 (3)	92 (*S*)
5	**L7e**	100 (3)	37 (*S*)	30	**L18f**	100 (3)	39 (*R*)
6	**L7f**	100 (3)	38 (*R*)	31	**L18g**	100 (3)	94 (*S*)
7	**L7g**	100 (3)	39 (*S*)	32	**L19a**	100 (3)	72 (*S*)
8	**L8a**	100 (3)	4 (*S*)	33	**L20a**	100 (3)	76 (*S*)
9	**L9a**	92 (3)	17 (*R*)	34	**L20g**	100 (3)	92 (*S*)
10	**L9d**	96 (3)	23 (*R*)	35	**L21g**	100 (3)	92 (*S*)
11	**L9e**	100 (3)	12 (*S*)	36	**L22g**	100 (3)	93 (*S*)
12	**L10a**	100 (3)	11 (*R*)	37	**L23g**	100 (3)	97 (*S*)
13	**L10d**	100 (3)	27 (*R*)	38	**L24a**	100 (3)	13 (*R*)
14	**L10e**	100 (3)	14 (*S*)	39	**L24f**	100 (3)	41 (*S*)
15	**L11d**	100 (3)	25 (*R*)	40	**L24g**	100 (3)	46 (*R*)
16	**L11e**	100 (3)	0	41	**L26a**	100 (3)	9 (*S*)
17	**L12d**	100 (3)	22 (*R*)	42	**L26f**	100 (3)	50 (*R*)
18	**L12e**	100 (3)	4 (*R*)	43	**L26g**	100 (3)	24 (S)
19	**L13d**	100 (3)	14 (*R*)	44	**L27a**	100 (3)	7 (S)
20	**L13e**	100 (3)	4 (*R*)	45	**L27f**	100 (3)	13 (*R*)
21	**L14a**	100 (3)	40 (*R*)	46	**L27g**	100 (3)	18 (*S*)
22	**L14d**	100 (3)	80 (*R*)	47	**L29f**	100 (3)	81 (*R*)
23	**L14e**	100 (3)	10 (*R*)	48	**L29g**	100 (3)	4 (*S*)
24	**L15a**	100 (3)	58 (*R*)	49	**L30f**	100 (3)	2 (*R*)
25	**L16f**	100 (3)	31 (*R*)	50	**L30g**	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.

In the first set of experiments, we studied the effect of the ligand parameters by applied them in the Pd-catalyzed allylic substitution of model linear substrate **S1** with dimethyl malonate as nucleophile. The results, which are presented in Table 5.1.1, 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 both, the phosphite and thioether/selenoether moieties as well as the configuration of the biaryl phosphite moiety. By selecting the correct

combination of ligand parameters high enantioselectivities (up to 97% ee) could be therefore achieved. In all cases, 100 % conversion were achieved in only 3 hours.

The first parameter to be studied is the effect of changing the substituents/ configuration in the biaryl phosphite moiety by comparing the results using ligands **L7a**-**g** (entries 1-7). We found a minor impact on enantioselectivities and activities by modifying the substituents; however, a chiral biaryl phosphite moiety must be present to achieve the highest enantioselectivity. Therefore, the ligand backbone is not capable to fix the tropoisomerization of the biaryl moiety.

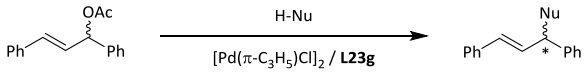
By comparing ligands **L7**-**L13** we also found that enantioselectivity is affected by the thioether substituent. The presence of a phenyl thioether group (ligands **L7**) has a positive effect on enantioselectivities. (i.e. entry 4 vs 8, 10, 13, 15, 17 and 19).The presence of either two methyl substituents to the carbon next to the phosphite moiety (ligands **L14** and **L15**, Table 5.1.1; entries 22 and 23 vs 4 and 5) or substituents to the carbon next to the thioether group (ligands **L16** and **L26** entries 25, 26 and 41-43) , also had a positive effect on enantioselectivity). However, the results with ligands **L17** and **L24** indicated a cooperative effect between the configurations of the carbon next to the phosphite functionality and the biaryl phosphite moiety, that results in a matched combination for ligands **L17g**, with an (*R*)-configuration of both the carbon next to the phosphite group and the biaryl phosphite moiety (92% ee; entry 29).

With ligands **L18**-**L23**, we studied the effect of different substituents to the carbon next to the phosphite moiety. The highest enantioselectivity (up to 97% ee) was obtained with Pd-**L23g** catalyst (entry 37).

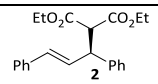
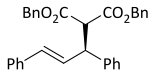
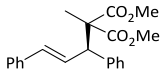
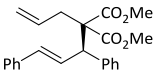
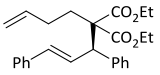
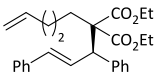
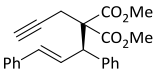
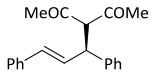
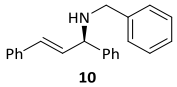
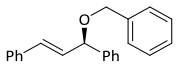
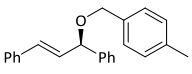
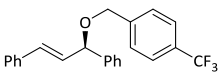
Finally, comparing the results with phosphite-selenoether ligands **L27**-**L30** with their thioether counterparts we found that the replacement of the sulphur by selenium hardly affected the catalytic performance (i.e. entry 29 vs 50).

With the best catalytic system in hand (Pd-**23g**), we next decided to study its scope by using several C-, N- and O- nucleophiles, among which are the little studied functionalized malonates, β-diketones and alkyl alcohols The results are shown in Table 5.1.2. Advantageously, we found that the catalytic performance is unaffected by the variations 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 importance are the high enantioselectivities obtanied with allyl-, butenyl-, pentenyl- and propargyl-substituted malonates, whose products are key intermediates in the synthesis of more complex chiral products.[1,5g,6], The addition of acetylacetone (compound **9**) also provided with similar high enantioselectivities (ee's up to 97%). Enantiocontrol was also excellent when a N-nucleophile such as benzylamine (compound **10**) were used. We could achieve high enantioselectivity when a range of O-nucleophiles were used. The efficient allylic substitution with this type of nucleophiles opens up a straightforward way for the preparation of aliphatic chiral ether for the synthesis of biologically active target.[7]

Table 5.1.2. Allylic substitution of **S1** with C-, N- and O-nucleophiles using Pd-**L23g** catalytic system.[a]



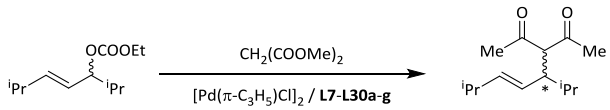
S1 **2-13**

Entry	Product	% Conv[b] (% Yield)	% ee[c]
1	 **2**	100 (91)	96% (*S*)
2	 **3**	100 (93)	97% (*S*)
3	 **4**	100 (89)	96% (*R*)
4	 **5**	100 (88)	98% (*R*)
5	 **6**	100 (90)	95% (*R*)
6	 **7**	100 (87)	94% (*R*)
7	 **8**	100 (88)	92% (*R*)
8	 **9**	100 (90)	97% (*S*)
9	 **10**	100 (87)	98% (*R*)
10[d]	 **11**	100 (82)	95% (*R*)
11[d]	 **12**	100 (86)	91% (-)
12[d]	 **13**	100 (86)	90% (-)

[a] 0.5 mol% $[PdCl(\eta^3\text{-}C_3H_5)]_2$, **L23g** (0.011 mmol), **S1** (1 mmol), CH_2Cl_2 (2 mL), BSA (3 eq), nucleophile (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. [d] Reactions carried out using 2 mol % $[PdCl(\eta^3\text{-}C_3H_5)]_2$, 4 mol % ligand and Cs_2CO_3 (3 equiv).

Despite this, few successful examples exist and most of them use phenols as O-nucleophiles.[5f,8] 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.

Table 5.1.3. Selected results for the Pd-catalyzed allylic alkylation of **S2** with dimethyl malonate using the ligand library **L7**-**L30a**-**g**.[a]



S2 **14**

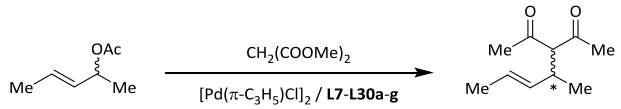
Entry	Ligand	%Conv (h)[b]	% ee[c]	Entry	Ligand	% Conv (h)[b]	% ee[c]
1	**L7a**	100 (24)	21 (*S*)	26	**L16g**	100 (24)	49 (*S*)
2	**L7b**	100 (24)	22 (*S*)	27	**L17a**	100 (24)	74 (*S*)
3	**L7c**	100 (24)	20 (*S*)	28	**L17f**	100 (24)	38 (*R*)
4	**L7d**	100 (24)	44 (*R*)	29	**L17g**	100 (24)	95 (*S*)
5	**L7e**	100 (24)	20 (*S*)	30	**L18f**	100 (24)	43 (*R*)
6	**L7f**	100 (24)	46 (*R*)	31	**L18g**	100 (24)	94 (*S*)
7	**L7g**	100 (24)	25 (*S*)	32	**L19a**	100 (24)	78 (*S*)
8	**L8a**	100 (24)	7 (*S*)	33	**L20a**	100 (24)	77 (*S*)
9	**L9a**	99 (24)	19 (*R*)	34	**L20g**	100 (24)	95 (*S*)
10	**L9d**	100 (24)	26 (*R*)	35	**L21g**	100 (24)	93 (*S*)
11	**L9e**	100 (24)	17 (*S*)	36	**L22g**	100 (24)	97 (*S*)
12	**L10a**	100 (24)	15 (*R*)	37	**L23g**	100 (24)	99 (*S*)
13	**L10d**	100 (24)	34 (*R*)	38	**L24a**	100 (24)	18 (*R*)
14	**L10e**	100 (24)	19 (*S*)	39	**L24f**	100 (24)	44 (*S*)
15	**L11d**	100 (24)	31 (*R*)	40	**L24g**	100 (24)	53 (*R*)
16	**L11e**	100 (24)	2 (*S*)	41	**L26a**	100 (24)	11 (*S*)
17	**L12d**	100 (24)	29 (*R*)	42	**L26f**	100 (24)	54 (*R*)
18	**L12e**	100 (24)	9 (*R*)	43	**L26g**	100 (24)	31 (*S*)
19	**L13d**	100 (24)	19 (*R*)	44	**L27a**	100 (24)	12 (*S*)
20	**L13e**	100 (24)	7 (*R*)	45	**L27f**	100 (24)	18 (*R*)
21	**L14a**	100 (24)	42 (*R*)	46	**L27g**	100 (24)	23 (*S*)
22	**L14d**	100 (24)	83 (*R*)	47	**L29f**	100 (24)	82 (*R*)
23	**L14e**	100 (24)	12 (*R*)	48	**L29g**	100 (24)	11 (*S*)
24	**L15a**	100 (24)	63 (*R*)	49	**L30f**	100 (24)	8 (*R*)
25	**L16f**	100 (24)	37 (*R*)	50	**L30g**	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.

Then, we applied our phosphite/thioether-selenoether ligand library **L7**-**L30a**-**g** in the Pd-catalyzed allylic substitution of substrate **S2**, a more sterically demanding than substrate **S1**, used previously.[1] This fact causes the necessity to slightly increase the ligand chiral pocket around the metal center in order to be capable of accommodate the substrate for obtaining.[1] Due to the flexibility of the biaryl phosphite moiety

together with the extra flexibility conferred by modifying the thioether/selenoether groups and the ligand backbone, we expect to be able to successfully tuning the ligand parameters to obtain high enantioselectivities.. Table 5.1.3 shows the results. The behavior of the modification on the ligand parameters follows the same pattern than for the allylic substitution of **S1**. Again, the alkylation product **14** was accessible in excellent enantioselectivity (ee's up to 99%) with the catalyst precursor containing ligand **L23g** (Table 5.1.3, entry 37). As expected, the activities were lower than in the alkylation reaction of **S1**.[1]

Table 5.1.4. Results for the Pd-catalyzed allylic alkylation of **S3** with dimethyl malonate using the ligand library **L7**-**L30a**-**g**.[a]



S3 **15**

Entry	Ligand	%Conv (h)[b]	% ee[c]	Entry	Ligand	% Conv (h)[b]	% ee[c]
1	**L7a**	100 (6)	11 (*S*)	25	**L16f**	100 (6)	72 (*R*)
2	**L7b**	100 (6)	9 (*S*)	26	**L16g**	100 (6)	69 (*S*)
3	**L7c**	100 (6)	10 (*S*)	27	**L17a**	100 (6)	21 (*S*)
4	**L7d**	100 (6)	59 (*R*)	28	**L17f**	100 (6)	71 (*R*)
5	**L7e**	100 (6)	12 (*S*)	29	**L17g**	100 (6)	50 (*S*)
6	**L7f**	100 (6)	62 (*R*)	30	**L18f**	100 (6)	60 (*R*)
7	**L7g**	100 (6)	12 (*S*)	31	**L18g**	100 (6)	42 (*S*)
8	**L8a**	100 (6)	3 (*S*)	32	**L19a**	100 (6)	22 (*S*)
9	**L9a**	100 (6)	15 (*R*)	33	**L19f**	100 (6)	82 (*R*)
10	**L9d**	100 (6)	21 (*R*)	34	**L20f**	100 (6)	86 (*R*)
11	**L9e**	100 (6)	19 (*S*)	35	**L20g**	100 (6)	39 (*S*)
12	**L10a**	100 (6)	8 (*R*)	36	**L24a**	100 (6)	27 (*R*)
13	**L10d**	100 (6)	22 (*R*)	37	**L24f**	100 (6)	48 (*R*)
14	**L10e**	100 (6)	15 (*S*)	38	**L24g**	100 (6)	29 (*S*)
15	**L11d**	100 (6)	20 (*R*)	39	**L26a**	100 (6)	6 (*R*)
16	**L11e**	100 (6)	10 (*S*)	40	**L26f**	100 (6)	72 (*R*)
17	**L12d**	100 (6)	24 (*R*)	41	**L26g**	100 (6)	64 (*S*)
18	**L12e**	100 (6)	7 (*R*)	42	**L27a**	100 (6)	12 (*S*)
19	**L13d**	100 (6)	40 (*R*)	43	**L27f**	100 (6)	48 (*R*)
20	**L13e**	100 (6)	8 (*R*)	44	**L27g**	100 (6)	9 (*S*)
21	**L14a**	100 (6)	8 (*R*)	45	**L29f**	100 (6)	59 (*R*)
22	**L14d**	100 (6)	64 (*R*)	46	**L29g**	100 (6)	39 (*S*)
23	**L14e**	100 (6)	29 (*R*)	47	**L30f**	100 (6)	49 (*R*)
24	**L15a**	100 (6)	13 (*R*)	48	**L30g**	100 (6)	15 (*S*)

[a] 0.5 mol% $[PdCl(\eta^3\text{-}C_3H_5)]_2$, ligand (0.011 mmol), **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. [c] Enantiomeric excesses determined by GC. Absolute configuration drawn in parentheses.

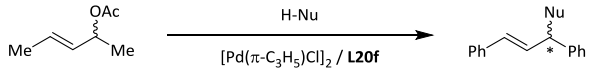
We then also tested ligands **L7**-**L30a**-**g** in the allylic substitution of the linear substrate **S3**, which is less sterically demanding than previously used substrates **S1** and **S2.** This fact causes that less catalytic systems have been successfully applied than for more hindered substrate **S1**.[3b,9] In contrast to previous hindered substrates a smaller

chiral pocket is needed for enantioselectivity to be high. [1] Due to the flexibility of our ligand design we also expected to successfully accommodate the chiral pocket to the steric demand of substrate **S3** and to obtain good enantioselectivities.

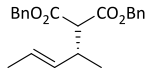
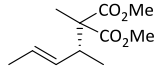
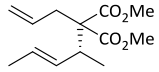
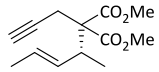
Table 5.1.4 shows the results, which indicated that we were able to fine-tune the ligands in order to obtain also high enantioselectivities in the alkylation of this demanding substrate (ee's up to 86%). The results indicate that although enantioselectivities are controlled by the same ligand parameters than 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 **L20f** (entry 34).

We next studied the allylic substitution of **S3** using several carbon nucleophiles. The results are shown in Table 5.1.5. Again, the catalyst precursor containing ligand **L20f** provided the best enantioselectivities (ee's ranging from 82% to 86%). In all cases, enantioselectivities were similar to those obtained using dimethyl malonate.

Table 5.1.5. Allylic substitution of **S3** with C-nucleophiles using Pd-**L20f** catalytic system.[a]



S3 **16-19**

Entry	Product	% Conv[b] (% Yield)	% ee[c]
1	 **16**	100 (88)	85% (*R*)
2	 **17**	100 (86)	84% (*R*)
3	 **18**	100 (90)	86% (*R*)
4	 **19**	100 (84)	82% (*R*)

[a] 0.5 mol% $[PdCl(\eta^3\text{-}C_3H_5)]_2$, **L20f** (0.011 mmol), **S3** (1 mmol), CH_2Cl_2 (2 mL), BSA (3 eq), nucleophile (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.

5.1.2.2. Allylic substitution of disubstituted cyclic substrates

The use of cyclic substrates, which have less sterically *anti* substituents, causes difficulties in the control of the enantioselectivity. These *anti* substituents are thought

to play a crucial role in the enantioselection observed with cyclic substrates in the corresponding Pd-allyl intermediates.

We tested the use of the chiral phosphite-thioether/selenoether ligands **L7**-**L30a**-**g** in the Pd-catalyzed allylic substitution of cyclic substrates with different ring sizes: *rac*-3-acetoxycyclohexene **S4** (widely used as a model substrate), *rac*-3-acetoxycyclopentene **S5** and *rac*-3-acetoxycycloheptene **S6**. Several C-nucleophiles were used under standard conditions.

We studied the effect of modifying the different ligand parameters by applying phosphite-thioether/selenoether ligand library (**L7**-**L30a**-**g**) in the Pd-catalyzed allylic substitution of model cyclic substrate **S4** with dimethyl malonate as nucleophile. The results are in Table 5.1.6 and 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 good enantioselectivities (up to 89% ee) could be therefore achieved in both enantiomers of the alkylated product.

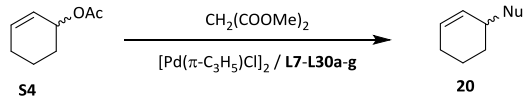
The first parameter to be studied is the effect of changing the substituents and the configuration in the biaryl moiety by comparing the results with ligands **L7a**-**g** (entries 1-7). First evidences showed an impact on the enantioselectivity with the modification of the substituents. Enantioselectivities are better when bulky trimethylsilyl substituents are present at the *ortho* positions of the biaryl phosphite moiety. (i.e. entry 3 vs 1-2). We also found that the configuration of the biaryl phosphite group controls the sense of the enantioselectivity. 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 **L7**-**L13** indicate that enantioselectivity is affected by the thioether substituent. Thus, ligands **L7**, containing a phenyl thioether group led to higher enantioselectivities. (i.e. entry 4 vs 8, 10, 13, 15, 17 and 19).The presence of two methyl substituents attached to the carbon close to the phosphite moiety (**L14** and **L15**) had a positive effect on enantioselectivity (Table 5.1.6; entries 22 and 23 vs 4 and 5), this fact follow the same tend as for linear substrates. Similarly, the use of ligands **L16** and **L26**, with substituents attached to the carbon next to the thioether group, also had a positive effect on enantioselectivity (entries 25, 26 and 41-43).The results using ligands **L17** and **L24** again 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 **L17g** and **L24f** (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 **L22g** and **L13g** (entries 37 and 38).

Finally, as observed for **S1**, comparing the results using phosphite-selenoether ligands **L27**-**L30** with their thioether counterparts we found that the catalytic performance is hardly affected by the replacement of the sulfur by selenium (i.e. entry 29 vs 50).

Table 5.1.6. Results for the Pd-catalyzed allylic alkylation of **S4** with dimethyl malonate using the ligand library **L7**-**L30a**-**g**.[a]

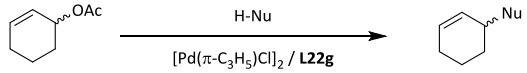


S4 **20**

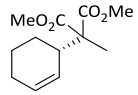
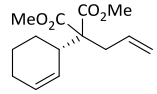
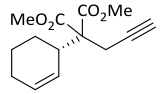
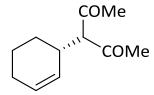
Entry	Ligand	%Conv (h)[b]	% ee[c]	Entry	Ligand	% Conv (h)[b]	% ee[c]
1	**L7a**	100 (6)	9 (*S*)	27	**L17a**	100 (6)	24 (*S*)
2	**L7b**	100 (6)	9 (*S*)	28	**L17f**	100 (6)	72 (*R*)
3	**L7c**	100 (6)	14 (*S*)	29	**L17g**	100 (6)	82 (*S*)
4	**L7d**	100 (6)	55 (*R*)	30	**L18f**	100 (6)	75 (*R*)
5	**L7e**	100 (6)	66 (*S*)	31	**L18g**	100 (6)	87 (*S*)
6	**L7f**	100 (6)	80 (*R*)	32	**L19a**	100 (6)	23 (*S*)
7	**L7g**	100 (6)	77 (*S*)	33	**L19f**	100 (6)	82 (*R*)
8	**L8a**	100 (6)	3 (*S*)	34	**L20a**	100 (6)	37 (*S*)
9	**L9a**	100 (6)	11 (*S*)	35	**L20g**	100 (6)	82 (*S*)
10	**L9d**	100 (6)	22 (*R*)	36	**L21g**	100 (6)	87 (*S*)
11	**L9e**	100 (6)	14 (*S*)	37	**L22g**	100 (6)	89 (*S*)
12	**L10a**	100 (6)	8 (*S*)	38	**L23g**	100 (6)	89 (*S*)
13	**L10d**	100 (6)	42 (*R*)	39	**L24a**	100 (6)	52 (*R*)
14	**L10e**	100 (6)	25 (*S*)	40	**L24f**	100 (6)	85 (*R*)
15	**L11d**	100 (6)	24 (*R*)	41	**L24g**	100 (6)	82 (*S*)
16	**L11e**	100 (6)	17 (*S*)	42	**L26a**	100 (6)	20 (*S*)
17	**L12d**	100 (6)	34 (*R*)	43	**L26f**	100 (6)	77 (*R*)
18	**L12e**	100 (6)	19 (*S*)	44	**L26g**	100 (6)	79 (*S*)
19	**L13d**	100 (6)	40 (*R*)	45	**L27a**	100 (6)	2 (*S*)
20	**L13e**	100 (6)	12 (*S*)	46	**L27f**	100 (6)	78 (*R*)
21	**L14a**	100 (6)	8 (*R*)	47	**L27g**	100 (6)	78 (*S*)
22	**L14d**	100 (6)	59 (*R*)	48	**L29f**	100 (6)	71 (*R*)
23	**L14e**	100 (6)	41 (*S*)	49	**L29g**	100 (6)	85 (*S*)
24	**L15a**	100 (6)	13 (*R*)	50	**L30f**	100 (6)	75 (*R*)
25	**L16f**	100 (6)	78 (*R*)	51	**L30g**	100 (6)	72 (*S*)
26	**L16g**	100 (6)	74 (*S*)				

[a] 0.5 mol% $[PdCl(\eta^3\text{-}C_3H_5)]_2$, ligand (0.011 mmol), **S4** (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.

Table 5.1.7. Allylic substitution of **S4** with C-nucleophiles using Pd-**L22g** catalytic system.[a]



S4 **21-24**

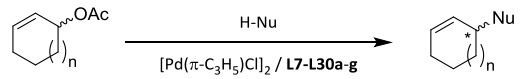
Entry	Product	% Conv[b] (% Yield)	% ee[c]
1	 **21**	100 (89)	88% (-)
2	 **22**	100 (91)	87% (-)
3	 **23**	100 (88)	91% (*S*)
4	 **24**	100 (84)	88% (-)

[a] 0.5 mol% [PdCl(η^3-C_3H_5)]$_2$, **L22g** (0.011 mmol), **S4** (1 mmol), CH_2Cl_2 (2 mL), BSA (3 eq), nucleophile (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.

With the best catalytic system in hand (Pd-**22g**), we next decided to study its scope by using other C-nucleophiles. The results are summarized in Table 5.1.7. Advantageously, we found that the catalytic performance is unaffected by the variations of the steric properties of the ester moiety and 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 98%). 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.[5g,10] The addition of acetylacetone (compound **24**) also proceeded with similar high enantioselectivities (ee's up to 88%).

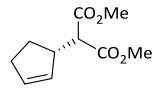
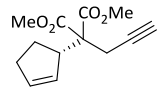
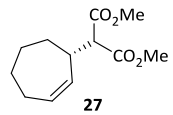
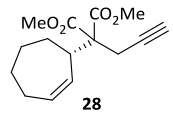
Encourage by the results obtained in the substitution of substrate **S4**, we decided to applied the catalysts that have provided the best enantioselectivities (Pd/**L7**-**L30a**-**g**) using other cyclic substrates with different ring size (**S5** and **S6**). The results, which are found in Table 5.1.8, indicated that ligands **L22f** and **L24g** can provided with good results in both enantiomers of the alkylated products **25**-**28**.

Table 5.1.8. Results for allylic substitution of **S5**-**S6** with C-nucleophiles using Pd-**L7**-**L30a**-**g** catalytic system.[a]



S5 n= 0
S6 n= 2

25-28

Entry	Product	Ligand	% Conv[b] (% Yield)	% ee[c]
1	 **25**	**L22f** **L24g**	100 (84) 100 (79)	82% (-) 80% (+)
2	 **26**	**L22f** **L24g**	100 (86) 100 (84)	80% (*S*) 79% (*R*)
3	 **27**	**L22f** **L24g**	100 (89) 100 (86)	92% (*S*) 91% (*R*)
4	 **28**	**L22f** **L24g**	100 (87) 100 (91)	91% (*S*) 87% (*R*)

[a] 0.5 mol% $[PdCl(\eta^3\text{-}C_3H_5)]_2$, **L** (0.011 mmol), **S5**-**S6** (1 mmol), CH_2Cl_2 (2 mL), BSA (3 eq), nucleophile (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.

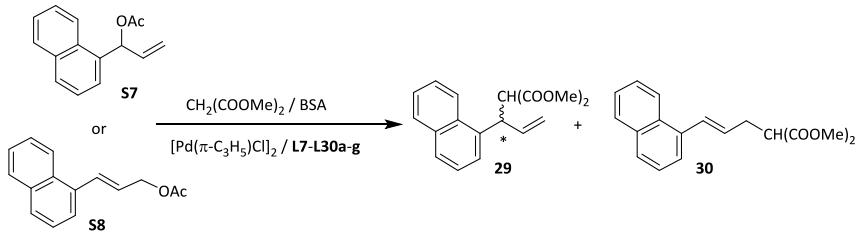
5.1.2.3. Allylic substitution of monosubstituted substrates

To further study the potential of these readily available ligands, we tested **L7**-**L30a**-**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. 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**.[11] The development of highly regio- and enantioselective Pd-catalysts is therefore still important.[9a,9e,12]

The results, which are summarized in Table 5.1.9, indicated that regio- and enantioselectivity is highly affected of the nature of the 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 ligands 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.[13] In other words, the results indicated that the

equilibration rates of isomeric allylic palladium intermediates are fast compared to the rate of nucleophilic attack.

Table 5.1.9. Results for the Pd-catalyzed allylic alkylation of **S7** and **S8** with dimethyl malonate using the ligand library **L7**-**L30a**-**g**.[a]



		S7			S8		
Entry	Ligand	%Conv (h)[b]	% b/l[b]	% ee[c]	%Conv (h)[b]	% b/l[b]	% ee[c]
1	**L7a**	100 (2)	60/40	8 (*R*)	100 (2)	55/45	7 (*R*)
2	**L7f**	100 (2)	50/50	33 (*S*)	100 (2)	50/50	33 (*S*)
3	**L7g**	100 (2)	50/50	48 (*R*)	100 (2)	50/50	48 (*R*)
4	**L8a**	100 (2)	55/45	3 (*R*)	100 (2)	55/45	4 (*R*)
5	**L9d**	100 (2)	45/55	12 (*S*)	100 (2)	45/55	11 (*S*)
6	**L9e**	100 (2)	40/60	16 (*R*)	100 (2)	40/60	18 (*R*)
7	**L10d**	100 (2)	55/45	36 (*S*)	100 (2)	55/45	36 (*S*)
8	**L10e**	100 (2)	50/50	41 (*R*)	100 (2)	50/50	40 (*R*)
9	**L11e**	100 (2)	55/45	28 (*R*)	100 (2)	55/45	28 (*R*)
10	**L12e**	100 (2)	50/50	34 (*R*)	100 (2)	50/50	32 (*R*)
11	**L13e**	100 (2)	55/45	41 (*R*)	100 (2)	55/45	39 (*R*)
12	**L14d**	100 (2)	50/50	16 (*S*)	100 (2)	50/50	16 (*S*)
13	**L14e**	100 (2)	55/45	35 (*R*)	100 (2)	55/45	35 (*R*)
14	**L15a**	100 (2)	50/50	10 (*S*)	100 (2)	50/50	9 (*S*)
15	**L16f**	100 (2)	65/35	31 (*S*)	100 (2)	65/35	30 (*S*)
16	**L16g**	100 (2)	55/45	42 (*R*)	100 (2)	55/45	42 (*R*)
17	**L17f**	100 (2)	55/45	29 (*R*)	100 (2)	55/45	29 (*R*)
18	**L17g**	100 (2)	80/20	23 (*S*)	100 (2)	80/20	25 (*S*)
19	**L18f**	100 (2)	50/50	24 (*R*)	100 (2)	50/50	24 (*R*)
20	**L18g**	100 (2)	80/20	35 (*S*)	100 (2)	80/20	36 (*S*)
21	**L19a**	100 (2)	40/60	38 (*S*)	100 (2)	40/60	38 (*S*)
22	**L19f**	100 (2)	45/55	26 (*R*)	100 (2)	45/55	26 (*R*)
23	**L19g**	100 (2)	75/25	35 (*S*)	100 (2)	75/25	35 (*S*)
24	**L24f**	100 (2)	65/35	54 (*R*)	100 (2)	65/35	53 (*R*)
25	**L24g**	100 (2)	50/50	19 (*S*)	100 (2)	50/50	19 (*S*)
26	**L26f**	100 (2)	55/45	18 (*R*)	100 (2)	55/45	17 (*R*)
27	**L26g**	100 (2)	65/35	41 (*S*)	100 (2)	65/35	41 (*S*)
28	**L27f**	100 (2)	60/40	14 (*R*)	100 (2)	50/50	13 (*R*)
29	**L27g**	100 (2)	85/15	38 (*S*)	100 (2)	80/20	37 (*S*)
30	**L30f**	100 (2)	50/50	26 (*R*)	100 (2)	60/40	24 (*R*)
31	**L30g**	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.

The use of ligands **L7**-**L13** 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 **L17** and **L24** 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 **L17g** (entry 18), albeit the highest enantioselectivity (up to 54% ee) was achieved using ligand **L24f** (entry 24).

5.1.3. Conclusions

A library of phosphite-thioether/selenoether ligands **L7**-**L30a**-**g** has been applied in the Pd-catalyzed allylic substitution reactions of several substrates including the more challenging monosubstituted 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.

5.1.4. Experimental part

5.1.4.1 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.[14] The synthesis of ligands **L7**-**L30a**-**g** is described in section 3.3 (Chapter 3).

5.1.4.2. 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 ^1H NMR and enantiomeric excesses were determined by HPLC. [12a] For compounds **15**, **17**, **20, 23**-**24** and **26**-**28**, conversion and enantiomeric excesses were determined by GC.[12a] For compounds **14** and **25**, conversion were measured by ^1H NMR and ee's were determined by ^1H NMR using $[Eu(hfc)_3]$.[12a]

5.1.4.3. 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 ^1H NMR and enantiomeric excesses were determined by HPLC.[12a]

5.1.4.4. 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.[12a]

5.1.4.5. 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.[12a]

5.1.5. Acknowledgments

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5.1.6. REFERENCES

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UNIVERSITAT ROVIRA I VIRGILI
SUSTAINABLE AND COST-EFFECTIVE DEVELOPMENT OF CHIRAL METAL-CATALYSTS FOR C-H AND C-X BOND FORMING REACTIONS
Carlota Borràs Noguera

5.2. Amino-P ligands from iminosugars: new readily available and modular ligands for enantioselective Pd-catalyzed allylic substitutions

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Abstract: *The synthesis of a new type of amino-phosphite/phosphinite/phosphine ligands containing a protected pyrrolidine-3,4-diol moiety is presented. These ligands are obtained in enantiomerically pure form, from readily available sugars. They thus contain the advantages of carbohydrates in terms of selection of the stereogenic carbons, polyfunctional groups able to modulate the electronic and sterical properties, and the general good stability of carbohydrate derivatives. They constitute a new type of P,N-ligands that have been used in the asymmetric Pd-catalyzed allylic reaction of acyclic and cyclic substrates with varied steric requirements, using different C- and N-nucleophiles. By selecting the ligand parameters (amine substituent, configuration of the carbons bearing the isopropylidene group, substituent/configuration for the phosphite moieties and the rigidity of the ligand) and several substrates with different electronic and steric requirements, asymmetric reactions with a number of C- and N-nucleophiles gave substituted compounds in which new stereogenic C-C and C-N bonds are formed with high enantioselectivities giving chiral molecules ready for further alkene transformations. Among the three groups of P,N-ligands (amino-P (P= phosphite, phosphinite and phosphine groups) the new amino-phosphite ligands gives the widest substrate and nucleophile scope, including the more challenging hindered linear and cyclic substrates. In particular, for carbohydrate derived amino-phosphite ligands and linear substrates, high enantioselectivity in the reactions requires an R-configuration of the binaphthyl moiety. However, for cyclic substrates both enantiomers of the alkylated products are obtained by simply setting out the configuration of the binaphthyl phosphite moiety. A detailed study of the Pd-π-allyl intermediates is also presented.*

5.2.1. Introduction

Catalysis has revolutionized the chemical industry because catalysts are used in the production of most chemicals, resulting in a multi-billion euro business. The development and improvement of catalysts are therefore keys for achieving a sustainable production of all sorts of chemicals. Chirality is a fundamental property for a large number of technologically and biologically relevant compounds.[1] Among the catalytic reactions leading to chiral products, asymmetric Pd-catalyzed allylic substitution creates new stereogenic C-C and C-X bonds creating chiral simple molecules that can be further transformed by taking advantage of the alkene

functionality.[2] Other advantages of the Pd-catalyzed allylic substitution are the high functional group tolerance and mild reaction conditions. Heterodonor compounds are among the most successful ligands reported to date for this process.[2] Their success derives mainly 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 the most studied.[2] Other heterodonor phosphine/phosphinite-ligands containing a more stable group than oxazolines (such thioether,[3] pyridine,[4] imine[5] and amine[6]) have also been studied. However, only a few of them have been successfully used and they are typically limited in substrate and nucleophile scope.[7] We have contributed with improvements in catalyst performance with mixed ligands that have biaryl phosphite moieties.[2h,8] We found that biaryl phosphite moieties improve substrate versatility because the flexibility of these groups allows the catalyst chiral pocket to adapt to the steric demands of the substrate.[8e]

Despite all the remarkable advances in catalyst design, still few ligands have been successfully applied in the allylic substitution of substrates with different electronic and steric proprieties using a large number of nucleophiles. "Privileged" ligands[9] with a wide substrate scope and suitable for a large number of nucleophiles would allow us to limit time-consuming ligand design and preparation, and would be the key for achieving the sustainable production of all the sorts of C–C and C–X bonds required for synthesizing complex organic compounds.

The search for such ligands that are easy to handle (solid and stable in air), easy to prepare from simple starting materials, and that are good for a broad range of substrates and nucleophiles, is a relevant topic in this reaction. Carbohydrates are particularly useful for preparing ligands because they are relative abundant in an enantiomerically pure form, present a wide stereochemical diversity, besides they are cheap and readily available. Their polifunctional structure facilitates its modular reactivity in terms of electronic and sterical effects.[10] Series of chiral ligands can be synthesized and screened in the search of the optimal ligand for each type of substrate.

In our search for more versatile and stable Pd-catalysts, we herein report the synthesis and application of a new sugar-based amino-phosphite/phosphinite/phosphine ligand library (**L49**–**L54a**–**d**; Figure 5.2.1) in the Pd-allylic substitution of substrates with different steric requirement with several nucleophiles. These ligands have been prepared from amino-alcohols **1**–**6**, which are obtained from commercially available cheap carbohydrates. We believe that the modular nature of the iminosugar backbone together with the appropriate choice of the P functionality would be crucial to control the configuration of the nitrogen upon coordination of the P-N ligands,[7] which in turn will aid in the development of efficient

ligands for this transformation. To achieve such a control, several ligand parameters have been easily tuned. We have therefore investigated the effect of systematic changing the substituent in the nitrogen group (**L49**–**L51**), the configuration of carbons bearing the isopropylidene group (ligands **L49** *vs* **L52**), the rigidity of the ligand backbone (ligands **L55**) and the substituent/configuration in the biaryl phosphite moiety (**a**–**d**). We also studied the effect of replacing the phosphite moiety by a phosphinite group (**L53**) or a phosphine group (**L54**). In this paper, we have also carried out the synthesis and elucidation of the Pd-π-allyl intermediates to explain the origin of enantioselectivity.

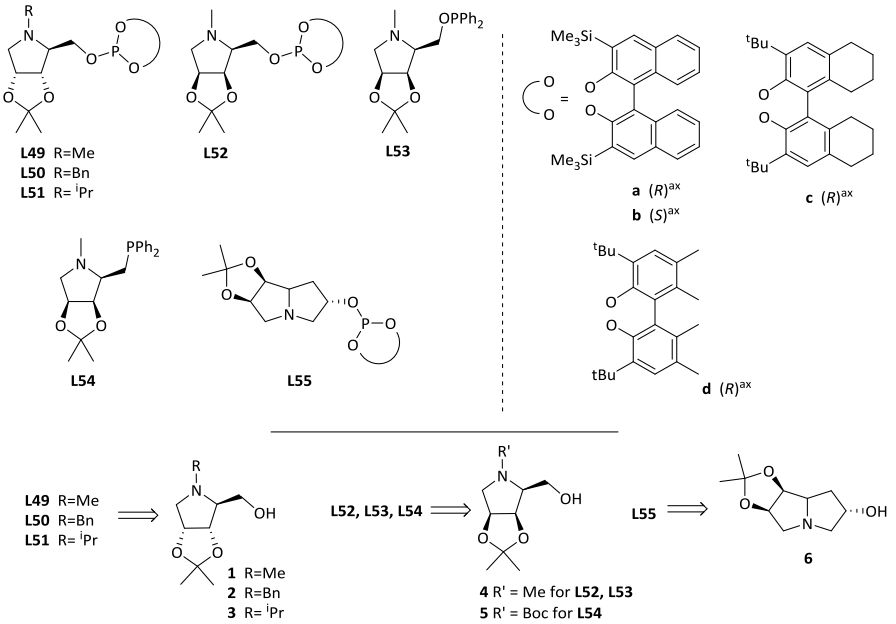
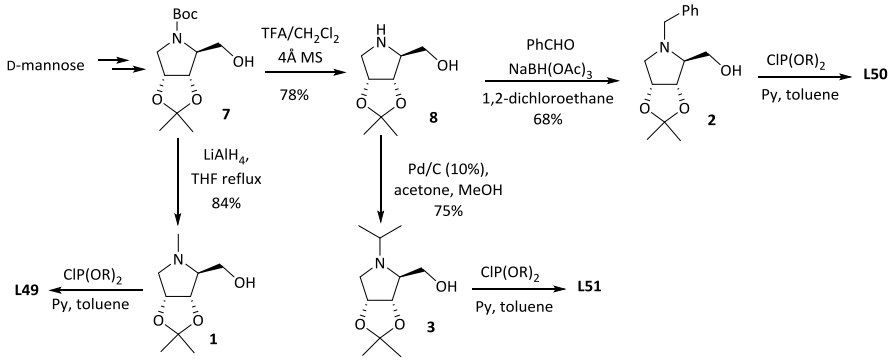


Figure 5.2.1. Amino-phosphite/phosphinite/phosphine ligands **L49**-**L55a**-**d** and their starting products, cyclic amino alcohols **1**–**6**.

5.2.2. Results and discussion

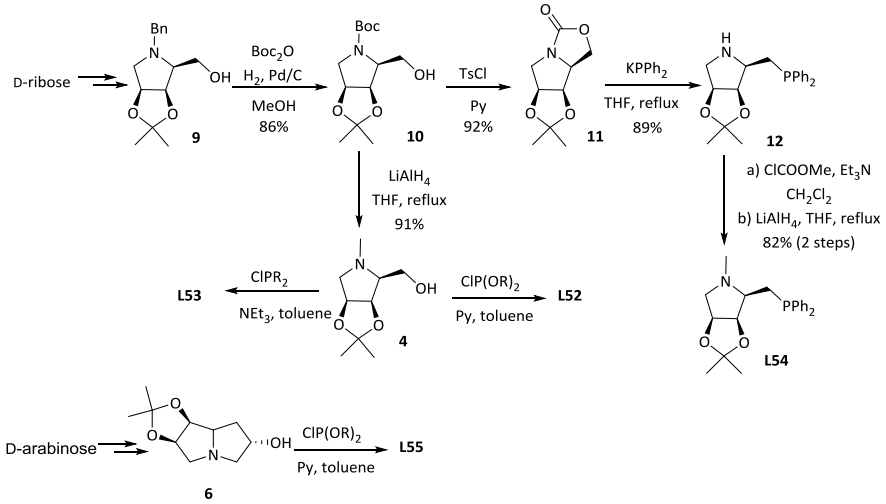
5.2.2.1. Synthesis of ligands

The synthesis of ligands **L49**–**L51** started from pyrrolidine alcohol **7**, easily obtained from D-mannose following the procedure recently reported by us.[11] Reduction of **7** with $LiAlH_4$ gave *N*-methyl pyrrolidine alcohol **1**. On its side, acidic deprotection of the Boc group of **7** followed by reductive amination with benzaldehyde and acetone afforded *N*-benzyl and *N*-isopropyl hydroxy pyrrolidine derivatives **2** and **3**, respectively. With these steps the desired diversity in the electronic and steric proprieties of the amine part was attained. Finally, reaction of amino-alcohols **1**, **2** and **3** with one equivalent of the corresponding phosphorochloridite ($ClP(OR)_2$; OR= **a**–**d**) formed *in situ* gave access to amino-phosphite ligands **L49**–**L51** with the desired substituent/configurations of the biaryl phosphite group.



Scheme 5.2.1.Synthesis of ligands **L49**-**L51**.

The preparation of ligands **L52**-**L53**, with a different configuration of the carbons bearing the isopropylidene group than **L49**-**L51**, is outlined in Scheme 5.2.2. Alcohol **9** was prepared from D-ribose as previously reported.[12] Protecting group manipulation afforded *N*-Boc derivative **10** that after reduction with $LiAlH_4$ gave *N*-methyl pyrrolidine alcohol **4**. Its reaction with $ClP(OR)_2$ or $ClPR_2$ furnished the corresponding phosphite/phosphinite ligands **L52** and **L53**. Standard tosylation of **10** did not afford the corresponding tosylate derivative, instead, cyclic carbamate **11** was obtained as previously described for ***ent*-10**.[11] Nucleophilic ring opening of **11** by treatment with $KPPh_2$ in THF at reflux gave phosphine **12**. Reaction with methoxycarbonyl chloride gave the corresponding carbamate which, after reduction with $LiAlH_4$, gave amino-phosphine ligand **L54** in 82% yield (2 steps). On the other hand, starting from D-arabinose, pyrrolizidine-alcohol **6** was obtained (Scheme 5.2.2).[13] Subsequent reaction with $ClP(OR)_2$ afforded the corresponding amino-phosphites **L55**.



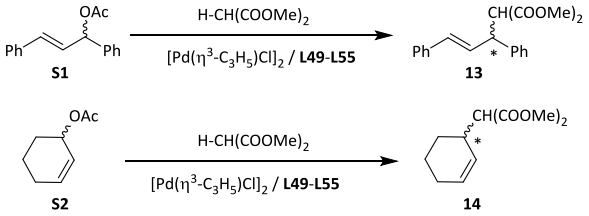
Scheme 5.2.2. Synthesis of ligands **L52**-**L55**.

Advantageously, the amino-phosphite ligands were found to be stable in air and resistant to hydrolysis, so they were further manipulated and stored in air. The

phosphinite and phosphine analogues (**L53** and **L54**), however, were less stable in air and were stored under argon. The formation of the ligands was confirmed by $^{31}P\{^{1}H\}$, ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra and mass spectrometry. The spectra assignments were supported by the information obtained from $^{1}H–^{1}H$ and $^{1}H–^{13}C$ correlation measurements. The $^{31}P\{^{1}H\}$, ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra showed the expected signals for these C_1–ligands. All NMR spectra showed only one isomer in solution. One singlet in the $^{31}P\{^{1}H\}$ NMR spectra was therefore observed. See experimental section for purification and characterization details.

5.2.2.2. *Allylic substitution of disubstituted substrates S1 and S2 with dimethyl malonate as nucleophile*

We initially tested the capacity of ligands **L49**–**L55a**–**d** by applying them in the allylic alkylation of two substrates with different steric requirement, the benchmark linear substrate **S1** and the more challenging cyclic substrate **S2**, using dimethyl malonate as nucleophile (Scheme 5.2.3). For substrate **S2** it is more difficult to control enantioselectivity, mainly because of the presence of less sterically *anti* substituents, which have a key role in the enantioselection found in the corresponding Pd-allyl intermediates. Enantioselectivities were found to depend on the ligand architecture and the substrate type (Table 5.2.1). While the best enantioselectivities for **S1** were achieved with ligands **L49a** and **L49d**, for cyclic substrate **S2** the best enantioselectivities in both enantiomers of the alkylated product were achieved using ligands **L49a**-**b** and **L55a**-**b**.



Scheme 5.2.3. Allylic substitution of disubstituted substrates **S1** and **S2** with dimethyl malonate as nucleophile.

Concerning the effect of the different P-donor groups the results indicated that replacing the phosphite (**L52**) moiety by a phosphinite or a phosphine group (ligands **L53** and **L54**) had a negative effect on enantioselectivity (Table 5.2.1; entry 9 vs 11-12). We also found that the chirality at the biaryl phosphite moiety controls the sense of enantioselectivity. Accordingly, ligands with *R* configuration at biaryl phosphite moiety, gave (*R*)-alkylated products, while ligands with *S* configuration at the biaryl phosphite group, gave (*S*)-alkylated products (e.g. entry 1 *vs* 2). In addition, for the lineal substrate **S1** there is a cooperative effect between the configuration of the biaryl phosphite moiety and the ligand backbone that results in a matched combination with ligand **L49a**, containing an *R*-biaryl phosphite group (entry 1 vs 2). This cooperative effect is less pronounced in the allylic substitution of cyclic substrate **S2** and both

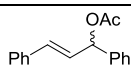
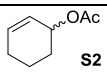
enantiomers of the alkylated products are therefore easily accessible by simply setting the configuration of the biaryl phosphite moiety (entries 1 and 2). Finally, for the cyclic substrate **S2** it is also seen that enantioselectivity is affected by the substituents of the biaryl phosphite group. Enantioselectivities are therefore the highest when $SiMe_3$ groups are present at the *ortho* positions of the biaryl phosphite moiety (entries 1–2 vs 3-4).

Comparing the results with ligands **L49**-**L51**, it can be seen that the nature of the amine substituent has an effect on enantioselectivity, which increases when less sterically demanding substituents are present (entries 1, 5 and 6).

The effect of configuration of carbons bearing the isopropylidene group on enantioselectivity was investigated, observing that is larger for substrate **S1** than **S2** (entries 1-2 vs 9-10).

We also studied the application of ligands **L55** with a more rigid ligand backbone since the nitrogen is constrained in a bicyclic structure. However, while the use of ligands **L55** has a negative effect on enantioselectivity for substrate **S1** (entries 1 and 2 vs 13 and 14) it has a little impact for substrate **S2** (entries 1 and 2 vs 13 and 14).

Table 5.2.1. Pd-catalyzed allylic substitution of substrates **S1**–**S2** using dimethyl malonate as nucleophile with P,N-ligands **L49–L55**.[a]

		 **S1**		 **S2**	
Entry	L	% Conv (h)[b]	% ee[c]	% Conv (h)[b]	% ee[c]
1	**L49a**	100 (6)	80 (*R*)	100 (12)	75 (*R*)
2	**L49b**	100 (6)	71 (*S*)	100 (12)	72 (*S*)
3	**L49c**	100 (6)	77 (*R*)	100 (12)	58 (*R*)
4	**L49d**	100 (6)	79 (*R*)	100 (12)	53 (*R*)
5	**L50a**	100 (6)	11 (*R*)	100 (12)	60 (*R*)
6	**L51a**	100 (6)	7 (*R*)	100 (12)	45 (*R*)
9	**L52a**	100 (6)	15 (*R*)	100 (12)	60 (*S*)
10	**L52b**	100 (6)	17 (*S*)	100 (12)	68 (*R*)
11	**L53**	100 (6)	6 (*S*)	100 (12)	38 (*S*)
12	**L54**	100 (24)	3 (*S*)	60 (24)	35 (*S*)
13	**L55a**	80 (6)	20 (*R*)	100 (12)	70 (*R*)
14	**L55b**	100 (6)	9 (*S*)	100 (12)	71 (*S*)
15[d]	**L55a**	100 (10)	87 (*R*)	100 (20)	81 (*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 measured by HPLC for **13** and by GC for **14**. Absolute configuration drawn in parentheses. [d] Reaction carried out at 0 °C.

Finally, enantioselectivity can be improved by controlling not only the structural but also the reaction parameters. In this case, enantioselectivity was further improved by lowering the reaction temperature to 0 °C (ee's up to 87% for **S1** and 81% for **S2**, entry 15).

5.2.2.3. Allylic substitution of other substrates and with other nucleophiles. Scope and limitations

The scope of Pd/**L49**-**L55a**-**d** catalysts was then extended to other substrates and nucleophiles. As an example, Figures 5.2.2 and 5.2.3 shows the results using ligand **L49a** which had provided together with ligands **L49d** (for **S1**), and **L49b** and **L55a**-**b** (for **S2**) one of the best results.

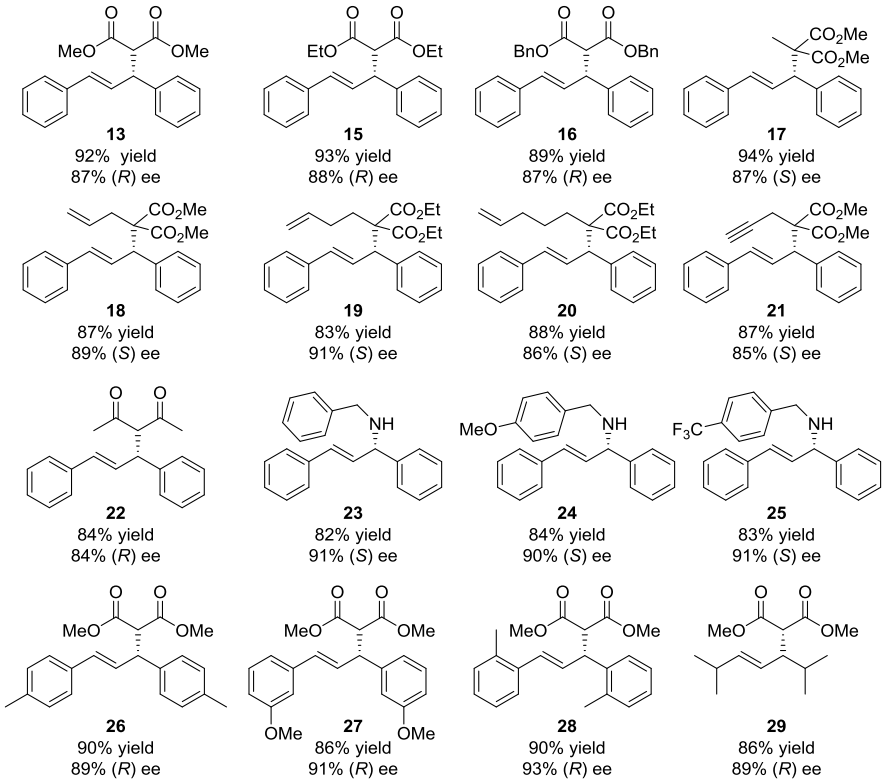


Figure 5.2.2. Allylic substitution of linear disubstituted substrates with C- and N- nucleophiles using Pd-**L49a** catalytic system. Reactions were run at 0°C with $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (0.5 mol %), CH_2Cl_2 as solvent, ligand (1.1 mol %), BSA (3 equiv), and KOAc. Full conversions were achieved after 12 h.

We initially considered the substitution of substrate **S1** with several nucleophiles. Advantageously, enantioselectivity was insensitive to the steric nature of the ester groups of the malonate nucleophiles (products **13**, **15**–**16**) and also to the replacement of the malonate by acetylacetone (product **22**) and benzylamine derivatives (products **23**–**25**). In addition, a broad range of malonates substituted with allyl-, butenyl, pentenyl- and propargyl-groups reacted with **S1** to provide the corresponding alkylated products **17**–**21** in high yields, and enantioselectivities comparable to those obtained with dimethyl malonate (ee's up to 91%). These results are important because products **18**–**21** can been used as intermediates for preparing more complex

chiral compounds.[14] Interestingly, enantioselectivities comparable to those achieved with **S1** were also achieved in the alkylation of other substrates (compounds **26**–**29**) including those more sterically demanding (compounds **28** and **29**, ee's up to 93% ee) than **S1**. These results show that the biaryl phosphite moiety in the Pd/**L1a** catalyst is able to adapt its chiral pocket and catalyze with comparable high enantioselectivities other linear substrates, with different steric and electronic properties, than **S1**.

Encouraged by the high enantioselectivity obtained in the alkylation of the challenging cyclic substrate **S2** (see Table 5.2.1) we then focused our attention to the allylic substitution of cyclic substrates. For the cyclohexenyl derivative **S2**, several C-nucleophiles were used. In all cases, enantioselectivities (ee's up to 83%, compounds **14**, **30**–**33**) were similar to those obtained when using dimethyl malonate, even when acetylacetone was used as nucleophile. High yields and enantioselectivities were also obtained in the allylic alkylation of a 7-membered cyclic substrate with dimethyl and propargyl-malonates (products **34** and **35**). Again, compounds **31**, **32** and **35** are relevant intermediates for the synthesis of chiral polycyclic compounds.[14a,14d] These results are among the best reported for these challenging cyclic substrates, even with synthetically useful nucleophiles other than dimethyl malonate, for which only few catalysts have afforded high enantioselectivities.

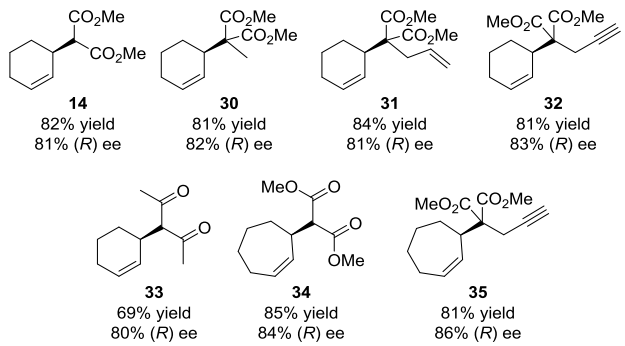
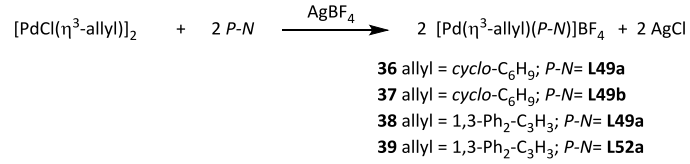


Figure 5.2.3. Allylic substitution of cyclic substrates with C-nucleophiles using Pd-**L49a** catalytic system. Reactions were run at 0°C with $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (0.5 mol %), CH_2Cl_2 as solvent, ligand (1.1 mol %), BSA (3 equiv), and KOAc. Full conversions were achieved after 24 h.

To sum up, the new sugar-based amino-phosphite ligands **L49a**-**d** and **L55a**–**b** have provided good results in different substrate types using several nucleophiles. The high activities and enantioselectivities (ee's up to 86%) obtained for cyclic substrates are particularly encouraging. This fact, along with the promising results obtained for a number of linear substrates (ee's up to 93%; including the challenging sterically demanding compounds **28** and **29**), open up the Pd-catalyzed allylic alkylation reactions to a new class of readily available, solid, air stable and modular ligands.

5.2.2.4. Mechanistic insights: study of the key Pd-π-allyl intermediates

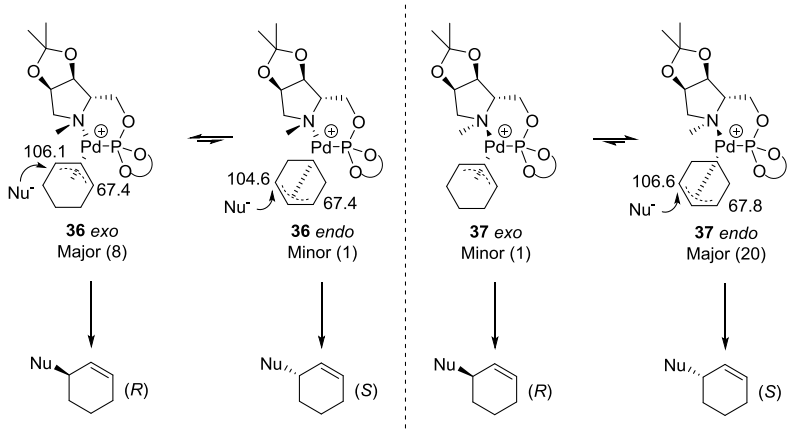
In the Pd-catalyzed allylic alkylation it has been found that the enantioselectivity is determined in the irreversible nucleophilic attack.[2] Consequently, the elucidation of Pd-π-allyl intermediates and the determination of their reactivity toward the nucleophile are key to understand their catalytic behavior. We therefore studied the Pd-π-allyl compounds **36**–**39** [Pd(η^3-allyl)(*P-N*)]BF_4 (*P-N* = **L49a**, **L49b** and **L52a**). These Pd-complexes, which contain cyclohexenyl and 1,3-diphenyl allyl groups, were prepared by using the previously reported method[15] from the [PdCl(η^3-allyl)]$_2$ and the corresponding ligand with silver tetrafluoroborate (Scheme 5.2.4). The complexes were characterized by mass spectrometry and by NMR (^{1}H, ^{13}C and ^{31}P). The spectral assignments were based on information from ^{1}H-^{1}H, ^{31}P-^{1}H, ^{1}H-^{1}H NOESY and ^{13}C-^{1}H experiments. The ESI-HR-MS showed the heaviest ions at m/z corresponding to the cation.



Scheme 5.2.4. Preparation of [Pd(η^3-allyl)(*P-N*)]BF_4 complexes **36**-**39**.

To understand the reversal in the sign of the enantioselectivity in the substitution of cyclic substrates when changing the configuration of the biaryl phosphite group (moving from **a** to **b**), we compared the Pd-1,3-cyclohexenyl-allyl intermediate **36**, which contains ligand **L49a** with its related counterpart Pd/**L49b** intermediate **37**. The VT-NMR study (30 ˚C to -80 ˚C) showed the presence of two isomers in equilibrium at a ratio of 1:8 and 20:1, respectively (Scheme 5.2.5). The major isomer of compound **36** was assigned by NOE to the Pd-η^3-*exo*, while the NOE indicated an *endo* disposition for major isomer of **37** (Figure 5.2.4). So, changes in the configuration of the phosphite moiety lead to changes in the ratio of the species that provide both enantiomers of the alkylated product. For the major isomer of complex **36**, the NOE indicates interaction between the hydrogen of the CH-N group with the central allyl proton, whereas for the major isomer of **37**, this interaction appears with one of the methylene groups of the cyclohexenyl moiety (Figure 5.2.4). These interactions are in agreement with an *exo* and an *endo* disposition of the major isomers of **36** and **37**, respectively. Moreover, the NOE also shows that for both isomers **36** the nitrogen adopts an *R*-configuration upon coordination, while for the major isomer of **37** it adopts an *S*-configuration. Thus, for isomers **36**, the NOE indicates interactions between hydrogens of the methyl amine group with the terminal allylic proton *trans* to the phosphite moiety, whereas for the major isomer of **37** this interaction appears with the hydrogen of one of the CH-O groups of the sugar backbone (Figure 5.2.4). For all isomers, the carbon chemical shifts indicate that the most electrophilic allyl C terminus is *trans* to the phosphite moiety (Scheme 5.2.5). If we assume that the nucleophilic attack takes place at the most

electrophilic carbon, for complex **36** the fact that the observed stereochemical outcome of the reaction (75% ee (*R*)) is similar to the diastereoisomeric excess of the Pd-isomers (de = 78% (*R*)) indicates that both isomers react at a similar rate. Therefore, for complex **36**, the enantioselectivity is mainly controlled by the population of the *exo* and *endo* isomers. However, for complex **37** the observed stereochemical outcome of the reaction (72% (*S*)) is different from the diastereomeric excess (90% (*S*)) of the Pd intermediates. This indicates that the minor isomer should react slightly faster than the major isomer and that enantioselectivity is also controlled by the different reactivity of the allyl intermediates towards the nucleophile.



Scheme 5.2.5. Diastereoisomeric Pd-η^3-allyl intermediates for **S2** with ligands **L49a** (isomers **36**) and **L49b** (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.

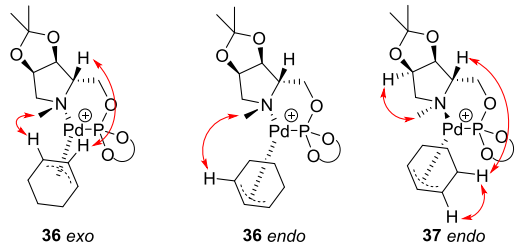
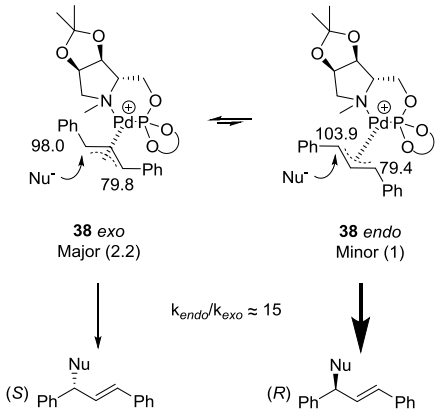


Figure 5.2.4. Relevant NOE contacts from the NOESY experiment of Pd-η^3-allyl intermediates **36** and **37**.

Finally, to evaluate the effect of the configuration of carbons bearing the isopropylidene group on the enatioselectivity obtained in the allylic alkylation of **S1**, we studied the Pd allylic intermediates with ligands **L49a** and **L52a** (**38** and **39**, respectively). Whereas ligand **L49a** provided high enantioselectivity (80% (*R*)), ligand **L52a** which differs in the configuration of the carbons bearing the isopropylidene group gave less enantioselectivity (17% (*S*)).



Scheme 5.2.6. Diastereoisomeric Pd-η^3-allyl intermediates for **S1** with ligand **L49a** (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.

The VT-NMR (30 ˚C to -85 ˚C) study of Pd-allyl intermediate **38**, with ligand **L49a**, showed a mixture of two isomers in equilibrium in a ratio of 2.2:1. The two isomers were assigned by NMR to the two *syn*/*syn exo* and *endo* isomers (Scheme 5.2.6). For both isomers the NOE shows interactions between the two terminal protons of the allyl group, which indicates a *syn*-*syn* disposition (Figure 5.2.5a). In addition, the NOE also indicates that for both isomers the nitrogen adopts an *R*-configuration upon coordination. For the major isomer the NOE also indicates interaction between the hydrogen of the CH-N group with the central allyl proton, whereas for the minor isomer there is a NOE interaction between the hydrogens of the methyl amine group with the hydrogen placed at the *ortho* position of one of the phenyl groups of the substrate. These interactions can be explained by assuming an *exo* disposition for the major isomer of **38** and an *endo* disposition for the minor isomer (Figure 5.2.5a). The carbon NMR chemical shifts indicate that the most electrophilic allyl carbon terminus is again *trans* to the phosphite moiety. Assuming that the nucleophilic attack takes place at the most electrophilic terminal carbon atom and the fact that the enantiomeric excess of the alkylation product (ee's up to 80% (*R*)) is higher than the diastereoisomeric excesses of the Pd-intermediates (de= 37% (*S*)), indicated that minor *endo* isomer must react faster than the *exo*. To prove this fact we used *in situ* NMR to study the reactivity of the Pd-intermediates with dimethyl malonate at low temperature (Figure 5.2.5b). Our results show that the minor *endo* isomer reacts around 15 times faster than the major *exo* isomer. If we take into account the relative reaction rates and the abundance of the reacting isomers, the theoretical ee should be 74% (*R*), which agrees with the ee obtained experimentally. We can therefore conclude that the nucleophilic attack takes place preferentially at the allyl terminus *trans* to the phosphite moiety of the minor Pd-intermediate. Consequently, in the case of substrate **S1** and ligand **L49a** the enantioselectivity seems to be controlled by the different reactivity of the allyl intermediates towards the nucleophile, rather than their population, as was the case for substrate **S2** when the same ligand **L49a** was used.

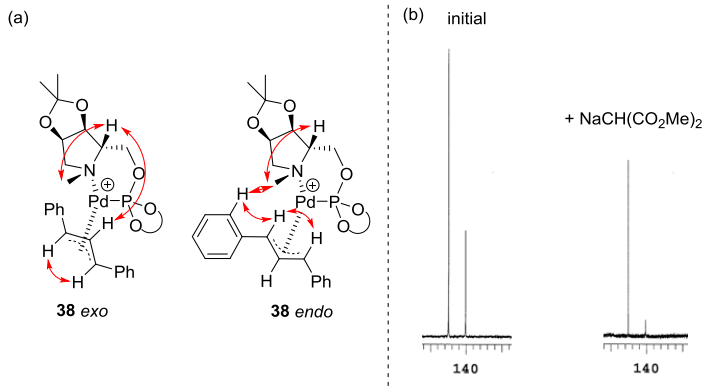
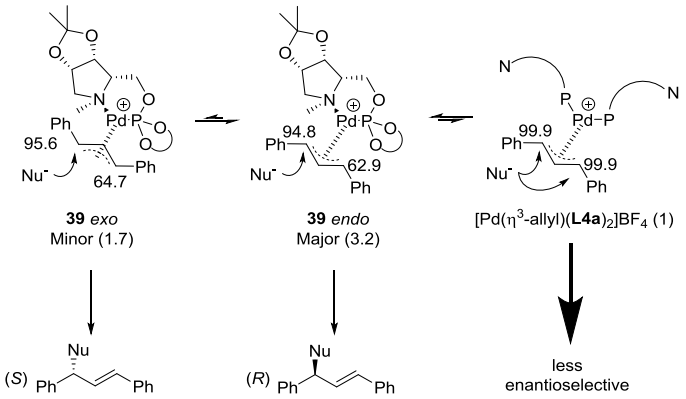


Figure 5.2.5. (a) Relevant NOE contacts from the NOESY experiment of Pd-η^3-allyl intermediates **38** *exo* and *endo*. (b) Reactivity of intermediates **38** towards sodium dimethyl malonate at -80 °C. ^{31}P-{^1H} NMR spectra before and after the addition of sodium dimethyl malonate in CD_2Cl_2.

In contrast to the previous study with ligand **L49a**, the VT-NMR (30 ˚C to -85 ˚C) of Pd-allyl intermediate **39**, with ligand **L52a**, had a mixture of three compounds in a ratio of 3.2:1.7:1. The two major ones were assigned to the two *syn*/*syn endo* and *exo* isomers **39** (see relevant NOE contacts in Figure 5.2.6), while the minor compound was assigned to Pd-allyl complex ([Pd(η^3-allyl)(**L52a**)$_2$]BF_4) in which two P-N ligands are coordinated in a monodentate fashion through the phosphite moiety (Scheme 5.2.7). Monodentate coordination of **L52a** in the minor species [Pd(η^3-allyl)(**L52a**)$_2$]BF_4 is clearly disclosed because the signals of the methyl amine group in the ^1H and ^{13}C NMR spectra are not shielded as is the case when the amino group coordinates to Pd. It should be pointed out that changes in the configuration of carbons bearing the isopropylidene group also lead to changes in the configuration of the nitrogen upon coordination to palladium from *R* (in isomers **38**) to *S* (in isomers **39**). Thus, for isomers **39**, the NOE indicates interactions between one of the methyl groups of the isopropylidene moiety with the methyl of the amino group (Figure 5.2.6). The fact that enantioselectivity was lower with the Pd/**L52a** catalyst than when the Pd/**L49a** catalyst was used may be due to the presence of [Pd(η^3-allyl)(**L52a**)$_2$]BF_4. Complexes of this type are known to give faster and less enantioselective reactions than their bidentate counterparts because they have more degrees of freedom.[16]

The study of the Pd-1,3-diphenylallyl intermediates therefore showed that for enantioselectivity to be high, the different ligand parameters need to be correctly combined to avoid the formation of species with ligands coordinated in monodentated fashion.



Scheme 5.2.7. Pd-η^3-allyl intermediates for **S1** with ligand **L52a** (isomers **39** and [Pd(η^3-allyl)(**L52a**)$_2$]BF_4). The relative amounts of each compound are shown in parentheses. The chemical shifts (in ppm) of the allylic terminal carbons are also shown.

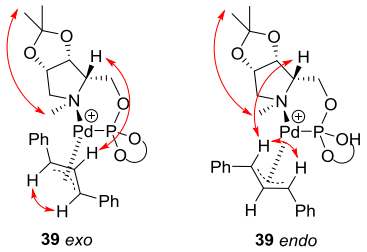


Figure 5.2.6. Relevant NOE contacts from the NOESY experiment of Pd-η^3-allyl intermediates **39** *exo* and *endo*.

5.2.3. Conclusions

A series of new iminosugar-phosphite/phosphinite/phosphine ligands have been applied in Pd-catalyzed allylic substitution reactions. These ligands are obtained in enantiomerically pure form from readily available sugars as starting materials. They thus contain the advantages of carbohydrates in terms of selection of the stereogenic carbons, polyfunctional groups able to modulate the electronic and sterical properties, and the general good stability of carbohydrate derivatives. Thus, several ligand parameters can be systematically varied so selectivities can been maximized for each substrate. By selecting the ligand components, we obtained good results in several substrates with different electronic and steric requirements and using a number of C- and N-nucleophiles (23 compounds in total with ee's up to 93%). For both substrate types (linear and cyclic), we found that the presence of biaryl phosphite groups in the ligand are needed for high enantioselectivity. This is advantageous because the iminosugar-phosphite ligands are air-stable solids in contrast to their amino-phosphinite/phosphine analogues. The effect of the remaining ligand parameters (amine substituent, the configuration of carbons bearing the isopropylidene group, the substituent/configuration of the phosphite moieties and the rigidity of the ligand) on the selectivity depend on each type of substrate. Particularly, for lineal substrates we

found that an *R*-configuration of the binaphthyl moiety is needed for high enantioselectivity. However, for cyclic substrates both enantiomers of the alkylated products can be obtained by simply setting the configuration of the binaphthyl phosphite moiety. Additionally, for cyclic substrates, in contrast to linear ones, enantioselectivity is also affected by the substituent of the biaryl phosphite group and there is a little impact by the configuration of carbons bearing the isopropylidene group and the rigidity of the ligand. In comparison with previous air instable amino-P ligands[6] (P=phosphine, aminophosphine and phosphinite groups) reported in the literature, the new amino-phosphite ligands provided a better substrate and nucleophile scope (i.e. including more challenging hindered linear and cyclic substrates, even using highly appealing nucleophiles such as those α-substituted with methyl, allyl, butenyl, pentenyl and propargyl groups). These results pave the way for the further development of modular amino-phosphite ligands, which are readily available and air stable, for the asymmetric Pd-catalyzed allylic substitution of several substrate types, including the more demanding cyclic ones, with a large number of nucleophiles.

Finally, the study of the Pd-π-allyl intermediates make it possible to understand the catalytic results obtained. It shows that for enantioselectivities to be high the ligand parameters need to be appropriately combined to either increase the difference in the population of the resulting Pd-allyl compounds (for cyclic substrate), or to increase the relative rates of the nucleophilic attack of each Pd-allyl intermediate, and also to avoid the formation of Pd-allyl intermediates with monodentated coordinated ligands (for linear substrates). This study also indicates that the sugar backbone is able to control the configuration of the amino group upon coordination, which in turn can be efficiently shifted from *R*- to *S*- by simply varying the configuration of the biaryl phosphite moiety.

5.2.4. Experimental Part

5.2.4.1. General remarks

All reactions were carried out using standard Schlenk techniques under an argon atmosphere, except for the preparation of pyrrolidine alcohols and their precursors. Commercial chemicals were used as received. Solvents were dried by means of standard procedures and stored under argon. Phosphorochloridites were easily prepared in one step from the corresponding biphenols and binols.[17] Racemic substrates **S1**, **S2**, 1,3-di-p-tolylallyl acetate, 1,3-bis(3-methoxyphenyl)allyl acetate, 1,3-di-o-tolylallyl acetate, 2,6-dimethylhept-4-en-3-yl acetate and cyclohept-2-en-1-yl acetate;[18] and Pd-allyl complexes $[Pd(\eta^3\text{-}1,3\text{-}Ph_2\text{-}C_3H_3)(\mu\text{-}Cl)]_2$[19] and $[Pd(\eta^3\text{-}cyclohexenyl)(\mu\text{-}Cl)]_2$[20] were prepared as previously reported. TLC was performed on silica gel HF_{254} (Merck), with detection by UV light charring with H_2SO_4, *p*-anisaldehyde, vanillin, ninhydrin, $KMnO_4$, phosphomolybdic acid or with Pancaldi reagent

[$(NH_4)_6MoO_4$, $Ce(SO_4)_2$, H_2SO_4, H_2O]. Silica gel 60 (Merck, 63–200 µm) was used for preparative chromatography. Optical rotations were measured in a 1.0 cm or 1.0 dm tube with a Jasco P-2000 spectropolarimeter. Infrared spectra were recorded with a Jasco FTIR-410 spectrophotometer. ^1H, $^{13}C\{^1H\}$ and $^{31}P\{^1H\}$ NMR spectra were recorded using a Bruker, AV300, AV500 and Varian Mercury-400 MHz spectrometers for solutions in $CDCl_3$, C_6D_6 and DMSO-d_6 at room temperature, except when indicated. Chemical shifts are relative to that of $SiMe_4$ (^1H and $^{13}C\{^1H\}$) as an internal standard or H_3PO_4 (^{31}P) as an external standard. ^1H and ^{13}C assignments were made on the basis of ^1H–^1H gCOSY, ^1H–^{13}C gHSQC and NOESY experiments. Mass spectra (CI and ESI) were recorded on Micromass AutoSpeQ and QTRAP (Applied Biosystems) y Orbitrap Elite spectrometers. NMR and mass spectra were registered in CITIUS (University of Seville) and in SRCiT (Universitat Rovira i Virgili).

(2*S*,3*S*,4*R*)-*N*-Methyl-2-hydroxymethyl-3,4-*O*-isopropyliden-pyrrolidine-3,4-diol (1)

To a suspension of $LiAlH_4$ (420 mg, 10.9 mmol) in anhydrous THF (22 mL) at 0 ˚C, a solution of **7**[10] (600 mg, 2.19 mmol) in anhydrous THF (22 mL) was added. The mixture was heated at reflux for 2.5 h and then cooled at 0 ˚C. Diethyl ether and sat. aq. sol. of Na_2SO_4 were successively added and the mixture was filtered through celite and washed with CH_2Cl_2. The solvent was evaporated and the residue was purified by chromatography column on silica gel (eluent: EtOAc/cyclohexane – 1/3) to produce **1** (345 mg, 84%) as a pale yellow oil. α_D^{24} - 19.9 (*c* 1.08, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$), δ: 1.11 (s, 3H, -C(C*H*$_3$)$_2$), 1.51 (s, 3H, -C(C*H*$_3$)$_2$), 2.36 (s, 3H, N-C*H*$_3$), 2.51-2.57 (m, 2H, H-2, H-5a), 2.61 (brs, 1H, OH), 3.33-3.39 (m, 1H, H-5b), 3.63 (dd, 1H, H-1'a, $J_{1'a\text{-}1'b}$ = 11.4, $J_{1'a\text{-}2}$ = 2.7), 3.72 (dd, 1H, H-1'b, $J_{1'b\text{-}2}$ = 3.6), 4.56-4.63 (m, 2H, H-3, H-4). ^{13}C NMR (75.4 MHz, $CDCl_3$), δ: 25.0 (-C(*C*H$_3$)$_2$), 27.3 (-C(*C*H$_3$)$_2$), 40.0 (N-*C*H$_3$), 59.3 (C-1'), 62.0 (C-5), 71.6 (C-2), 77.8, 82.2 (C-3, C-4), 113.1 (-*C*(CH$_3$)$_2$). HRMS (ESI) *m/z:* calcd for $C_9H_{18}NO_3$: 188.1281 $[M+H]^+$; found 188.1276.

(2*S*,3*S*,4*R*)-2-Hydroxymethyl-3,4-*O*-isopropyliden-pyrrolidine-3,4-diol (8)

To a solution of **7**[10] (203 mg, 0.74 mmol) in anhydrous CH_2Cl_2 (10 mL) with 4 Å MS at 0 ˚C, was added anhydrous trifluoroacetic acid (1.9 mL). The mixture was stirred at r.t. for 1 h and then was filtered and the solvent was evaporated. The residue was dissolved in anhydrous CH_2Cl_2 and Ambersep 900 was added. The resulting mixture was filtered and the solvent was evaporated. The residue was purified by chromatography column on silica gel (eluent: CH_2Cl_2/MeOH – 10/1, 1% Et_3N) to produce **8** (101 mg, 78%) as a pale yellow oil. α_D^{27} - 26.2 (*c* 1.0, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$), δ: 1.30 (s, 3H, -C(C*H*$_3$)$_2$), 1.47 (s, 3H, -C(C*H*$_3$)$_2$), 3.08 (dd, 1H, H-5a, $J_{5a\text{-}5b}$ = 13.5, $J_{5a\text{-}4}$ = 4.2), 3.19 (d, 1H, H-5b), 3.39 (dd, 1H, H-1'a, $J_{1'a\text{-}1'b}$ = 11.1, $J_{1'a\text{-}2}$ = 8.7), 3.49 (dd, 1H, H-2, $J_{2\text{-}1'b}$ = 4.2), 3.65 (dd, 1H, H-1'b), 4.50 (d, 1H, H-3, $J_{3\text{-}4}$ = 5.4), 4.63 (brs, 2H, OH, NH), 4.76 (t, 1H, H-4). ^{13}C NMR (75.4 MHz, $CDCl_3$), δ: 24.0 (-C(*C*H$_3$)$_2$), 26.3 (-C(*C*H$_3$)$_2$), 51.3 (C-5), 59.5 (C-1'), 66.5 (C-2), 81.0 (C-4), 82.7 (C-3), 111.6 (-*C*(CH$_3$)$_2$). HRMS (ESI) *m/z:* calcd for $C_8H_{16}NO_3$: 174.1125 $[M+H]^+$; found 174.1121.

(2*S*,3*S*,4*R*)-*N*-Benzyl-2-hydroxymethyl-3,4-*O*-isopropyliden-pyrrolidine-3,4-diol (2)

To a solution of **8** (125 mg, 0.72 mmol) in anhydrous 1,2-dichloroethane (7.5 mL), benzaldehyde (0.15 mL, 1.44 mmol) and $NaBH(OAc)_3$ (320 mg, 1.51 mmol) were successively added. The mixture was stirred at r.t. for 3 h and then, sat. aq. sol. of $NaHCO_3$ (15 mL) was added. The aqueous phase was extracted (× 4) with EtOAc. The organic layers were dried with Na_2SO_4, filtered and evaporated. The residue was purified by chromatography column on silica gel (eluent: Et_2O/cyclohexane – 3/1→Et_2O) to produce **2** (128 mg, 68%) as a pale yellow oil. α_D^{28} + 41.3 (*c* 0.94, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 1.32 (s, 3H,-C(C*H*$_3$)$_2$), 1.54 (s, 3H, -C(C*H*$_3$)$_2$), 2.39 (brs, 1H, OH), 2.61-2.66 (m, 1H, H-5a), 2.94-2.97 (m, 1H, H-2), 3.17-3.23 (m, 1H, H-5b), 3.57 (dd, 1H, H-1'a, $J_{1'a\text{-}1'b}$ = 11.1, $J_{1'a\text{-}2}$ = 3.6), 3.60 (d, 1H, C*H*$_2$Ph, $J_{H\text{-}H}$ = 12.9), 3.65 (dd, 1H, H-1'b, $J_{1'b\text{-}2}$ = 3.9), 3.98 (d, 1H, C*H*$_2$Ph), 4.56-4.63 (m, 2H, H-3, H-4), 7.23-7.36 (m, 5H, H-arom.). ^{13}C NMR (75.4 MHz, $CDCl_3$), δ: 25.0 (-C(*C*H$_3$)$_2$), 27.4 (-C(*C*H$_3$)$_2$), 58.3 (*C*H$_2$Ph), 58.6 (C-5), 59.6 (C-1'), 70.1 (C-2), 78.6, 82.7 (C-3, C-4), 112.9 (-*C*(CH$_3$)$_2$), 127.5, 128.6, 128.9, 138.5 (aromatic carbons). HRMS (ESI) *m/z:* calcd for $C_{15}H_{22}NO_3$: 264.1594 $[M+H]^+$; found 264.1594.

(2*S*,3*S*,4*R*)-*N*-Isopropyl-2-hydroxymethyl-3,4-*O*-isopropyliden-pyrrolidine-3,4-diol (3)

To a solution of compound **8** (121 mg, 0.70 mmol) in MeOH (1.5 mL), acetone (0.26 mL, 3.49 mmol) and Pd/C 10% (cat.) were added. The reaction mixture was stirred under H_2 overnight. The catalyst was filtered through celite and washed with MeOH. The solvent was evaporated and the residue was purified by chromatography column on silica gel (eluent: CH_2Cl_2/MeOH – 30/1→20/1) to produce **3** (113 mg, 75%) as a pale yellow oil. α_D^{27} + 13.3 (*c* 0.79, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 1.00 (d, 3H, C*H*$_3$, $J_{H\text{-}H}$ = 6.3), 1.09 (d, 3H, C*H*$_3$), 1.31 (s, 3H,-C(C*H*$_3$)$_2$), 1.50 (s, 3H, C(C*H*$_3$)$_2$), 2.32 (brs, 1H, OH), 2.77 (dd, 1H, H-5a, $J_{5a\text{-}5b}$ = 10.2, $J_{5a\text{-}4}$ = 4.8), 2.97-3.06 (m, 2H, (CH$_3$)$_2$C*H*, H-2), 3.18 (dd, 1H, H-5b, $J_{5b\text{-}4}$ = 6.0), 3.52 (dd, 1H, H-1'a, $J_{1'a\text{-}1'b}$ = 10.8, $J_{1'a\text{-}2}$ = 2.7), 3.63 (dd, 1H, H-1'b, $J_{1'b\text{-}2}$ = 3.6), 4.52 (dd, 1H, H-3, *J* = 6.6, *J* = 3.0), 4.56-4.62 (m, 1H, H-4). ^{13}C NMR (75.4 MHz, $CDCl_3$), δ: 15.7 (*C*H$_3$), 22.3 (*C*H$_3$), 25.3 (-C(*C*H$_3$)$_2$), 27.6 (-C(*C*H$_3$)$_2$), 48.0 ((CH$_3$)$_2$*C*H), 51.6 (C-5), 59.6 (C-1'), 65.8 (C-2), 78.4 (C-4), 83.0 (C-3), 112.5 (-*C*(CH$_3$)$_2$). HRMS (ESI) *m/z:* calcd for $C_{11}H_{22}NO_3$: 216.1594 $[M+H]^+$; found 216.1589.

(2*S*,3*R*,4*S*)-*N*-*terc*-Butoxycarbonyl-2-hydroxymethyl-3,4-*O*-isopropyliden-pyrrolidine-3,4-diol (10)

To a solution of compound **9**[11] (2.44 g, 9.28 mmol) in MeOH (70 mL), Boc_2O (2.02 g, 18.6 mmol) and Pd/C 10% (0.63 g) were added. The reaction mixture was stirred under H_2 for 3 h. The catalyst was filtered through celite and washed with MeOH. The solvent was evaporated and the residue was purified by chromatography column on silica gel (eluent: EtOAc/cyclohexane – 1/2) to give **10** (2.18 g, 86%) as a colourless oil. α_D^{24} +41.8 (*c* 1.00, CH_2Cl_2). NMR and IR data are in accordance with those of its

enantiomer.[11] HRMS (ESI) *m/z:* calcd for $C_{13}H_{23}NO_5Na$: 296.1468 $[M+Na]^+$; found 296.1465.

(2*S*,3*R*,4*S*)-*N*-Methyl-2-hydroxymethyl-3,4-*O*-isopropyliden-pyrrolidine-3,4-diol (4)

To a suspension of $LiAlH_4$ (206 mg, 5.43 mmol) in anhydrous THF (11 mL) at 0 ˚C, a solution of **10** (292.6 mg, 1.09 mmol) in anhydrous THF (11 mL) was added. The mixture was heated at reflux for 2.5 h and then cooled at 0 ˚C. Diethyl ether and sat. aq. sol. of Na_2SO_4 were successively added and the mixture was filtered through celite and washed with CH_2Cl_2. The solvent was evaporated and the residue was purified by chromatography column on silica gel (eluent: EtOAc/MeOH– 7/1→5:1) to produce **4** (184.2 mg, 91%) as a pale yellow solid. α_D^{27} + 72.5 (*c* 0.8, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 1.30 (s, 3H, -C(C*H*$_3$)$_2$), 1.51 (s, 3H, -C(C*H*$_3$)$_2$), 2.06-2.13 (m, 1H, H-2), 2.19 (dd, 1H, H-5a, $J_{5a\text{-}5b}$ = 11.4, $J_{5a\text{-}4}$ = 4.5), 2.32 (s, 3H, N-C*H*$_3$), 3.25 (d, 1H, H-5b), 3.42 (brs, 1H, OH), 3.84 (dd, 1H, H-1'a, $J_{1'a\text{-}1'b}$ = 11.7, $J_{1'a\text{-}2}$ = 6.0), 3.91 (dd, 1H, H-1'b, $J_{1'b\text{-}2}$ = 3.6), 4.61 (dd, 1H, H-4, $J_{4\text{-}3}$ = 6.3), 4.70 (dd, 1H, H-3, $J_{3\text{-}2}$ = 5.1). ^{13}C NMR (75.4 MHz, $CDCl_3$), δ: 24.3 (-C(*C*H$_3$)$_2$), 25.9 (-C(*C*H$_3$)$_2$), 40.3 (N-*C*H$_3$), 59.7 (C-1'), 61.7 (C-5), 69.7 (C-2), 78.0 (C-4), 81.8 (C-3), 111.3 (-*C*(CH$_3$)$_2$). HRMS (ESI) *m/z:* calcd for $C_9H_{18}NO_3$: 188.1281 $[M+H]^+$; found 188.1277.

(6*S*,7*R*,7a*S*)-6,7-O-Isopropyliden-tetrahydropyrrolo[1,2-c]-oxazol-3-ona-6,7-diol (11)

To a solution of **10** (1.06 g, 3.89 mmol) in anhydrous pyridine (15 mL) at 0 ˚C, TsCl (1.89 g, 9.74 mmol) was slowly added. After stirring at r.t. overnight, the solvent was evaporated and the residue was purified by chromatography column on silica gel (eluent: EtOAc/cyclohexane – 1/1→2/1) to produce **11** (713 mg, 92%) as a white solid. α_D^{22}+25.6 (c 0.82, CH_2Cl_2). HRMS (ESI) *m/z:* calcd for $C_9H_{13}NO_4Na$: 222.0737 $[M+Na]^+$; found 222.0735. NMR and IR data are in accordance with those of its enantiomer.[10]

(2*S*,3*R*,4*S*)-2-Diphenylphosphinomethyl-3,4-*O*-isopropyliden-pyrrolidine-3,4-diol (12)

To a solution of **11** (147 mg, 0.74 mmol) in anhydrous THF (6.0 mL) at 0 ˚C, $KPPh_2$ (0.5 M in THF, 1.8 mL, 0.89 mmol) was slowly added. The mixture was heated at reflux for 2 h and then cooled to r.t. IRA-120H$^+$ was added and the resulting mixture was filtered through celite and washed with CH_2Cl_2. The solvent was evaporated and the residue was purified by chromatography column on silica gel (eluent: Et_2O/acetone – 10/1, 1% Et_3N) to produce **12** (26 mg, 89%) as a colourless oil. α_D^{22} +63.2 (*c* 0.57, CH_2Cl_2). ^{31}P NMR (121.5 MHz, $CDCl_3$), δ: -20.9. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 1.31 (s, 3H, -C(C*H*$_3$)$_2$), 1.46 (s, 3H, -C(C*H*$_3$)$_2$), 1.95 (brs, 1H, NH), 2.37 (dd, 1H, H-1'a, $J_{1'a\text{-}1'b}$ = 13.2, $J_{1'a\text{-}2}$ = 8.1), 2.43 (dd, 1H, H-1'b, $J_{1'b\text{-}2}$ = 6.3), 2.50-2.62 (m, 2H, H-2, H-5a), 3.02 (d, 1H, H-5b, $J_{5b\text{-}5a}$ = 13.5), 4.57 (dd, 1H, H-3, $J_{3\text{-}4}$ = 5.7, $J_{3\text{-}2}$ = 3.9), 4.61-4.64 (m, 1H, H-4), 7.29-7.35 (m, 6H, H-arom.), 7.42-7.53 (m, 4H, H-arom.). ^{13}C NMR (75.4 MHz, $CDCl_3$), δ: 24.1 (-C(*C*H$_3$)$_2$), 26.0 (-C(*C*H$_3$)$_2$), 27.3 (d, $J_{C\text{-}P}$ = 13.2, C-1'), 53.2 (C-5), 61.5 (d, $J_{C\text{-}P}$ = 16.3, C-2), 81.8 (d, $J_{C\text{-}P}$ = 4.5, C-3), 82.2 (C-4), 110.6 (-*C*(CH$_3$)$_2$), 128.4 (C-arom.), 128.5 (d, $J_{C\text{-}P}$ = 8.4,

C-arom.), 128.6 (d, J_{C-P} = 6.7, C-arom.), 128.9 (C-arom.), 132.8 (d, J_{C-P} = 19.1, C-arom.), 133.1 (d, J_{C-P} = 19.3, C-arom.), 138.6 (d, J_{C-P}= 13.0, C_{arom}-P), 138.9 (d, J_{C-P} = 13.0, C_{arom}-P). HRMS (ESI) *m/z:* calcd for $C_{20}H_{25}NO_2P$: 342.1617 $[M+H]^+$; found 342.1609.

5.2.4.2. General procedure for the preparation of the amino-phosphite ligands L49–L52a–d and L55a–b

The corresponding phosphorochloridite (1.1 mmol) produced in situ was dissolved in toluene (5 mL) and pyridine (3.8 mmol, 0.3 mL) was added. The corresponding alcohols **1**–**4** and **6** (1 mmol) was azeotropically dried with toluene (3x1 mL) and dissolved in toluene (5 mL) to which pyridine (3.8 mmol, 0.3 mL) was added. The solution was transferred slowly at 0 °C to the solution of the phosphorochloridite. The reaction mixture was stirred overnight at 80 °C, and the pyridine salts were removed by filtration. Evaporation of the solvent gave a white foam, which was purified by flash chromatography in alumina (eluent: toluene/triethylamine – 100/1) to produce the corresponding ligand as a white solid.

L49a: Yield: 72.5 mg (28%). ^{31}P NMR (161.9 MHz, C_6D_6), δ: 132.9. ^{1}H NMR (400 MHz, C_6D_6), δ: 0.52 (s, 9H, CH_3, $SiMe_3$), 0.54 (s, 9H, CH_3, $SiMe_3$), 1.17 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 1.96 (s, 3H, CH_3, NMe), 2.37 (dd, 1H, CH_2-N, $^2J_{H-H}$ =9.6 Hz, $^3J_{H-H}$ =4.8 Hz), 2.47 (m, 1H, CH), 2.89 (dd, 1H, CH_2-N, $^2J_{H-H}$ =9.6 Hz, $^3J_{H-H}$ =6.1 Hz), 3.45 (m, 1H, CH_2-OP), 4.11 (m, 1H, CH_2-OP), 4.33 (m, 1H, CH-O), 4.53 (m, 1H, CH-O), 6.85 (m, 2H, CH=), 7.01 (m, 1H, CH=), 7.04-7.13 (m, 1H, CH=), 7.24 (d, 1H, CH=, $^3J_{H-H}$ =8.5 Hz), 7.36 (d, 1H, CH=, $^3J_{H-H}$ =8.5 Hz), 7.69 (d, 2H, CH=, $^3J_{H-H}$ =8.5 Hz), 8.12 (d, 2H, CH=, $^3J_{H-H}$ =8.5 Hz). ^{13}C NMR (100.6 MHz, C_6D_6), δ: -0.2 (CH_3, $SiMe_3$), -0.1 (CH_3, $SiMe_3$), 1.0 (CH_3, $SiMe_3$), 24.9 (CH_3), 27.2 (CH_3), 39.3 (CH_3, NMe), 61.8 (CH_2-N), 62.3 (CH_2-OP), 70.1 (CH), 77.8 (CH-O), 82.3 (CH-O), 112.5 (C), 122.5 – 153.1 (aromatic carbons). TOF-MS (ESI+): *m/z:* calcd for $C_{35}H_{44}NO_5PSi_2$: 668.2388 $[M+Na]^+$; found 668.2390.

L49b: Yield: 100.0 mg (40%). ^{31}P NMR (161.9 MHz, C_6D_6), δ: 136.5. ^{1}H NMR (400 MHz, C_6D_6), δ: 0.50 (s, 9H, CH_3, $SiMe_3$), 0.51 (s, 9H, CH_3, $SiMe_3$), 1.10 (s, 3H, CH_3), 1.47 (s, 3H, CH_3), 2.02 (s, 3H, CH_3, NMe) 2.42 (dd, 1H, CH_2-N, $^2J_{H-H}$ =9.6 Hz, $^3J_{H-H}$ =4.6 Hz), 2.61 (m, 1H, CH), 2.95 (m, 1H, CH_2-N), 3.53 (m, 1H, CH_2-OP), 4.09 (m, 1H, CH_2-OP), 4.24 (m, 1H, CH-O), 4.32 (m, 1H, CH-O), 6.86 (m, 2H, CH=), 7.02 (m, 1H, CH=), 7.12 (m, 1H, CH=), 7.24 (d, 1H, CH=, $^3J_{H-H}$ =8.5 Hz), 7.33 (d, 1H, CH=, $^3J_{H-H}$ =8.5 Hz), 7.69 (d, 2H, CH=, $^3J_{H-H}$ =8.2 Hz), 8.10 (d, 2H, CH=, $^3J_{H-H}$ =8.2 Hz). ^{13}C NMR (100.6 MHz, C_6D_6), δ: -0.2 (CH_3, SiMe3), -0.2 (CH_3, $SiMe_3$), 1.1 (CH_3, $SiMe_3$), 24.9 (CH_3), 27.2 (CH_3), 39.5 (CH_3, NMe), 61.9 (CH_2-N), 64.1 (CH_2-OP), 70.3 (CH), 77.9 (CH-O), 82.4 (CH-O), 112.6 (C), 122.3 – 152.9 (aromatic carbons). TOF-MS (ESI+): *m/z:* calcd for $C_{35}H_{44}NO_5PSi_2$: 668.2388 $[M+Na]^+$; found 668.2387.

L49c: Yield: 71.5 mg (22%). ^{31}P NMR (161.9 MHz, C_6D_6), δ: 129.6. ^{1}H NMR (400 MHz, C_6D_6), δ: 1.98 (s, 3H, CH_3), 2.11 (m, 2H, CH_2), 2.28 (s, 3H, CH_3) 2.31 (m, 6H, CH_2), 2.38 (s, 18H, CH_3, ^{t}Bu), 2.92 (s, 3H, CH_3, NMe), 3.07 (m, 1H, CH_2), 3.35 (m, 9H, CH_2, CH, CH_2-N), 3.77 (dd, 1H, CH_2-N, $^2J_{H-H}$ =9.5 Hz, $^3J_{H-H}$ =6.1 Hz), 4.31 (m, 1H, CH_2-OP), 4.86 (m, 1H, CH_2-OP), 5.18 (m, 1H, CH-O), 5.34 (m, 1H, CH-O), 7.96 (m, 2H, CH=). ^{13}C NMR (100.6 MHz,

C_6D_6), δ: 23.6 (CH_2), 23.8 (CH_2), 23.9 (CH_2), 25.7 (CH_2), 28.0 (CH_2), 28.1 (CH_2), 28.3 (CH_3), 30.3 (CH_3), 30.4 (CH_2), 31.7 (CH_3, ^{t}Bu), 31.9 (CH_3, ^{t}Bu), 32.0 (CH_3, ^{t}Bu), 35.3 (C, ^{t}Bu), 35.4 (C, ^{t}Bu), 40.2 (CH_3, NMe), 62.7 (CH_2-N), 63.5 (CH_2-OP), 71.0 (CH), 78.9 (CH-O), 83.3 (CH-O), 113.3 (C), 126.1 – 139.3 (aromatic carbons). TOF-MS (ESI+): *m/z:* calcd for $C_{37}H_{52}NO_5P$: 644.3475 $[M+Na]^+$; found 644.3479.

L49d: Yield: 118.4 mg (41%). ^{31}P NMR (161.9 MHz, C_6D_6), δ: 127.5. ^{1}H NMR (400 MHz, C_6D_6), δ: 1.14 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 1.54 (s, 18H, CH_3, ^{t}Bu) 1.64 (s, 3H, CH_3), 1.74 (s, 3H, CH_3), 2.02 (s, 3H, CH_3), 2.04 (s, 3H, CH_3), 2.07 (s, 3H, CH_3, NMe), 2.43 (dd, 1H, CH_2-N, $^2J_{H-H}$ =9.6 Hz, $^3J_{H-H}$ =4.7 Hz), 2.58 (dd, 1H, CH, $^2J_{H-H}$ =8.6 Hz, $^3J_{H-H}$ =4.0 Hz), 2.93 (dd, 1H, CH_2-N, $^2J_{H-H}$ =9.6 Hz, $^3J_{H-H}$ =6.1 Hz), 3.49 (m, 1H, CH_2-OP), 4.10 (m, 1H, CH_2-OP), 4.34 (m, 1H, CH-O), 4.53 (m, 1H, CH-O), 7.17 (m, 1H, CH=), 7.18 (m, 1H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6), δ: 16.2 (CH_3), 16.4 (CH_3), 20.0 (CH_3), 20.1 (CH_3), 24.9 (CH_3), 27.2 (CH_3), 29.8 (CH_3), 31.2 (CH_3, ^{t}Bu), 31.3 (CH_3, ^{t}Bu), 34.6 (C, ^{t}Bu), 34.7 (C, ^{t}Bu), 39.3 (CH_3, NMe), 61.9 (CH_2-N), 62.4 (CH_2-OP), 70.3 (CH), 77.9 (CH-O), 82.5 (CH-O), 112.4 (C), 125.3 – 146.2 (aromatic carbons). TOF-MS (ESI+): *m/z:* calcd for $C_{33}H_{48}NO_5P$: 592.3162 $[M+Na]^+$; found 592.3165.

L50a: Yield: 167.2 mg (50%). ^{31}P NMR (161.9 MHz, C_6D_6), δ: 133.6. ^{1}H NMR (400 MHz, C_6D_6), δ: 0.47 (s, 9H, CH_3, $SiMe_3$), 0.48 (s, 9H, CH_3, $SiMe_3$), 1.16 (s, 3H, CH_3), 1.47 (s, 3H, CH_3), 2.51 (dd, 1H, CH_2-N, $^2J_{H-H}$ =10.3 Hz, $^3J_{H-H}$ =3.6 Hz), 2.76 (dd, 1H, CH_2-N, $^2J_{H-H}$ =10.3 Hz, $^3J_{H-H}$ =3.6 Hz) 2.92 (m, 1H, CH), 3.22 (d, 1H, CH_2Ph, $^2J_{H-H}$ =13.3 Hz), 3.36 (m, 1H, CH_2-OP), 3.64 (d, 1H, CH_2Ph, $^2J_{H-H}$ =13.3 Hz), 4.07 (m, 1H, CH_2-OP), 4.27 (m, 1H, CH-O), 4.59 (dd, 1H, CH-O, $^2J_{H-H}$ =6.6 Hz, $^3J_{H-H}$ =2.6 Hz), 6.84 (m, 2H, CH=), 7.03 (m, 7H, CH=), 7.20 (d, 1H, CH=, $^3J_{H-H}$ =8.6 Hz), 7.32 (d, 1H, CH=, $^3J_{H-H}$ =8.6 Hz), 7.65 (d, 2H, CH=, $^3J_{H-H}$ =8.4 Hz), 8.07 (d, 2H, CH=, $^3J_{H-H}$ =4.7 Hz). ^{13}C NMR (100.6 MHz, C_6D_6), δ: -0.4 (CH_3, $SiMe_3$), -0.1 (CH_3, $SiMe_3$), 0.0 (CH_3, $SiMe_3$), 24.9 (CH_3), 27.2 (CH_3), 56.9 (CH_2Ph), 58.5 (CH_2-N), 62.8 (CH_2-OP), 67.9 (CH), 78.6 (CH-O), 82.7 (CH-O), 112.1 (C), 122.4 – 153.0 (aromatic carbons). TOF-MS (ESI+): *m/z:* calcd for $C_{41}H_{48}NO_5PSi_2$: 744.2701 $[M+Na]^+$; found 744.2703.

L51a: Yield: 148.9 mg (47%). ^{31}P NMR (161.9 MHz, C_6D_6), δ: 134.24. ^{1}H NMR (400 MHz, C_6D_6), δ: 0.49 (s, 9H, CH_3, $SiMe_3$), 0.51 (s, 9H, CH_3, $SiMe_3$), 0.69 (d, 3H, CH_3, ^{i}Pr, $^2J_{H-H}$ =6.3 Hz) 0.78 (d, 3H, CH_3, ^{i}Pr, $^2J_{H-H}$ =6.3 Hz), 1.21 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 2.63 (m, 3H, CH_2-N, CH, ^{i}Pr), 3.11 (m, 1H, CH), 3.38 (m, 1H, CH_2-OP), 3.97 (m, 1H, CH_2-OP), 4.35 (m, 1H, CH-O), 4.60 (dd, 1H, CH-O, $^2J_{H-H}$ =6.5 Hz, $^3J_{H-H}$ =1.2 Hz), 6.82 (t, 2H, CH=, $^3J_{H-H}$ =11.3 Hz), 7.08 (m, 2H, CH=), 7.19 (d, 1H, CH=, $^3J_{H-H}$ =8.6 Hz), 7.29 (d, 1H, CH=, $^3J_{H-H}$ =8.5 Hz), 7.65 (m, 2H, CH=), 8.08 (d, 2H, CH=, $^3J_{H-H}$ =9.3 Hz). ^{13}C NMR (100.6 MHz, C_6D_6), δ: -0.3 (CH_3, $SiMe_3$), -0.2 (CH_3, $SiMe_3$), -0.1 (CH_3, $SiMe_3$), 17.0 (CH_3, ^{i}Pr), 21.8 (CH_3, ^{i}Pr), 25.2 (CH_3), 27.3 (CH_3), 47.9 (CH, ^{i}Pr), 52.8 (CH_2-N), 62.8 (CH_2-OP), 64.6 (CH), 78.5 (CH-O), 82.7 (CH-O), 111.7 (C), 122.4 – 153.0 (aromatic carbons). TOF-MS (ESI+): *m/z:* calcd for $C_{37}H_{48}NO_5PSi_2$: 696.2701 $[M+Na]^+$; found 696.2700.

L52a: Yield: 71 mg (27%). ^{31}P NMR (161.9 MHz, C_6D_6), δ: 135.6. ^{1}H NMR (400 MHz, C_6D_6), δ: 0.55 (s, 9H, CH_3, $SiMe_3$), 0.57 (s, 9H, CH_3, $SiMe_3$), 1.14 (s, 3H, CH_3), 1.37 (s, 3H,

CH_3), 1.55 (dd, 1H, CH_2-N, $^2J_{H-H}$ =10.8 Hz, $^3J_{H-H}$ =4.6 Hz), 1.87 (s, 3H, CH_3, NMe), 2.01 (m, 1H, CH), 2.88 (d, 1H, CH_2-N, $^2J_{H-H}$ =10.8 Hz), 3.59 (m, 1H, CH_2-OP), 4.07 (m, 1H, CH-O), 4.28 (m, 1H, CH-O), 4.52 (m, 1H, CH_2-OP), 6.84 (m, 2H, CH=), 7.04 (m, 2H, CH=), 7.29 (dd, 2H, CH=, $^3J_{H-H}$ =15.1 Hz, $^3J_{H-H}$ =8.4 Hz), 7.68 (m, 2H, CH=), 8.12 (d, 2H, CH=, $^3J_{H-H}$ =5.2 Hz). ^{13}C NMR (100.6 MHz, C_6D_6), δ: -0.2 (CH_3, $SiMe_3$), -0.1 (CH_3, $SiMe_3$), 1.1 (CH_3, $SiMe_3$), 25.1 (CH_3), 26.0 (CH_3), 40.2 (CH_3, NMe), 62.5 (CH_2-N), 62.7 (CH_2-OP), 69.4 (CH), 77.9 (CH-O), 80.2 (CH-O), 110.8 (C), 122.3 – 153.3 (aromatic carbons). TOF-MS (ESI+): *m/z:* calcd for $C_{35}H_{44}NO_5PSi_2$: 668.2388 $[M+Na]^+$; found 668.2390.

L52b: Yield: 112.9 mg (43%). ^{31}P NMR (161.9 MHz, C_6D_6), δ: 137.7. ^{1}H NMR (400 MHz, C_6D_6), δ: 0.54 (s, 9H, CH_3, $SiMe_3$), 0.55 (s, 9H, CH_3, $SiMe_3$), 1.14 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 1.50 (dd, 1H, CH_2-N, $^2J_{H-H}$ =10.8 Hz, $^3J_{H-H}$ =4.6 Hz), 1.66 (s, 3H, CH_3, NMe), 2.00 (m, 1H, CH), 2.80 (d, $^2J_{H-H}$ =10.8 Hz, 1H, CH_2-N), 4.03 (m, 3H, CH_2-OP, CH-O), 4.36 (m, 1H, CH-O), 6.83 (m, 2H, CH=), 7.08 (m, 2H, CH=), 7.25 (m, 2H, CH=), 7.65 (m, 2H, CH=), 8.06 (s, 2H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6), δ: -0.2 (CH_3, $SiMe_3$), -0.1 (CH_3, $SiMe_3$), 0.00 (CH_3, $SiMe_3$), 1.0 (CH_3, $SiMe_3$), 25.1 (CH_3), 25.9 (CH_3), 39.8 (CH_3, NMe), 62.2 (CH_2-N), 62.6 (CH_2-OP), 69.8 (CH), 77.9 (CH-O), 80.1 (CH-O), 110.8 (C), 122.2 – 153.0 (aromatic carbons). TOF-MS (ESI+): *m/z:* calcd for $C_{35}H_{44}NO_5PSi_2$: 668.2388 $[M+Na]^+$; found 668.2386.

L55a: Yield: 51.9 mg (20%). ^{31}P NMR (161.9 MHz, C_6D_6), δ: 142.2. ^{1}H NMR (400 MHz, C_6D_6), δ: 0.43 (s, 3H, CH_3, $SiMe_3$), 0.46 (s, 15H, CH_3, $SiMe_3$), 1.09 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 1.57 (m, 2H, CH_2-CHOP), 2.67 (dd, 1H, CH_2, $^2J_{H-H}$ =13.3 Hz, $^3J_{H-H}$ =5.6 Hz), 2.78 (dd, 1H, CH_2, $^2J_{H-H}$ =11.4 Hz, $^3J_{H-H}$ =4.9 Hz) 2.90 (d, 1H, CH_2, $^2J_{H-H}$ =13.3 Hz), 3.15 (m, 2H, CH_2, CH), 4.21 (m, 2H, CH-O), 4.37 (m, 1H, CH-OP), 6.81 (m, 2H, CH=), 7.03 (m, 2H, CH=), 7.18 (d, 1H, CH=, $^3J_{H-H}$ =7.5 Hz), 7.30 (d, 1H, CH=, $^3J_{H-H}$ =10.3 Hz), 7.66 (m, 2H, CH=), 8.06 (s, 1H, CH=), 8.08 (s, 1H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6), δ: -0.2 (CH_3, $SiMe_3$), 0.0 (CH_3, $SiMe_3$), 25.1 (CH_3), 26.8 (CH_3), 37.0 (CH_2-CHOP), 59.5 (CH_2), 61.3 (CH_2), 70.5 (CH), 78.5 (CH-OP), 81.1 (CH-O), 84.9 (CH-O), 111.2 (C), 122.3 – 157.2 (aromatic carbons). TOF-MS (ESI+): *m/z:* calcd for $C_{36}H_{44}NO_5PSi_2$: 680.2388 $[M+Na]^+$; found 680.2389.

L55b: Yield: 53.2 mg (20%). ^{31}P NMR (161.9 MHz, C_6D_6), δ: 141.0. ^{1}H NMR (400 MHz, C_6D_6), δ: 0.45 (s, 9H, CH_3, $SiMe_3$), 0.47 (s, 9H, CH_3, $SiMe_3$), 1.15 (s, 3H, CH_3), 1.51 (m, 4H, CH_3, CH_2-CHOP), 1.68 (m, 1H, CH_2-CHOP), 2.65 (dd, 1H, CH_2, $^2J_{H-H}$ =13.1 Hz, $^3J_{H-H}$ =5.8 Hz), 2.84 (m, 2H, CH_2, CH_2), 3.07 (t, 1H, CH, $^2J_{H-H}$ =8.4 Hz), 3.18 (m, 1H, CH_2), 4.19 (d, 1H, CH-O, $^2J_{H-H}$ =6.2 Hz), 4.30 (m, 1H, CH-O), 4.39 (m, 1H, CH-OP), 6.82 (m, 2H, CH=), 7.03 (m, 2H, CH=), 7.21 (d, 1H, CH=, $^3J_{H-H}$ =8.5 Hz), 7.33 (d, 1H, CH=, $^3J_{H-H}$ =8.5 Hz), 7.65 (d, 2H, CH=, $^3J_{H-H}$ =8.0 Hz), 8.07 (s, 1H, CH=), 8.08 (s, 1H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6), δ: -0.2 (CH_3, $SiMe_3$), 0.0 (CH_3, $SiMe_3$), 25.2 (CH_3), 26.8 (CH_3), 37.8 (CH_2-CHOP), 59.5 (CH_2), 60.4 (CH_2), 70.6 (CH), 78.4 (CH-OP), 81.2 (CH-O), 84.9 (CH-O), 111.2 (C), 122.3 – 152.3 (aromatic carbons). TOF-MS (ESI+): *m/z:* calcd for $C_{36}H_{44}NO_5PSi_2$: 680.2388 $[M+Na]^+$; found 680.2391.

5.2.4.3. Procedure for the preparation of the amino-phosphinite ligand L53

Pyrrolidine-hydroxyl compound **4** (93.1 mg, 0.5mmol) 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 addition of the corresponding chlorophosphine (0.55 mmol) via syringe. The reaction was stirred for 1 h 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. Yield: 30 mg (15%). ^{31}P NMR (161.9 MHz, C_6D_6), δ: 116.1. ^{1}H NMR (400 MHz, C_6D_6), δ: 1.00 (s, 3H, CH_3), 1.33 (s, 3H, CH_3), 1.97 (s, 3H, CH_3-N), 2.34 (m, 1H, CH_2-N), 2.60 (m, 1H, CH-N), 2.79 (m, 1H, CH_2-N), 3.67 (m, 2H, CH_2-O), 4.12 (m, 1H, CH-O), 4.32 (m, 1H, CH-O), 6.86 (m, 7H, CH=), 7.41 (m, 2H, CH=), 7.83 (m, 1H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6), δ: 24.0 (CH_3), 26.4 (CH_3), 38.6 (CH_3-N), 58.3 (CH_2-O), 61.1 (CH_2-N), 70.9 (CH-N), 77.0 (CH-O), 81.5 (CH-O), 111.8 (CMe_2), 126.6 – 130.9 (aromatic carbons). TOF-MS (ESI+): *m/z:* calcd for $C_{21}H_{26}NO_3P$: 394.1543 $[M\text{-}Na]^+$; found 394.1538.

5.2.4.4. Preparation of the amino-phosphine ligand (2*S*,3*R*,4*S*)-*N*-Methyl-2-diphenylphosphinomethyl-3,4-*O*-isopropyliden-pyrrolidine-3,4-diol (L54)

To a solution of **12** (94 mg, 0.28 mmol) in anhydrous CH_2Cl_2 (1.5 mL) at 0 ˚C, Et_3N (43 µL, 0.30 mmol) and $ClCO_2CH_3$ (24 µL, 0.30 mmol) were successively added. The mixture was stirred at 0 ˚C for 3 h. HCl (0.1 M) (6 mL) was added and the aqueous phase was extracted (× 3) with CH_2Cl_2. The organic layers were washed with sat. aq. sol. of $NaHCO_3$, dried with Na_2SO_4, filtered and evaporated. The resulting crude was dissolved in anhydrous THF (2 mL) and added to a suspension of $LiAlH_4$ (32 mg, 0.83 mmol) in anhydrous THF (1.0 mL) at 0˚C. The reaction mixture was heated at reflux for 2 h and then cooled at 0˚C. Diethyl ether and sat. aq. sol. of Na_2SO_4 were successively added and the mixture was filtered through celite and washed with CH_2Cl_2. The solvent was evaporated and the residue was purified by chromatography column on silica gel (eluent: EtOAc/cyclohexane – 1/2) to produce **L54** (81 mg, 82%) as a colourless oil. α_D^{24} +167.5 (0.58, CH_2Cl_2). ^{31}P NMR (202 MHz, C_6D_6), δ: -21.1. ^{1}H NMR (500 MHz, C_6D_6), δ: 1.27 (s, 3H, -C(C*H*$_3$)$_2$), 1.59 (s, 3H,-C(C*H*$_3$)$_2$), 2.02 (s, 3H, N-C*H*$_3$), 1.54 (dd, 1H, H-5a, $J_{5a\text{-}5b}$ = 10.5, $J_{5a\text{-}4}$ = 5.0), 1.71-1.76 (m, 1H, H-2), 2.44 (dt, 1H, H-1'a, $J_{1'a\text{-}1'b}$ = 13.5, $J_{1'a\text{-}2}$ = $J_{1'a\text{-}P}$ = 2.5), 2.72-2.77 (m, 1H, H-1'b), 3.03 (d, H-5b, 1H,), 4.18 (dd, 1H, H-4, $J_{4\text{-}3}$ = 6.0), 4.51 (dd, 1H, H-3, $J_{3\text{-}2}$ = 4.5), 7.01-7.13 (m, 6H, H-arom.), 7.49-7.52 (m, 2H, H-arom.), 7.54-7.57 (m, 2H, H-arom.). ^{13}C NMR (125.7 MHz, C_6D_6), δ: 25.7 (-C(*C*H$_3$)$_2$), 26.6 (-C(*C*H$_3$)$_2$), 26.7 (d, $J_{C\text{-}P}$ = 13.9, C-1'), 39.6 (N-*C*H$_3$), 62.7 (C-5), 68.1 (d, $J_{C\text{-}P}$ = 20.6, C-2), 78.3 (C-4), 81.5 (d, $J_{C\text{-}P}$ = 3.6, C-3), 111.2 (-*C*(CH$_3$)$_2$), 128.4 (C-arom.), 128.6 (d, $J_{C\text{-}P}$ = 6.2, C-arom.), 128.8 (d, $J_{C\text{-}P}$ = 6.8, C-arom.), 129.0 (C-arom.), 132.9 (d, $J_{C\text{-}P}$ = 18.1, C-arom.), 133.6 (d, $J_{C\text{-}P}$ = 19.8, C-arom.), 139.7 (d, $J_{C\text{-}P}$ = 15.0, C_{arom}-P), 140.4 (d, $J_{C\text{-}P}$ = 13.4, C_{arom}-P). HRMS (ESI) *m/z:* calcd for $C_{21}H_{27}NO_2P$: 356.1774 $[M+H]^+$; found 356.1768.

5.2.4.5. General procedure for the preparation of [Pd(η^3-allyl)(P-N)]BF_4 (36–39)

The ligand (0.05 mmol) and the complex [Pd(μ-Cl)(η^3-1,3-allyl)]$_2$ (0.025 mmol) were dissolved in CD_2Cl_2 (1.5 ml) at rt under argon. $AgBF_4$ (9.8 mg, 0.05 mmol) was added after 30 min, and the mixture was stirred for 30 min. The mixture was then filtered through Celite under argon, and the resulting solutions were analyzed by NMR spectroscopy. The complexes were precipitated as pale yellow solids by adding hexane.

[Pd(η^3-1,3-cyclohexenyl)(L49a)]BF_4 (36). Yield: 37.7 mg (82%). MS HR-ESI [found 832.2227, $C_{41}H_{53}NO_5PPdSi_2$ $(M\text{-}BF_4)^+$ requires 832.2229]. Major isomer (89%): ^{31}P NMR (161.9 MHz, CD_2Cl_2, 298 K), δ: 140.7 (s, 1P). ^{1}H NMR (400 MHz, CD_2Cl_2, 298 K), δ: 0.51 (s, 9H, CH_3, CH_3-Si), 0.53 (s, 9H, CH_3, CH_3-Si), 0.88-2.21 (m, 6H, CH_2), 1.41 (s, 3H, CH_3), 1.57 (s, 3H, CH_3), 3.12 (s, 3H, CH_3-N), 3.17 (m, 1H, CH), 3.37 (b, 1H, CH allyl *trans* to N), 3.44 (bd, 1H, CH_2-N, *J*= 12.4 Hz), 3.99 (dd, 1H, CH_2-N, $^2J_{H\text{-}H}$= 12.4 Hz, $^3J_{H\text{-}H}$= 3.6 Hz), 4.42-4.49 (b, 2H, CH_2-O), 5.02 (m, 2H, CH-O), 5.41 (m, 1H, CH allyl *central*), 6.05 (m, 1H, CH allyl *trans* to P), 6.92 (d, 1H, CH=, $^3J_{H\text{-}H}$= 8.0 Hz), 7.12 (d, 1H, CH=, $^3J_{H\text{-}H}$= 8.4 Hz), 7.24 (m, 1H, CH=), 7.31 (m, 1H, CH=), 7.47 (m, 1H, CH=), 7.55 (m, 1H, CH=), 7.98 (d, 1H, CH=, $^3J_{H\text{-}H}$= 8.0 Hz), 8.04 (d, 1H, CH=, $^3J_{H\text{-}H}$= 8.0 Hz), 8.19 (s, 1H, CH=), 8.22 (s, 1H, CH=). ^{13}C NMR (100.6 MHz, CD_2Cl_2, 298 K), δ: -0.1 (CH_3-Si), 0.5 (CH_3-Si), 19.9 (CH_2), 24.4 (CH_3), 26.0 (CH_3), 27.0 (CH_2), 28.2 (b, CH_2), 51.4 (CH_3-N), 65.5 (d, CH_2-O, $J_{C\text{-}P}$= 6.1 Hz), 67.4 (d, CH allyl *trans* to N, $J_{C\text{-}P}$= 8.4 Hz), 68.7 (CH_2-N,), 75.2 (d, CH, $J_{C\text{-}P}$= 2.3 Hz), 77.9 (CH-O), 79.8 (CH-O), 106.1 (d, CH allyl *trans* to P, $J_{C\text{-}P}$= 39.4 Hz), 113.6 (d, CH allyl *central*, $J_{C\text{-}P}$= 6 Hz), 114.7 (CMe_2), 120.6-151.5 (aromatic carbons). Minor isomer (11%): ^{31}P NMR (161.9 MHz, CD_2Cl_2, 298 K), δ: 142.7 (s, 1P). ^{1}H NMR (400 MHz, CD_2Cl_2, 298 K), δ: 0.46 (s, 9H, CH_3, CH_3-Si), 0.59 (s, 9H, CH_3, CH_3-Si), 0.88-2.21 (m, 6H, CH_2), 1.36 (s, 3H, CH_3), 1.56 (s, 3H, CH_3), 3.17 (m, 1H, CH), 3.22 (s, 3H, CH_3-N), 3.37 (b, 1H, CH allyl *trans* to N), 3.44 (bd, 1H, CH_2-N, *J*= 12.4 Hz), 3.92 (dd, 1H, CH_2-N, $^2J_{H\text{-}H}$= 12.6 Hz, $^3J_{H\text{-}H}$= 4.0 Hz), 4.42-4.51 (b, 2H, CH_2-O), 5.02 (m, 2H, CH-O), 5.83 (m, 1H, CH allyl *central*), 6.28 (m, 1H, CH allyl *trans* to P), 6.98 (d, 1H, CH=, $^3J_{H\text{-}H}$= 8.0 Hz), 7.10 (d, 1H, CH=, $^3J_{H\text{-}H}$= 8.0 Hz), 7.24 (m, 1H, CH=), 7.28 (m, 1H, CH=), 7.48 (m, 1H, CH=), 7.51 (m, 1H, CH=), 7.98 (m, 1H, CH=), 8.03 (d, 1H, CH=, $^3J_{H\text{-}H}$= 8.0 Hz), 8.16 (s, 1H, CH=), 8.20 (s, 1H, CH=). ^{13}C NMR (100.6 MHz, CD_2Cl_2, 298 K), δ: 0.0 (CH_3-Si), 0.5 (CH_3-Si), 19.3 (CH_2), 24.3 (CH_3), 25.9 (CH_3), 26.9 (CH_2), 29.6 (CH_2), 50.9 (CH_3-N), 65.3 (d, CH_2-O, $J_{C\text{-}P}$= 10.2 Hz), 66.5 (b, CH allyl *trans* to N), 69.6 (CH_2-N,), 75.02 (b, CH), 79.3 (CH-O), 80.8 (CH-O), 104.6 (d, CH allyl *trans* to P, $J_{C\text{-}P}$= 42.6 Hz), 113.9 (d, CH allyl *central*, $J_{C\text{-}P}$= 8 Hz), 116.1 (CMe_2), 120.6-151.5 (aromatic carbons).

[Pd(η^3-1,3-cyclohexenyl)(L49b)]BF_4 (37). Yield: 35 mg (76%). MS HR-ESI [found 832.2233, $C_{41}H_{53}NO_5PPdSi_2$ $(M\text{-}BF_4)^+$ requires 832.2229]. Major isomer (96%): ^{31}P NMR (161.9 MHz, CD_2Cl_2, 298 K), δ: 142.5 (s, 1P). ^{1}H NMR(400 MHz, CD_2Cl_2, 298 K), δ: 0.47 (s, 9H, CH_3, CH_3-Si), 0.55 (s, 9H, CH_3, CH_3-Si), 0.88-1.17 (m, 3H, CH_2), 1.35 (s, 3H, CH_3), 1.58 (s, 3H, CH_3), 1.59 (m, 1H, CH_2), 1.82 (m, 1H, CH_2), 2.12 (m, 1H, CH_2), 3.34 (s, 3H, CH_3-N), 3.48 (m, 1H, CH), 3.59 (bd, 1H, CH_2-N, *J*= 13.6 Hz), 3.67 (m, 1H, CH allyl *trans* to

N), 3.75 (dd, 1H, CH_2-N, $^2J_{H-H}$= 13.6 Hz, $^3J_{H-H}$= 5.6 Hz), 4.15 (m, 1H, CH_2-O), 4.45 (m, 1H, CH_2-O), 4.71 (m, 1H, CH-O), 4.96 (m, 1H, CH-O), 5.49 (m, 1H, CH allyl *central*), 6.14 (m, 1H, CH allyl *trans* to P), 6.94 (d, 1H, CH=, $^3J_{H-H}$= 8.8 Hz), 7.13 (d, 1H, CH=, $^3J_{H-H}$= 8.4 Hz), 7.22 (m, 1H, CH=), 7.32 (m, 1H, CH=), 7.47 (m, 1H, CH=), 7.56 (m, 1H, CH=), 7.99 (d, 1H, CH=, $^3J_{H-H}$= 8.4 Hz), 8.04 (d, 1H, CH=, $^3J_{H-H}$= 8.0 Hz), 8.20 (s, 1H, CH=), 8.23 (s, 1H, CH=). ^{13}C NMR (100.6 MHz, CD_2Cl_2, 298 K), δ: 0.8 (CH_3-Si), 20.7 (CH_2), 23.8 (CH_3), 26.4 (CH_3), 27.4 (CH_2), 28.5 (CH_2), 53.4 (CH_3-N), 66.4 (d, CH_2-O, J_{C-P}= 6.8 Hz), 67.2 (d, CH_2-N, J_{C-P}= 8.3 Hz), 67.8 (b, CH allyl *trans* to N), 75.9 (CH), 80.0 (CH-O), 81.2 (CH-O), 106.6 (d, CH allyl *trans* to P, J_{C-P}= 38.7 Hz), 113.4 (d, CH allyl *central*, J_{C-P}= 10.7 Hz), 114.2 (CMe_2), 121.3-151.9 (aromatic carbons). Minor isomer (4%): ^{31}P NMR (161.9 MHz, CD_2Cl_2, 298 K), δ: 141.8 (s, 1P).

[Pd(η^3-1,3-diphenylallyl)(L49a)]BF_4 (38). Yield: 40 mg (78%). MS HR-ESI [found 944.2539, $C_{50}H_{57}NO_5PPdSi_2$ $(M\text{-}BF_4)^+$ requires 944.2542]. Major isomer (70%): ^{31}P NMR (161.9 MHz, CD_2Cl_2, 298 K), δ: 145.0 (s, 1P). ^{1}H NMR (400 MHz, CD_2Cl_2, 298 K), δ: 0.64 (s, 9H, CH_3, CH_3-Si), 0.67 (s, 9H, CH_3, CH_3-Si), 1.27 (s, 3H, CH_3), 1.39 (s, 3H, CH_3), 2.57 (s, 3H, CH_3-N), 3.01 (bd, 1H, CH_2-N, *J*= 13.6 Hz), 3.18 (m, 1H, CH), 4.09 (bd, 1H, CH_2-N, *J*= 13.6 Hz), 4.59 (m, 1H, CH_2-O), 4.93 (m, 1H, CH_2-O), 5.22 (m, 1H, CH allyl *trans* to N), 5.30 (m, 1H, CH-O), 5.31 (m, 1H, CH-O), 5.78 (m, 1H, CH allyl *trans* to P), 5.8 (m,1H, CH=), 6.62 (m, 1H, CH allyl *central*), 6.2 – 8.3 (m, 19H, CH=). ^{13}C NMR (100.6 MHz, CD_2Cl_2, 298 K), δ: 0.5 (CH_3-Si), 0.8 (CH_3-Si), 23.0 (CH_3), 25.7 (CH_3), 50.1 (CH_3-N), 63.7 (CH_2-N), 67.4 (d, CH_2-O, J_{C-P}= 4.0 Hz), 77.0 (CH), 78.4 (CH-O), 78.5 (CH-O), 79.8 (CH allyl *trans* to N), 98.0 (d, CH allyl *trans* to P, J_{C-P}= 35.7 Hz), 111.5 (d, CH allyl *central*, J_{C-P}= 6.2 Hz), 113.2 (CMe_2), 120.4-151.9 (aromatic carbons). Minor isomer (30%): ^{31}P NMR (161.9 MHz, CD_2Cl_2, 298 K), δ: 140.2 (s, 1P). ^{1}H NMR (400 MHz, CD_2Cl_2, 298 K), δ: 0.52 (s, 9H, CH_3, CH_3-Si), 0.76 (s, 9H, CH_3, CH_3-Si), 1.27 (s, 3H, CH_3), 1.49 (s, 3H, CH_3), 2.83 (m, 1H, CH), 2.84 (bd, 1H, CH_2-N, *J*= 13.2 Hz), 2.57 (s, 3H, CH_3-N), 4.08 (bd, 1H, CH_2-N, *J*= 13.2 Hz), 4.56 (m, 1H, CH allyl *trans* to N), 4.75 (m, 1H, CH_2-O), 4.81 (m, 1H, CH_2-O), 5.30 (m, 1H, CH-O), 5.35 (m, 1H, CH-O), 5.59 (m, 1H, CH allyl *trans* to P), 6.82 (m, 1H, CH allyl *central*), 6.2 – 8.3 (m, 20H, CH=). ^{13}C NMR (100.6 MHz, CD_2Cl_2, 298 K), δ: 0.6 (CH_3-Si), 0.7 (CH_3-Si), 23.90 (CH_3), 26.0 (CH_3), 49.8 (CH_3-N), 61.0 (CH_2-N), 64.4 (b, CH_2-O), 75.4 (CH), 78.4 (CH-O), 78.5 (CH-O), 79.4 (CH allyl *trans* to N), 103.9 (d, CH allyl *trans* to P, J_{C-P}= 32.7 Hz), 114.4 (d, CH allyl *central*, J_{C-P}= 12.2 Hz), 114.5 (CMe_2), 120.4-151.9 (aromatic carbons).

[Pd(η^3-1,3-diphenylallyl)(L52a)]BF_4 (39). Yield: 44 mg (83%). Major isomer (67%): ^{31}P NMR (161.9 MHz, CD_2Cl_2, 298 K), δ: 135.0 (s, 1P). ^{1}H NMR (400 MHz, CD_2Cl_2, 298 K), δ: 0.45 (s, 9H, CH_3, CH_3-Si), 0.75 (s, 9H, CH_3, CH_3-Si), 1.21 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 2.70 (s, 3H, CH_3-N), 3.22 (m, 1H, CH), 3.36 (dd, 1H, CH_2-N, *J*= 14.0 Hz, *J*= 5.6 Hz), 3.72 (m, 1H, CH_2-N), 4.50-4.64 (m, 2H, CH-O), 4.70 (m, 1H, CH_2-O), 4.82 (m, 1H, CH allyl *trans* to N), 4.86 (m, 1H, CH_2-O), 5.32 (m, 1H, CH allyl *trans* to P), 6.57-6.67 (m, 1H, CH allyl *central*), 5.8 – 8.3 (m, 20H, CH=). ^{13}C NMR (100.6 MHz, CD_2Cl_2, 298 K), δ: 0.3 (CH_3-Si), 0.7 (CH_3-Si), 22.9 (CH_3), 25.5 (CH_3), 53.1 (CH_3-N), 63.7 (CH_2-O), 64.1 (CH_2-N), 64.7

(CH allyl *trans* to N), 76.0 (CH), 80.5 (CH-O), 80.8 (CH-O), 95.6 (d, CH allyl *trans* to P, J_{C-P}= 35.7 Hz), 111.5 (d, CH allyl *central*, J_{C-P}= 11.4 Hz), 112.8 (CMe_2), 120.3-151.7 (aromatic carbons). Minor isomer (35%): ^{31}P NMR (161.9 MHz, CD_2Cl_2, 298 K), δ: 137.7 (s, 1P). ^{1}H NMR (400 MHz, CD_2Cl_2, 298 K), δ: 0.51 (s, 9H, CH_3, CH_3-Si), 0.66 (s, 9H, CH_3, CH_3-Si), 1.22 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 3.22 (m, 1H, CH_3-N), 3.71 (m, 1H, CH_2-N), 3.80 (m, 1H, CH_2-N), 4.01 (m, 1H, CH), 4.50-4.64 (m, 2H, CH-O), 4.69 (m, 1H, CH_2-O), 4.82 (m, 1H, CH_2-O), 5.09 (m, 1H, CH allyl *trans* to N), 5.54 (m, 1H, CH allyl *trans* to P), 6.57-6.67 (m, 1H, CH allyl *central*), 5.8 – 8.3 (m, 20H, CH=). ^{13}C NMR (100.6 MHz, CD_2Cl_2, 298 K), δ: -0.2 (CH_3-Si), 0.5 (CH_3-Si), 22.4 (CH_3), 24.0 (CH_3), 48.6 (CH_3-N), 61.7 (CH_2-N), 63.7 (CH_2-O), 62.9 (CH allyl *trans* to N), 77.8 (CH), 80.5 (CH-O), 80.2 (CH-O), 94.8 (d, CH allyl *trans* to P, J_{C-P}= 36.5 Hz), 111.9 (d, CH allyl *central*, J_{C-P}= 11.4 Hz), 113.0 (CMe_2), 120.3-151.7 (aromatic carbons). [Pd(η^3-1,3-diphenylallyl)(**L52a**)$_2$]BF_4 (8%): ^{31}P NMR (161.9 MHz, CD_2Cl_2, 298 K), δ: 137.7 (s, 1P). ^{1}H NMR (400 MHz, CD_2Cl_2, 298 K), δ: 0.55 (s, 9H, CH_3, CH_3-Si), 0.63 (s, 9H, CH_3, CH_3-Si), 1.18 (s, 3H, CH_3), 1.27 (s, 3H, CH_3), 1.81 (m, 1H, CH_3-N), 2.52 (m, 1H, CH), 2.87 (b, 2H, CH_2-N), 4.50-4.64 (m, 2H; CH-O), 4.57 (m, 1H, CH_2-O), 4.90 (m, 1H, CH_2-O), 5.85 (m, 2H, CH allyl *terminal*), 6.57-6.67 (m, 1H, CH allyl *central*), 5.8 – 8.3 (m, 20H, CH=). ^{13}C NMR (100.6 MHz, CD_2Cl_2, 298 K), δ: -0.1 (CH_3-Si), 0.0 (CH_3-Si), 23.1 (CH_3), 24.5 (CH_3), 42.5(CH_3-N), 60.7 (b, CH_2-N), 69 (b, CH_2-O), 76.9-77.1 (CH-O), 77.6-77.8 (CH), 99.9 (m, CH allyl *terminal*), 112.0 (b, CH allyl *central*), 112.3 (CMe_2), 120.3-151.7 (aromatic carbons).

5.2.4.6. Study of the reactivity of the [Pd(η^3-allyl)(L)]BF_4 with sodium malonate by in situ NMR spectroscopy[21]

A solution of in situ prepared [Pd(η^3-allyl)(L)]BF_4 (L=amino-phosphite, 0.05 mmol) in CD_2Cl_2 (1 ml) was cooled in the NMR spectrometer to -80 ˚C. At this temperature, a solution of cooled sodium malonate (0.1 mmol) was added. The reaction was then followed by ^{31}P NMR spectroscopy. The relative reaction rates were calculated using capillary that contained a solution of triphenylphosphine in CD_2Cl_2 as the external standard.

5.2.4.7. Typical procedure for the allylic alkylation of disubstituted linear and cyclic substrates

A degassed solution of [PdCl(η^3-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 (3 mg, 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 $MgSO_4$. Conversions were measured by ^{1}H NMR and enantiomeric excesses were determined either by HPLC (compounds **13**, **15**–**22** and **26**–**28**) or by GC (compounds **14** and **30**–**35**) or by ^{1}H NMR using [Eu(hfc)$_3$] (compound **29**).

5.2.4.8. 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 ligand (0.0055 mmol) in dichloromethane (0.5 mL) was stirred for 30 min. Subsequently, a solution of *rac*-1,3-diphenyl-3-acetoxyprop-1-ene (**S1**) (0.5 mmol) in dichloromethane (1.5 mL), the corresponding amine (1.5 mmol), *N*,*O*-bis(trimethylsilyl)-acetamide (370 µL, 1.5 mmol) and KOAc (3 mg, 0.03 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 $MgSO_4$. Conversions were measured by ^1H NMR and enantiomeric excesses were determined by HPLC.[8e]

5.2.5. Acknowledgments

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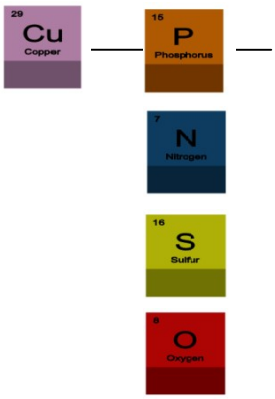
SUSTAINABLE AND COST-EFFECTIVE DEVELOPMENT OF CHIRAL METAL-CATALYSTS FOR C-H AND C-X BOND FORMING REACTIONS
Carlota Borràs Noguera

Chapter 6

ASYMMETRIC Cu-CATALYZED PROPARGYLIC SUBSTITUTION



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SUSTAINABLE AND COST-EFFECTIVE DEVELOPMENT OF CHIRAL METAL-CATALYSTS FOR C-H AND C-X BOND FORMING REACTIONS
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6.1. Copper-catalyzed propargylic substitution using chiral tridentated ligands and N- and C-nucleophiles

Carlota Borràs, Oscar Pàmies and Montserrat Diéguez preliminary results.

Abstract: A tridentated imine-based ligand family (**L57-L61**) was successfully synthesized in few steps procedure. The synthetic strategy used allowed us to systematically modify the chelating atoms. Although poor enantioselectivities were only achieved in the amination of propargylic acetates **S1-S3** (ee's up to 25%) and low-to-moderated enantioselectivities were only achieved in the alkylation reaction of **S1** (ee's up to 60%)

6.1.1. Introduction

Propargylic compounds are common design in many natural products, fine chemicals and synthetic pharmaceuticals. The presence of the nucleophilic triple bond and acidic terminal acetylenic hydrogen in many cases, convert these propargylic compounds in a highly potential for a wide variety of transformations.[1]

In contrast with the metal-catalyzed allylic substitution reactions, much less attention has been paid to metal-catalyzed propargylic substitution reactions of propargylic alcohol derivatives with nucleophiles.

In this chapter, we wish to give a new push to the catalytic potential of different tridentated imine based ligands in the copper-catalyzed propargylic substitution by screening several combination of phosphine, thioether, hydroxyl and nitrogen-containing compounds. For this purpose we designed a small but structurally valuable library ligands **L56**-**L61** (Figure 6.1.1). These ligands are based on the successful chiral tridentated P,N,N ligand **L56** developed by Hu and coworkers and their demonstration to be highly efficient for the Cu-catalyzed enantioselective propargylic amination of propargylic acetates with both primary and secondary amines as nucleophiles.[2] We investigated the effect on catalytic performance of systematically changing the nature of the chelating atom (**L56**, **L58**-**L61**) and steric effects (**L56**-**L57**). We also studied two different types of nucleophiles to give propargylic amination (using amine as nuclephile) and propargylic alkylation (using enamides as nucleophile) of propargylic acetates. Different substrates with aromatic (**S1**) and alkylic (**S2**-**S3**) substituents have also been investigated.

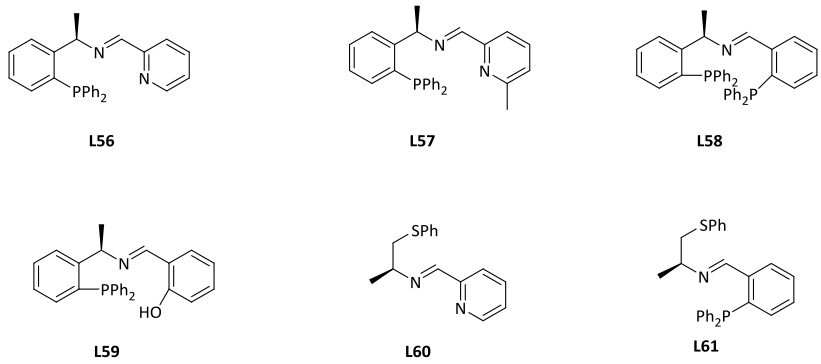


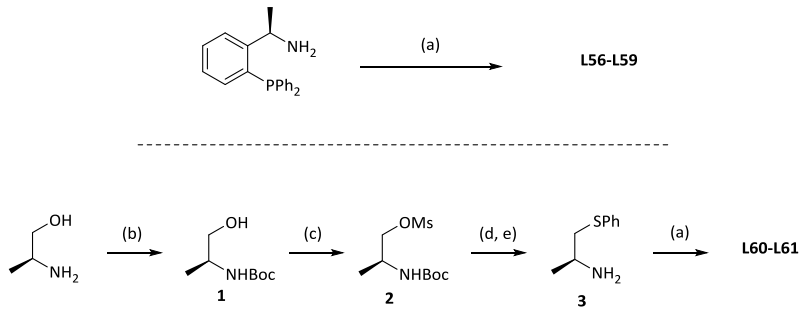
Figure 6.1.1. Chiral tridentated imine-based ligand family **L56**-**L61**.

6.1.2. Results and discussion

6.1.2.1. Synthesis of ligands

The synthesis of tridentate ligands **L56**-**L61** is shown in Scheme 6.1.1. Ligands **L56**-**L59** have been prepared in only one step from commercially available (*R*)-1-[2-(diphenylphosphino)phenyl]ethylamine with the corresponding aldehyde in presence of toluene and molecular sieves 4 Å (Scheme 6.1.1; step a). Ligands **L60**-**L61** have been prepared from commercially available L-alaninol in five steps. First step is the protection of the alcohol with di-*tert*-butyl dicarbonate in the presence of triethylamine to give the protected compound **1** (Scheme 6.1.1, step b). Compound **1** was transformed to intermediate **2** by treatment with methanesulfonyl chloride and triethylamine (Scheme 6.1.1; step c). Subsequent reaction with NaSPh provided direct access to protected amino-thioether, which was easily deprotected by reaction with trifluoroacetic acid and dicloromethane (Scheme 6.1.1, steps d and e). Last step is the same than for ligands **L56**-**L59**, coupling of the amine with the corresponding aldehyde affords the desired ligands **L60**-**L61** (Scheme 6.1.1; step a).

The ^{1}H, ^{31}P and ^{13}C NMR spectra were as expected for these C_1-tridentated ligands (see Section 6.1.4).

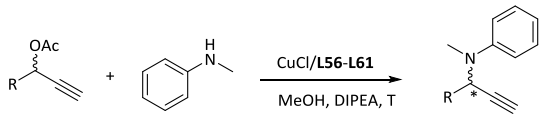


Scheme 6.1.1. Syntesis of ligands **L56**-**L61**. a) R'-CHO, molecular sieves 4 Å, toluene; b) Boc_2O, NEt_3, THF; c) MsCl, NEt_3, CH_2Cl_2; d) PhSH, NaH, THF; e) TFA, CH_2Cl_2.

6.1.2.2. Asymmetric Cu-catalyzed propargylic amination

In a first set of experiments we tested ligands **L56**-**L61** in the Cu-catalyzed propargylic amination of propargylic acetates with different electronic and steric properties: (*rac*)-1-phenylprop-2-yn-1-yl acetate (**S1**), (*rac*)-but-3-yn-2-yl acetate (**S2**) and (*rac*)-1-cyclohexylprop-2-yn-1-yl acetate (**S3**). In all cases the catalyst were generated *in situ* from CuCl and the corresponding ligand. *N*-Methylaniline was used as a model nucleophile because enables the efficiency of the various ligand systems to be compared directly with those found in the literature. The preliminary results are shown in Table 6.1.1. The use of ligand **L57**, which contains a methyl substituent at 6 position of the pyridyl moiety, had a negative effect on enantioselectivity (e.g. in the amination of **S1**, enantioselectivity drops from 90% to 25% ee when using ligand **L57** instead of **L56**; entry 1 vs 2). Similarly, the use of ligands **L58** and **L59**, in which the pyridine group has been respectively replaced by a phosphine and an alcohol moiety, also leads to a substantial decrease in enantioselectivity (entries 3-4 vs 1). The replacement of the phosphine group in ligand **L56** with a thioether group (ligand **L60**) also proceeded with much lower enantioselectivity (ee's up to 11%, entry 5). Finally, as observed when using ligand **L58**, the introduction of a phosphine moiety instead of the pyridyl group in thioether-based ligand **L61** also had a detrimental effect on enantioselectivity (entry 6).

Table 6.1.1. Asymmetric Cu-catalyzed propargylic amination of **S1**-**S3** using ligands **L56**-**L61**.[a]



		S1		S2		S3	
Entry	Ligand	% Conv[b]	% ee[c]	% Conv[b]	% ee[c]	% Conv[b]	% ee[c]
1	**L56**	100	90 (*S*)	62	78 (*R*)	25	78 (*S*)
2	**L57**	83	25 (*S*)	31	nd[d]	58	8 (*S*)
3	**L58**	40	4 (*S*)	34	30 (*R*)	49	20 (*S*)
4	**L59**	37	15 (*S*)	7	nd[d]	15	nd[d]
5	**L60**	100	11 (*S*)	32	6 (*S*)	18	10 (*R*)
6	**L61**	85	2 (*R*)	62	<2	30	nd[d]

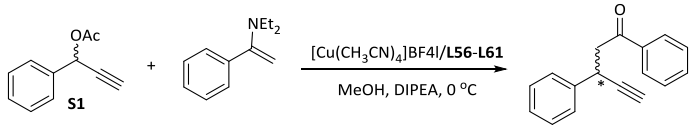
[a] Reactions conditions: CuCl (0.015 mmol), ligand (0.03 mmol), *N*-methylaniline (0.36 mmol), DIPEA (0.36 mmol), MeOH (2 mL), 18 h, T= 0 °C (for substrate **S1**) and 25 °C (for substrates **S2**-**S3**). [b] Conversion measured by ^{1}H-NMR. [c] Enantiomeric excesses measured by chiral HPLC. [d] nd= not determined.

6.1.2.3. Asymmetric Cu-catalyzed propargylic alkylation

We also carried out a preliminary investigation on the effectiveness of ligands **L56**-**L61** in the Cu-catalyzed propargylic alkylation of 1-phenylprop-2-yn-1-yl acetate (**S1**)

using *N,N*-diethyl-1-phenylethen-1-amine as nucleophile. In all cases the catalyst were generated *in situ* from $[Cu(CH_3CN)_4]BF_4$ and the corresponding ligand. The preliminary results, which are shown in Table 6.1.2., indicated a similar trend than in the propargylic amination of **S1**. Thus, the replacement of the pyridyl group in ligand **L56** by a 6-methyl pyridyl (ligand **L57**), by a phosphino (ligand **L58**) or by a hydroxyl moiety (ligand **L59**) had a negative effect on enantioselectivity (entry 1 vs 2-4). Similarly, switching the phosphine group in ligand **L56** by a thioether group (ligand **L60** and **L61**) had a detrimental effect on enantioselectivity (entry 1 vs 5-6).

Table 6.1.2. Asymmetric Cu-catalyzed propargylic alkylation of **S1** using ligands **L56**-**L61**.[a]



Entry	Ligand	% Conv[b]	% ee[c]
1	**L56**	100	85 (*+*)
2	**L57**	46	60 (*+*)
3	**L58**	49	33 (*+*)
4	**L59**	56	5 (-)
5	**L60**	51	15 (-)
6	**L61**	21	<2

[a] Reactions conditions: $[Cu(CH_3CN)_4]BF_4$ (0.015 mmol), ligand (0.03 mmol), *N,N*-diethyl-1-phenylethen-1-amine (0.36 mmol), DIPEA (0.36 mmol), MeOH (2 mL), 18 h, T= 0 °C. [b] Conversion measured by ^{1}H-NMR. [c] Enantiomeric excesses measured by chiral HPLC.

6.1.3. Conclusions

Five new tridentated ligands (**L57**-**L61**) have been successfully synthesized in few simple steps procedure from commercially available starting material. The synthetic procedure used allowed the systemic variation of the chelating atoms. These new ligands have applied in the amination reaction of three different propargylic acetates (**S1**-**S3**) with different steric requirements using *N*-methylaniline as a nucleophile. Unfortunately, poor enantioselectivities were only achieved in all cases (ee's up to 25% ee). Moreover, they have been also applied in the alkylation reaction of substrate **S1** using a N,N-diethyl-1-phenylethen-1-amine. In these cases, enantioselectivities are slightly higher than previous amination reactions, but, only poor-to-moderated results have been obtained (up to 60% ee's).

6.1.4. Experimental Part

6.1.4.1. General remarks

All reactions were carried out using standard Schlenk techniques under an atmosphere of argon. Commercial chemicals were used as received. Solvents were dried by standard procedures and stored under argon. Ligand **L61**[3] and compounds **1**[4] and **2**[5] were prepared as previous reported. ^{1}H, $^{13}C\{^{1}H\}$ and $^{31}P\{^{1}H\}$ NMR spectra were recorded using a Varian Mercury-400 MHz spectrometer for solutions in $CDCl_3$ and C_6D_6 at room temperature. Chemical shifts are relative to that of $SiMe_4$ (^{1}H and $^{13}C\{^{1}H\}$) 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.

6.1.4.2. General procedure for the preparation of ligands L57-L61

To a solution of corresponding amine (1 mmol) in 8 mL of toluene was added the corresponding aldehyde (1 mmol) and anhydrous molecular sieves 4 Å (200 mg). The reaction mixture was refluxed for 8 h, and then cooled to room temperature. The reaction mixture was diluted with 5 mL of deoxygenated CH_2Cl_2, and $MgSO_4$ were removed by the filtration. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography under argon (toluene/Et_3N, 10/0.1) to afford a white solid.

L57: Yield: 290 mg (71%). ^{31}P NMR (C_6D_6), δ: -16.6 (s). ^{1}H NMR (C_6D_6), δ: 1.44 (d, 3H, CH_3, $^{2}J_{H-H}$= 6.6 Hz), 2.56 (s, 3H, CH_3, Py), 5.49 (m, 1H, CH), 7.13 (m, 1H, CH=), 7.13 (d, 2H, CH=, $^{3}J_{H-H}$= 7.6 Hz), 7.27 (m, 10H, CH=), 7.56 (t, 1H, CH=, $^{3}J_{H-H}$= 7.7 Hz), 7.75 (d, 1H, CH=, $^{3}J_{H-H}$= 7.8 Hz), 7.80 (m, 1H, CH=), 8.23 (s, 1H, CH=N). ^{13}C NMR (C_6D_6), δ: 24.4 (CH_3, py), 24.9 (CH_3), 66.2 (CH), 118.4-157.8 (aromatic carbons), 161.2 (CH=N).

L58: Yield: 130 mg (23%). ^{31}P NMR (C_6D_6), δ: -16.7 (s), -12.2 (s). ^{1}H NMR (C_6D_6), δ: 1.18 (d, 3H, CH_3, $^{2}J_{H-H}$= 6.4 Hz), 5.30 (m, 1H, CH), 6.84 (m, 2H, CH=), 7.09 (t, 1H, CH=, $^{3}J_{H-H}$= 7.5 Hz), 7.26 (m, 22H, CH=), 7.49 (m, 1H, CH=), 7.73 (m, 1H, CH=), 8.59 (s, 1H, CH=N). ^{13}C NMR (C_6D_6), δ: 24.9 (CH_3), 66.5 (CH), 126.7-149.8 (aromatic carbons), 158.7 (CH=N).

L59: Yield: 111 mg (27%). ^{31}P NMR (C_6D_6), δ: -15.9 (s). ^{1}H NMR (C_6D_6), δ: 1.50 (d, 3H, CH_3, $^{2}J_{H-H}$= 6.5 Hz), 5.32 (m, 1H, CH), 6.79 (m, 2H, CH=), 6.94 (m, 2H, CH=), 7.13 (m, 1H, CH=), 7.31 (m, 12H, CH=), 7.64 (m, 1H, CH=), 7.82 (s, 1H, CH=N). ^{13}C NMR (C_6D_6), δ: 24.9 (CH_3), 65.5 (CH), 116.8-160.9 (aromatic carbons), 163.7 (CH=N).

L60: Yield: 88.4 mg (35%). ^{1}H NMR (C_6D_6), δ: 1.36 (d, 3H, CH_3, $^{2}J_{H-H}$= 6.4 Hz), 3.15 (d, 2H, CH_2-S, $^{2}J_{H-H}$= 6.7 Hz), 3.59 (m, 1H, CH-N), 7.10 (m, 1H, CH=), 7.25 (m, 5H, CH=), 7.67 (m, 1H, CH=), 7.89 (m, 1H, CH=), 8.31 (s, 1H, CH=N), 8.63 (m, 1H, CH=). ^{13}C NMR (C_6D_6), δ: 21.9 (CH_3), 41.0 (CH_2), 65.4 (CH), 121.7-154.3 (aromatic carbons), 161.3 (CH=N).

L61: Yield: 48 mg (11%). ^{31}P NMR (C_6D_6), δ: -13.2 (s). ^{1}H NMR (C_6D_6), δ: 1.07 (d, 3H, CH_3, $^{2}J_{H-H}$= 4.8 Hz), 2.86 (d, 2H, CH_2-S, $^{2}J_{H-H}$= 6.7 Hz), 3.30 (m, 1H, CH-N), 6.78 (m, 1H, CH=), 7.05 (m, 1H, CH=), 7.22 (m, 16H, CH=), 7.83 (m, 1H, CH=), 8.75 (s, 1H, CH=N). ^{13}C

NMR (C_6D_6), δ: 21.6 (CH_3), 40.9 (CH_2-S), 65.1 (CH-N), 125.6-139.3 (aromatic carbons), 159.2 (CH=N)..

6.1.4.3. Procedure for the preparation of intermediate amino-thioether 3

PhSH (2.7 mL, 25.41 mmol) was added to a solution of NaH (2.10 g in 60% oil, 52.5 mmol) and THF (11mL) at -15 ˚C after 1 h a solution of compound **2**[5] (2.8 g, 11.05 mmol) and THF was added to a stirred mixture. After 16 h the reaction mixture was quenched with H_2O (10 mL) and THF is evaporated under vacuum. The aqueous phase was extracted with CH_2Cl_2 and washed with brine. The organic phases was dried with $MgSO_4$, which were removed by the filtration. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel flash-chromatography (petroleum ether/AcOEt, 18/1) to afford a colorless oil. Yield: 1.5 g (50%). ^{1}H NMR (C_6D_6), δ: 1.21 (d, 3H, CH_3, $^2J_{H-H}$= 6.7 Hz), 1.42 (s, 9H, CH_3, ^{t}Bu, NHBoc), 2.97 (m, 1H, CH_2-S), 3.13 (m, 1H, CH-N), 3.91 (m, 1H, CH_2-S), 4.60 (b, 1H, NH), 7.16 (t, 1H, CH=, $^3J_{H-H}$= 7.3 Hz), 7.27 (m, 2H, CH=), 7.38 (d, 2H, CH=, $^3J_{H-H}$= 7.5 Hz).

To a solution of a protected thioether compound (1.5 g, 5.61 mmol) and CH_2Cl_2 (90 mL), TFA (50 mL) was added. The reaction mixture was stirred overnight at room temperature. After evaporate the TFA the crude was purified by flash chromatography (CH_2Cl_2/MeOH/NEt_3 – 20/1/0.25) to afford the compound **3**. Yield: 1.0 g (quantitative). ^{1}H NMR (C_6D_6), δ: 1.29 (d, 3H, CH_3, $^2J_{H-H}$= 6.5 Hz), 3.03 (m, 2H, CH_2-S), 3.21 (m, 1H, CH-N), 6.03 (b, 2H, NH), 7.21 (m, 1H, CH=), 7.27 (m, 2H, CH=), 7.36 (d, 2H, CH=, $^3J_{H-H}$= 7.1 Hz). ^{13}C NMR (C_6D_6), δ: 18.9 (CH_3), 39.7 (CH_2-S), 47.0 (CH-N), 127.1-130.4 (aromatic carbons).

6.1.4.4. General procedure of Cu-catalyzed propargylic amination

CuCl (1.5 mg, 0.015 mmol) and corresponding ligand (0.03 mmol) were stirred in 1 mL of anhydrous methanol under argon atmosphere for 1 h. The mixture was cooled to 0 ˚C and then a solution of propargylic acetate (0.3 mmol), *N*-methylaniline (0.36 mmol) and *N,N*-diisopropylethylamine (0.36 mmol) in 1 mL of anhydrous methanol was added. The reaction was kept at 0 ˚C for **S1** and at RT for **S2** and **S3** for 18 h. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography with petroleum ether and ethyl acetate as eluent. The enantiomeric excesses of substituted products from **S1**-**S3**[2] were determined using the conditions previously described.

6.1.4.5. General procedure of Cu-catalyzed propargylic alkylation

Under an argon atmosphere, $Cu(CH_3CN)_4ClO_4$ (8.3 mg, 0.015 mmol) and chiral tridentate P,N,N ligand (0.03 mmol) were dissolved in 2 mL of MeOH. The resulting mixture was stirred at room temperature for 1 h, and then was cooled to 0 °C. Enamine (0.36 mmol), propargylic acetate 1 (0.3 mmol), 2 mL of MeOH and *N,N*-diisopropylethylamine (0.36) were added sequentially. The reaction mixture was stirred at 0 °C for 18 h, and then was concentrated in vacuo. The residue was purified through flash column chromatography (EtOAc/petroleum ether = 1/40) to afford the

corresponding propargylic ketone. The enantiomeric excesses of substituted products from **S1**[6] were determined using the conditions previously described.

6.1.5. Acknowledgments

Financial support from the Spanish Ministry of Economy and Competitiveness (CTQ2016-74878-P) and European Regional Development Fund (AEI/FEDER, UE), the Catalan Government (2014SGR670 and 2017SGR1472), and the ICREA Foundation (ICREA Academia award to M.D) is gratefully acknowledged.

6.1.6. REFERENCES

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UNIVERSITAT ROVIRA I VIRGILI
SUSTAINABLE AND COST-EFFECTIVE DEVELOPMENT OF CHIRAL METAL-CATALYSTS FOR C-H AND C-X BOND FORMING REACTIONS
Carlota Borràs Noguera

Chapter 7

CONCLUSIONS

UNIVERSITAT ROVIRA I VIRGILI
SUSTAINABLE AND COST-EFFECTIVE DEVELOPMENT OF CHIRAL METAL-CATALYSTS FOR C-H AND C-X BOND FORMING REACTIONS
Carlota Borràs Noguera

7. Conclusions

1. Chapter 3. Asymmetric hydrogenation reactions. The conclusions of this chapter can be summarized as follows:
   - Five different 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 structurally valuable cyclohexane-based phosphite/phosphinite-thioether ligand library has been synthesized in only two steps from commercially available cyclohexene oxide. They have been applied in the hydrogenation of 40 minimally functionalized olefins, including some relevant examples with poorly coordinative groups obtaining high enantioselectivities (ee's up to 99%). Their simple backbone gives simple NMR spectra, with reduced overlap, which facilitates the identification of relevant intermediates. Therefore, by combining HP-NMR spectroscopy and DFT calculations, we were able to identify the catalytically competent Ir-dihydride alkene species, which made it possible to explain the enantioselectivity obtained. We found that, similarly to the classical Halpern-mechanism for asymmetric hydrogenation with Rh-catalysts, the minor intermediate, which is less stable, is converted to the major product enantiomer.
   - A new binaphtyl-based phosphite-thioether ligand family was successfully synthesized from commercially available (*R*)-BINOL and evaluated in the asymmetric Ir-catalyzed hydrogenation of minimally functionalyzed olefins. Good-to-excellent enantioselectivities (ee's up to 99%) have been obtained for a range of tri- and disubstituted olefins, including lactone and lactame substrates and in alkenyl boronic ester containing substrates.
   - A large modular phosphite-thioether/selenoether ligand library has been successfully synthesized from L-tartaric acid and D-mannitol. Improving most approach reported to date, these ligands have been successfully applied (ee's up to 99%) in both the Rh- and Ir-catalyzed asymmetric hydrogenation of a wide variety of functionalized and unfunctionalyzed olefins (45 compounds in total). We found that enantioselectivity in this process 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.

- We show the first application of a carbene-thioether ligand in the Ir-catalyzed asymmetric hydrogenation of minimally functionalized olefins. Comparing the effectiveness of this thioether-carbene ligand with its related phosphinite and phosphite-based ligands. We found that carbene-thioether ligand provided lower activity and enantioselectivity than their related analogues modified with phosphinite and phosphite groups. Enantioselectivity is highly dependent on both the ligand and the substrate parameters. It should be mentioned the good enantioselectivities (ee's up to 98%) achieved for several substrate types, such as trisubstituted α,β-unsaturated enones, esters and lactones, tri- and disubstituted enol phosphinates and (3,3-dimethylbut-1-en-2-yl)benzene with this very simple ligand scaffold.
- A modular pyrrolidine-based phosphine/phosphite-O/S ligand library has been applied in the hydrogenation of minimally functionalized olefins. These ligands have been synthesized from readily available D-mannose, D-ribose and D-arabinose. We found that their effectiveness at transferring the chiral information in the product can be tuned by correctly choosing the ligand components and the substrates. High enantioselectivities could therefore be achieved in the asymmetric hydrogenation of selected tris- and disubstituted substrates (ee's up to 99%). In comparison with related successful proline-based P,O ligand, the introduction of a readily available sugar and more rigid bicyclic backbone, had a positive effect on enantioselectivity extending the range of substrates that can been reduced, including several 1,1-disubstituted allylic acetates. In addition, our ligands contained a diphenyl phosphine moiety instead of the bulkier phosphine groups found in related proline-based P,O ligands, which are made from much more expensive chlorophosphine precursors and made them less stable ligands.

2. Chapter 4. Asymmetric Ir-catalyzed hydrogenation of ketones. The conclusions of this chapter can be summarized as follows:
   - A new class of tridentated phosphite/phosphinite/phosphine-amino-oxazoline/pyridine ligand library has been synthesized in good to moderated yields following a direct synthetic route. These ligands were designed for a future specific application in the hydrogenation of simple ketones.

3. Chapter 5. Asymmetric Pd-catalyzed allylic substitution. The conclusions of this chapter can be summarized as follows:
   - The previous readily available library of phosphite-thioether/selenoether ligands has also been applied in the Pd-catalyzed allylic substitution

reactions of several substrates including the more challenging monosubstituted ones, using a broad range of C-, N- and O-nucleophiles. Enantioselectivities can be tuned by correctly choosing the ligand parameters (ee's up to 99%).

- New iminosugar-phosphite/phosphinite/phosphine ligands have been applied in Pd-catalyzed allylic substitution reactions. By selecting the ligand components, we obtained good results in several substrates with different electronic and steric requirements and using a number of C- and N-nucleophiles (23 compounds in total with ee's up to 93%). In comparison with previous air instable amino-P ligands (P=phosphine, aminophosphine and phosphinite groups) reported in the literature, the new amino-phosphite ligands provided a better substrate and nucleophile scope (i.e. including more challenging hindered linear and cyclic substrates, even using highly appealing nucleophiles such as those α-substituted with methyl, allyl, butenyl, pentenyl and propargyl groups). The study of Pd-π-allyl intermediates shows that for enantioselectivities to be high the ligand parameters need to be appropriately combined to either increase the difference in the population of the resulting Pd-allyl compounds (for cyclic substrate), or to increase the relative rates of the nucleophilic attack of each Pd-allyl intermediate, and also to avoid the formation of Pd-allyl intermediates with monodentated coordinated ligands (for linear substrates). This study also indicates that the sugar backbone is able to control the configuration of the amino group upon coordination, which in turn can be efficiently shifted from *R*- to *S*- by simply varying the configuration of the biaryl phosphite moiety.

4. Chapter 6. Asymmetric Cu-catalyzed propargylic substitution. The conclusions of this chapter can be summarized as follows:
   - A tridentated imine-based ligand family was successfully synthesized in a few steps procedure. The synthetic strategy used allowed us to systematically modify the chelating atoms. These ligands have been applied in the propargylic amination (ee's up to 25%) and alkylation (up to 60% ee's) of three propargylic acetates .

UNIVERSITAT ROVIRA I VIRGILI
SUSTAINABLE AND COST-EFFECTIVE DEVELOPMENT OF CHIRAL METAL-CATALYSTS FOR C-H AND C-X BOND FORMING REACTIONS
Carlota Borràs Noguera

Chapter 8

SUMMARY

UNIVERSITAT ROVIRA I VIRGILI
SUSTAINABLE AND COST-EFFECTIVE DEVELOPMENT OF CHIRAL METAL-CATALYSTS FOR C-H AND C-X BOND FORMING REACTIONS
Carlota Borràs Noguera

8. Resum (Summary)

L'obtenció de compostos enantiomèricament purs ha esdevingut una necessitat que ha conduit a un important progrés en la catàlisi asimètrica, principalment usant compostos organometàl·lics quirals. Entre les diferents estratègies en l'optimització dels catal·litzadors per aconseguir elevades selectivitats i activitats, el disseny i correcta selecció de lligands quirals, modificant-ne les seves propietats és fonamental i la més utilitzada. Que un lligand sigui fàcil de sintetitzar a partir de compostos de partida accessibles i que aquests lligands siguin estables i fàcils de manipular, tenen un elevat interès en la industria.

En aquest context, el principal objectiu d'aquesta tesi és la síntesi de diferents famílies de lligands quirals, acomplint els requisits prèviament esmentats, i la seva posterior aplicació a diverses reaccions asimètriques d'elevat interès industrial: hidrogenació d'olefines funcionalitzades i no funcionalitzades catalitzada per Rh i Ir, hidrogenació de cetones catalitzada per Ir, reaccions de substitució al·lílica catalitzades per Pd i reaccions de substitució propargílica catalitzada per Cu. S'han sintetitzat diverses famílies fosfit/fosfinit-tioèter/selenoèter, carbè-tioèter, amino-fosfit/fosfinit/fosfina, i varies famílies de lligands tridentats.

En el primer capítol (introducció), es fa un repàs del les característiques més rellevants per a cadascuna de les reaccions que s'estudien en aquesta tesi, explicant el mecanisme i els lligands més significants. El següent capítol consisteix en la presentació dels diferents objectius en els que es basa aquesta tesi.

El tercer capítol, presenta cinc apartats on es discuteix la síntesi de varies llibreries de lligands quirals i l'aplicació en reaccions d'hidrogenació d'olefines. La primera secció consta de l'article titulat *Ir-catalyzed asymmetric hydrogenation with simple cyclohexane-based P/S ligands: In situ HP-NMR and DFT calculations for the characterization of reaction intermediate,* on es descriu la síntesi I l'aplicació de lligands fosfit/fosfinit-tioèter en la hidrogenació d'olefines no funcionalitzades catalitzada per iridi. A més a més, en aquest treball, s'han realitzat estudis de ressonància magnètica nuclear d'alta pressió i estudis teòric per tal d'identificar intermedis de reacció i poder definir l'origen de la enantioselectivitat.

En la segona part es descriu el treball titulat *Ir-catalyzed asymmetric hydrogenation of minimally functionalized alkenes using binaphthyl-based phosphite-thioether ligands*. Aquest consisteix en la síntesi de lligands fosfit-tioèter, derivats del (*R*)-Binol. També es presenten els resultats preliminars obtinguts de la seva aplicació a la hidrogenació catalitzada per iridi en diferents tipus de substrat mínimament funcionalitzats.

La tercera part inclou el treball titulat *A readily assembled carbohydrate derived phosphite-thioether/selenoether ligand library for a broad range of M-catalyzed asymmetric hydrogenation*, on es descriu la síntesi i aplicació de lligands fosfit-tioèter/selenoèter, derivats de L-àcid tartaric o del D-manitol, en les reaccions

d'hidrogenació asimètriques, catalitzades per Rh i Ir, de diverses olefines funcionalitzades i no funcionalitzades. L'alta modularitat d'aquests lligands ha permès obtenir elevades enantioselectivitats (fins a un excés enantiomeric del 99%).

En la quarta secció es presenta el següent treball *Pyrrolidine-based P,O ligands from carbohydrates: Easily accessible and modular ligands for the Ir-catalyzed asymmetric hydrogenation of minimally functionalized olefins*, on s'exposa la síntesi i la següent aplicació de la familia de lligands fosfina/fosfit-O/S derivats de la pirrolidina en la hidrogenació de olefines mínimament funcionalitzades catalitzada per iridi s'han obtingut elevades enantioselectivitats (de fins al 99%) per una selecció de substrats amb diferents requeriments.

En l'ultim apartat d'aquest capítol, es mostra el treball anomenat *Application of a carbene-thioether ligand in the Ir-catalyzed hydrogenation of minimally functionalized olefins. Comparison with their analogues phosphinite and phosphite ligands*. En aquest apartat es fa un estudi comparatiu entre un lligand carbè-tioèter i els seus anàlegs fosfinit/fosfit-tioèter en l'aplicació d'aquests en la reacció de hidrogenació catalitzada per iridi d'un ventall de substrats amb diferents geometries i característiques.

En el següent capitol (Capítol 4) es presenta un treball titulat *Synthesis of tridentated phosphite/phosphinite/phosphine-amino-oxazoline/pyridine ligands for iridium-catalyzed hydrogenation of simple ketones*, on s'exposa la síntesi d'una familia de lligands tridentats, amb diferents característiques electròniques i estèriques, per a la futura aplicació d'aquests en la hidrogenació de cetones simples catalitzada per iridi.

En el cinquè capítol es mostren dos treballs on s'apliquen dues famílies de lligands en la reacció de substitució al·lílica catalitzada per pal·ladi. En al primera secció, es presenta el treball anomenat *Application of a high modular carbohydrate-derived phosphite-thioether/selenoether ligand library for asymmetric Pd-catalyzed allylic substitution reaction*, on s'aplica la família fosfit-tioèter/selenoèter prèviament descrita en la tercera secció del tercer capítol en la reacció de substitució al·lilica catalitzada per Pd. Seleccionant els paràmetres estructurals adequats, s'ha pogut identificar lligands capaços de proveir altes enantioselectivitats en l'alquilació de substrats amb diferents requeriments estèrics utilitzant un ample ventall de nucleòfils de carboni, nitrogen i oxigen.

El segon apartat del capítol consta de l'article titulat *P-amino ligands from iminosugars: New readily available and modular ligands for the asymmetric Pd-catalyzed allylic substitution reaction*, on es mostra la síntesi de la família de lligands amina-fosfit/fosfinit/fosfina, derivats de la pirrolidina i la seva posterior aplicació en la reacció de substitució al·lílica catalitzada per pal·ladi. S'obtenen excel·lents enantioselectivitats per un ampli ventall de substrats amb diferents propietats, tant estèriques com electròniques, i varis nucleòfils tant de carboni com de nitrogen. També es van fer estudis dels intermedis de reacció per poder entendre els resultats catal·lítics obtinguts.

Finalment, en el sisè capítol, es mostra el treball anomenat *Copper-catalyzed propargylic substitution using chiral tridentated ligands and N- and C-nucleophiles*. En aquesta secció es presenta la síntesi d'una família de lligands tridentats i els estudis preliminars de la seva aplicació en la reacció de substitució propargíl·lica catalitzada per Cu utilitzant dos tipus de nucleòfils, amina i enamina.

UNIVERSITAT ROVIRA I VIRGILI
SUSTAINABLE AND COST-EFFECTIVE DEVELOPMENT OF CHIRAL METAL-CATALYSTS FOR C-H AND C-X BOND FORMING REACTIONS
Carlota Borràs Noguera

Chapter 9

APPENDIX

UNIVERSITAT ROVIRA I VIRGILI
SUSTAINABLE AND COST-EFFECTIVE DEVELOPMENT OF CHIRAL METAL-CATALYSTS FOR C-H AND C-X BOND FORMING REACTIONS
Carlota Borràs Noguera

9. List of papers and meeting contributions

9.1. List of papers

1. Borràs, Carlota; Biosca, Maria; Pàmies, Oscar; Diéguez, Montserrat; "Ir-catalyzed asymmetric hydrogenation with simple cyclohexane-based P/S ligands: In situ HP-NMR and DFT calculations for the characterization of reaction intermediates", *Organometallics*, **2015**, *34*, 5321.
2. Borràs, Carlota; Pastor, Isidro; Pàmies, Oscar; Diéguez, Montserrat; "Ir-catalyzed asymmetric hydrogenation of minimally functionalized alkenes using binaphthyl-based phosphate-thioether ligands", preliminary results.
3. Borràs, Carlota; Margalef, Jèssica; Alegre, Sabina; Alberico, Elisabeta; Pàmies, Oscar; Diéguez, Montserrat; "A readily assembled carbohydrate derived phosphate-thioether/selenoether ligand library for a broad range of M-catalyzed asymmetric hydrogenation", manuscript to be submitted.
4. Borràs, Carlota; Elías-Rodríguez, Pilar; Carmona, Ana T.; Faiges, Jordi; Robina, Inmaculada; Pàmies, Oscar; Diéguez, Montserrat; "Pyrrolidine-based P,O ligands from carbohydrates: Easily accessible and modular ligands for the Ir-catalyzed asymmetric hydrogenation of minimally functionalized olefins", manuscript to be submitted.
5. Borràs, Carlota; Mazloomi, Zahra; de la Cruz Sanchez, Pol; Faiges, Jordi; Pàmies, Oscar; Diéguez, Montserrat; "Application of a carbene-thioether ligand in the Ir-catalyzed hydrogenation of minimally functionalized olefins. Comparison with their analogues phosphinite and phosphite ligands", preliminary results.
6. Borràs, Carlota; Pàmies, Oscar; Diéguez, Montserrat; "Synthesis of tridentated phosphite/phosphinite/phosphine-amino-oxazoline/pyridine ligands for iridium-catalyzed hydrogenation of simple ketones", in progress.
7. Borràs, Carlota; Margalef, Jèssica; Alegre, Sabina; Alberico, Elisabeta; Pàmies, Oscar; Diéguez, Montserrat; "Application of a high modular carbohydrate-derived phosphite-thioether/selenoether ligand library for asymmetric Pd-catalyzed allylic substitution reaction", manuscript to be submitted.
8. Borràs, Carlota; Elías-Rodríguez, Pilar; Carmona, Ana T.; Robina, Inmaculada; Pàmies, Oscar; Diéguez, Montserrat; "Amino-P Ligands from Iminosugars: New Readily Available and Modular Ligands for Enantioselective Pd-Catalyzed Allylic Substitutions" *Organometallics*, DOI: 10.1021/acs.organomet.8b00140.
9. Borràs, Carlota; Pàmies, Oscar; Diéguez, Montserrat; "Copper-catalyzed propargylic substitution using chiral tridentated ligands and N- and C-nucleophiles", preliminary results.

9.2. Meeting contributions

1. **Authors:** Borràs, Carlota; Pàmies, Oscar; Diéguez, Montserrat
Title: P-S Ligands for the highly enantioselective Ir-catalyzed hydrogenation of minimally functionalized olefins
Type of presentation: Poster
Meeting: GEQO XXXII Meeting
Place: Tarragona, Spain
Year: September 2014

2. **Type of presentation:** Organization and attendance
Meeting: CARISMA Meeting
Place: Tarragona, Spain
Year: March 2015

3. **Authors:** Borràs, Carlota; Pàmies, Oscar; Diéguez, Montserrat
Title: Phosphite-thioether ligands for asymmetric Ir-catalyzed hydrogenation of minimally functionalized olefins
Type of presentation: Poster
Meeting: OMCOS18 IUPAC International Symposio¡um
Place: Sitges, Spain
Year: June-July 2015

4. **Type of presentation:** Attendance
Meeting: VII Journées Franco-Catalanes
Place: Toulouse, France
Year: January 2016

5. **Authors:** Borràs, Carlota; Biosca, Maria; Pàmies, Oscar; Diéguez, Montserrat
Title: Ir-catalyzed asymmetric hydrogentation of unfunctionalized olefins using novel P/S ligands: In situ HP-NMR and DFT calculation for the characterization of reaction intermediates
Type of presentation: Oral presentation
Meeting: Novena trobada de joves investigadors dels països catalans
Place: Perpignan, France
Year: February 2016

6. **Authors:** Borràs, Carlota; Biosca, Maria; Pàmies, Oscar; Diéguez, Montserrat
Title: New simple P-S ligands for asymmetric Ir-catalyzed hydrogenation: characterization of reaction intermediates by in situ HP-NMR and DFT calculations
Type of presentation: Poster and Oral presentation
Meeting: XXXVI Reunión bienal de la Sociedad Española de Química
Place: Sitges, Spain
Year: June 2017

9.3. PhD research abroad

1. CNRS - Laboratoire de chimie de coordination, Toulose
Under the supervision of Prof. Rinaldo Poli and Dr. Eric Manoury
April-June 2015

2. Universitat d'Alacant , Alacant
Under the supervision of Dr. Isidro M. Pastor
November 2016

UNIVERSITAT ROVIRA I VIRGILI
SUSTAINABLE AND COST-EFFECTIVE DEVELOPMENT OF CHIRAL METAL-CATALYSTS FOR C-H AND C-X BOND FORMING REACTIONS
Carlota Borràs Noguera

UNIVERSITAT ROVIRA I VIRGILI
SUSTAINABLE AND COST-EFFECTIVE DEVELOPMENT OF CHIRAL METAL-CATALYSTS FOR C-H AND C-X BOND FORMING REACTIONS
Carlota Borràs Noguera

UNIVERSITAT ROVIRA I VIRGILI
SUSTAINABLE AND COST-EFFECTIVE DEVELOPMENT OF CHIRAL METAL-CATALYSTS FOR C-H AND C-X BOND FORMING REACTIONS
Carlota Borràs Noguera

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