DESIGN OF TAILOR-MADE CHIRAL LIGAND LIBRARIES FOR C-X BOND FORMING REACTIONS. STUDY OF THE KEY INTERMEDIATES BY NMR AND DFT

Marc Magre Rosich

Marc Magre Rosich

Design of tailor-made chiral ligand libraries for C-X bond forming reactions. Study of the key intermediates by NMR and DFT

PhD Thesis

Supervised by Prof. Dr. Montserrat Diéguez and Dr. Oscar Pàmies

Departament de Química Física i Inorgànica

UNIVERSITAT ROVIRA i VIRGILI

Tarragona, July 2016

UNIVERSITAT ROVIRA I VIRGILI
DESIGN OF TAILOR-MADE CHIRAL LIGAND LIBRARIES FOR C-X BOND FORMING REACTIONS. STUDY OF THE KEY INTERMEDIATES BY NMR AND DFT
Marc Magre Rosich

UNIVERSITAT ROVIRA I VIRGILI
DEPARTAMENT DE QUÍMICA FÍSICA I INORGÀNICA
Campus Sescelades
Marcel·lí Domingo, s/n
43007 Tarragona
Tel. +34 977 55 81 37
Fax +34 977 55 95 63
www.quimica.urv.es

UNIVERSITAT ROVIRA i VIRGILI

FEM CONSTAR que aquest treball, titulat "*Design of tailor-made chiral ligand libraries for C-X bond forming reactions. Study of the key intermediates by NMR and DFT*", que presenta Marc Magre Rosich per a l'obtenció del títol de Doctor, ha estat realitzat sota la nostra direcció al Departament de Química Física i Inorgànica d'aquesta universitat i que acompleix els requeriments per poder optar a Menció Internacional.

Tarragona, 8 de Juny del 2016

Els directors de la tesi doctoral

Prof. Dr. Montserrat Diéguez Fernández

Dr. Oscar Pàmies Ollé

UNIVERSITAT ROVIRA I VIRGILI
DESIGN OF TAILOR-MADE CHIRAL LIGAND LIBRARIES FOR C-X BOND FORMING REACTIONS. STUDY OF THE KEY INTERMEDIATES BY NMR AND DFT
Marc Magre Rosich

Agraïments / Acknowledgments

Ha arribat el dia d'agrair totes aquelles persones que han estat al meu costat i han fet que aquest camí que tanta pujada fa, sigui més fàcil.

Primer de tot, agrair als meus *jefes*, a la Prof. Montserrat Diéguez i al Dr. Oscar Pàmies. Gràcies a vosaltres he tingut la oportunitat de poder fer allò que més desitjava just acabar la carrera, que era dedicar-me a la investigació. Moltes gràcies per tot, de veritat.

També agrair a tothom del departament Professors i companys, que amb amables paraules o simplement amb uns "*hola*" i "*adéu*" quan te'ls creuaves, han format part d'aquest viatge. Gràcies per tot. També agrair al Josep i sobretot a la Raquel, qui et soluciona qualsevol problema, administratiu, de seguretat o de material. Moltes gràcies! Sense tu aquell laboratori seria una mica més *caos*! I no podria oblidar-me del Ramón. Moltes gràcies per estar al RMN sempre que se't necessitava.

I have been at the University of Nottingham, joining Prof. Simon Woodward group, twice. The first time, when I was an Erasmus Student in 2012. I only have good memories from that time. It was my first research project I was fully involved in, and I really enjoyed working in SW's group. Many thanks Simon. Many thanks for being so grateful and being so open to share your knowledge with others. I really appreciated your advices as a researcher but also as a boss. Also all people I met that during my first time there, specially Martta and Andrej, who had to teach me all about working in a lab. Thank you for being so patient!

A totes aquelles persones de la facultat que en algun moment o altre han estat al meu costat. Emma i Isma, els orgànics *guais*! Jajaja un plaer haver-vos conegut. Que tot us vagi molt bé. Als Químics-Físics, Mulet i Magda. Mulet, ara ja per Florida com a post-doc. Moltíssima sort. Magda, quasi 10 anys veient-nos cada dia, i acabant el doctorat quasi junts. Ha estat un plaer haver compartit tant bons moments junts, la carrera, Riviera Maya, i tots els moments a l'Office mentre us escalfàveu el dinar! Molta sort pel final de la tesi!

Durant tots aquests 5 anys he pogut treballar i conviure amb molta gent, i molts d'ells ja no hi són. Cristina Solé, Jessica Cid, Sabina, Mercè, Jessica Llop. Moltes gràcies per tot, pels bons consells, per la vostra ajuda i per la vostra amistat durant aquests anys! En especial, al Dr Mazuela. Javi, moltes gràcies per tot. Moltes gràcies per ensenyar com moure'm pel laboratori i com treballar. Moltes gràcies per aquells bons moments compartint vitrina. I també a la Dr. Elisabet Mercadé. Te'n recordes d'aquell estiu del 2010? Quan em vas veure tot tímid darrere la taula de la vitrina... qui ho hauria dit que hauríem acabat tenint tant bona amistat. Moltes gràcies pels consells pre-escriptura de tesis, gràcies per ajudar-me i fer-me memòria de tot el *papeleo* de la beca... i per alegrar-me el dia! Ets una gran persona, i espero que tot et vagi molt bé.

Quan vam començar el màster, vam entrar molta gent de cop, amb qui vaig compartir el màster i amb molts ells, el doctorat. Marlene, Cola i Míriam. Moltes gràcies pels bons

moments. Espero que us vagi molt bé. En especial a la Laia, al Gerard i al Xavi. Els 3 ja sou doctors, i em compartit màster i l'aventura del doctorat. Gràcies.

Com he dit abans, durant 5 anys tens la sort de conèixer molta gent, tant al laboratori de Tarragona com a fora de Tarragona. He tingut la sort d'anar d'estada a Dublín i per segon cop a Nottingham i la experiència ha estat brutal.

I would like to thank Prof. Pat Guiry for accepting me in his group at UCD in 2014. Those 3 months there were amazing. I really enjoyed working in Dublin, especially in your group. Many thanks for explaining me all your chemistry and taking care of me, as if I was one of your PhD students. I will never forget that experience. I felt like I were at home. People there were very friendly and very helpful. I would like to thank them all but specially to Dr. Mark Jackson. Many thanks for your patience, for all those emails before coming to Dublin and all those after leaving UCD. Many, many thanks. Now you are already Dr. Jackson, and I am sure you will have a great future!

In 2015 I joined Prof. Simon Woodard group at University of Nottingham for a second time. It was a short period there, but I could really enjoy the group and the chemistry I did there. Many thanks to all people there, all SW group, specially Laurcence and Darren, for being so patience every time I asked them all my doubts. And obviously, to Prof. Woodard, for accepting me for a second time. Many, many thanks.

Als últims d'arribar, però que heu marcat petjada com si ens coneguéssim de tota la vida: Myriam, Nanette, Jordi Royes, Jordi Creus, Marc, Enrico, Thierry, Núria i Toni. Myriam and Nanette, it has been a pleasure to meet you during my thesis. I wish you all the best! Royes! El noi de Fraga i del Madrid...! Un plaer haver-te pogut conèixer. Molta sort pel màster, que sabent com ets, no et farà falta. Que vagi tot molt bé! Jordi Creus! El doctorand rodamón. Espero que vagi molt bé per Bcn, Tgn o Toulouse, ja no sé ben bé per on pares. Molta sort! Marc, el *petit*, el company de taula del seminari, molta sort en la tesi! Enrico, ya estàs en la ultima recta del doctorado. El último *sprint* y ya es tuya! Mucha suerte! Thierry, el noi de Llagostera! Moltes gràcies pel bon humor, les bromes i sobretot pels grans consells de post-doc expert. Moltes gràcies! Que vagi molt bé aquesta nova etapa! Molta sort! Núria, la *Targarina*. Un plaer haver compartit amb tu els últims anys de doctorat. Per tots els dinars a l'*office*, totes les bromes i el bon humor que gastes! La *burilla* arribarà lluny, segur! Molta sort! Antoniuuu! El *phosphitoman*, ha estat un plaer haver compartit setmanes i caps de setmana amb tu. Trobaré a faltar les *rajades* castelleres... Ets un crack i un *cocu*, arribaràs molt lluny, n'estic segur! Que vagi molt bé el que queda de doctorat.

Els *carmencitos* veteranos... Franchurito i Alberto. Franchurito, el *Chico polariod*, el *hipster* del lab... Moltes gràcies pels bons moments, per seguir les meves anades d'olla al seminari o al lab. S'agraeix que algú segueixi la *locura* del moment...i tu donaves molt bé la talla! Que vagi molt bé la recta final! T'aniré seguint per Instagram!

Alberto! El *tio de Burriana*. Ha estat un plaer haver compartit amb tu quasi 4 anys de doctorat. Ets un tio súper pencaire, intel·ligent i segur que arribaràs molt lluny. Que et vagi molt bé el futur!!

Las dos *post-doc/jefas* veteranas. Itziar y Ana B. ¡No sé cuánto hace que llegasteis al grupo, pero parece que hubierais empezado al mismo tiempo que yo! Muchas gracias por los buenos consejos, sobre todo a tí Ana, ya que, en este último tramo de tesis, al igual que a Thierry, no he parado de preguntaros muchas inquietudes, y me las habéis resuelto de sobras. ¡Muchas gracias! ¡Espero veros a las 2 en un futuro no muy lejano, quien sabe dónde, pero preferiría que fuera tomando una buena cerveza!

No voldria semblar sectari, però el volgut deixar el Lab 217 pel final...

Efrem i Fàtima (veus que encara et considero del grup, eehh!)! Els dos us desitjo molta sort. Comenceu ara i us espera un camí dur, però coneixent-vos, us en sortireu de sobres. Fàtima, espero que estigui anant molt bé per Alemanya, i a tu Efrem, molta sort per la URV.

Lutz, the German guy who joint out group for 3 months! Thanks a lot for being so friendly, giving always good advices (related to chemistry or not). We are still in touch after so many years...You know, every time you are free, come to visit me, I will do the same! All the best for you!

Zahra, I met you almost 2 years ago when you joined our group. Since the first day, we have been laughing, making jokes and enjoying all days in the lab. Every time I have needed any help, you were there. And that makes you being a great woman and also scientist. I wish you all the best for your future, here in Spain, in Iran or wherever you go. Good luck!

Maria i Carlota, Carlota i Maria. Maria, ja fa uns anys que compartim laboratori. I queden poques coses que et pugui dir i que no sàpigues. Ha estat un plaer haver treballat colze a colze amb tu. Gràcies per la teva paciència...sé que aguantar-me no és fàcil. Sobretot quan t'anava demanant els resultats dels DFT... jajaja. Espero que et vagi tot molt bé, perquè t'ho mereixes. Ets una gran persona i una gran científica. A tu Carlota et conec des de la carrera. I després vas començar el doctorat i fins ara junts! Ja saps que es un plaer treballar i conviure amb tu. Encara que moltes vegades discutim, perquè als dos ens agrada massa tenir la raó, mai arriben a més aquestes discussions. Et desitjo molta sort pel que et queda de doctorat, i per tota la vida en endavant. Perquè t'ho mereixes. Espero que mai perdem el contacte, i ens anem trobant pel camí (ja saps, et tinc guardada a contactes al mòbil! xD).

I l'ultima qui queda per agrair, a la persona més bona que conec, tant personal com científicament parlant. Margalef, *Jessiquinha, Margalinha*... tots els noms que t'he pogut arribar a dir... Tots dos sabem que els principis son durs...i diria que si no hagués estat per tu, pels ànims i les converses al principi del doctorat, res hauria estat el mateix. Per tots els moments de complicitat, des del 2007 que començàvem la carrera, treballs i presentacions; el màster i el doctorat (incloent la fase *pre*-tesis)...fins al 2016... quasi

10 anys junts! I quins 10 anys! Saps que trobaré moltíssim a faltar aquelles discussions davant la vitrina...amb el permanent en mà, i començant a guixar el vidre (amb lo que ens agrada a nosaltres guixar...). No sé que et deparará el futur, però per aquelles coses del *Karma*, tindràs tot allò que desitgis, perquè ho vals i t'ho mereixes. Espero que ens trobem aviat, que els nostres camins es tornin a creuar, i m'expliquis que tal tot. Molta sort companya d'aventures!

Em queda agrair als amics, a l'*ACA team*, la família que es tria, als amics de tota la vida. Sou collonuts, des de petits junts, i sempre com ara! Gràcies per ser-hi, pels grans moments i totes les estones junts...I les que queden!

I com sempre es diu, deixo el millor pel final. Agrair-vos a vosaltres, papa, mama, Roser i Marc. Moltes gràcies per tot, per aguantar-me quan estava insuportable, per ser-hi sempre que us he necessitat, encara que no ho demanés. Gràcies per fer-me la vida més fàcil durant aquests 5 anys tant complicats i d'horaris impossibles. Una gran part d'aquesta tesi és gràcies a vosaltres. Moltes gràcies!

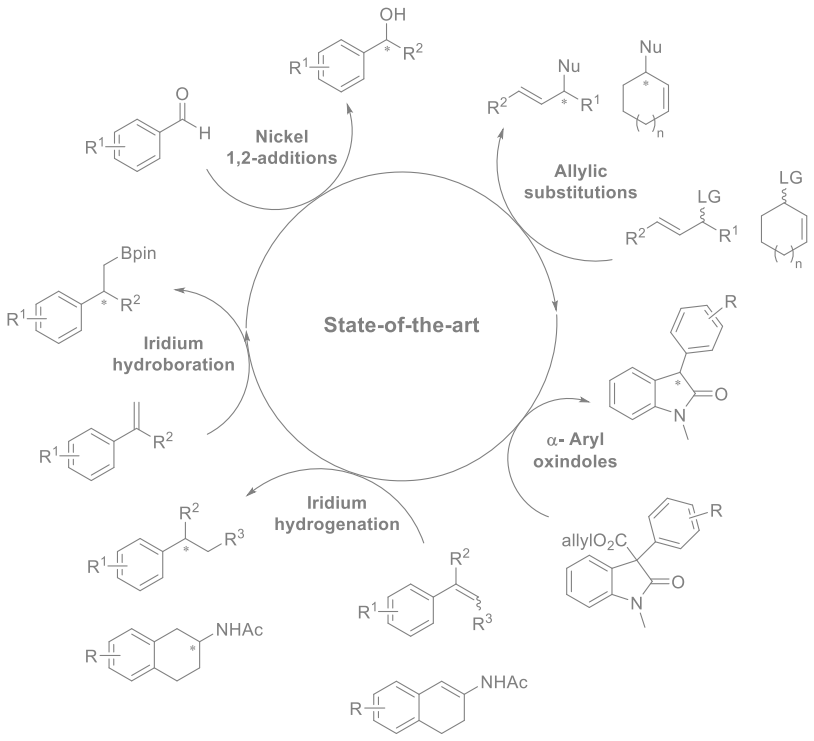
Agrair també al Minsterio de Ciencia e Innovación per atorgar-me la beca FPI dins del projecte CTQ2010-15835. D'igual manera, agrair al Ministeri Espanyol per la beca CTQ2013–40568, a la Generalitat de Catalunya per la beca 2014SGR670 i la Fundació ICREA per als premis atorgats als meus supervisors, Oscar Pàmies i Montserrat Diéguez, dels quals el grup se n'ha beneficiat.

Moltes gràcies! Thank you very much!

Table of Contents

Chapter 1

Introduction



UNIVERSITAT ROVIRA I VIRGILI
DESIGN OF TAILOR-MADE CHIRAL LIGAND LIBRARIES FOR C-X BOND FORMING REACTIONS. STUDY OF THE KEY INTERMEDIATES BY NMR AND DFT
Marc Magre Rosich

1. Introduction

Fine chemicals and natural product chemistry rely on enantiomerically pure compounds. The growing demand on these compounds has stimulated the research for efficient asymmetric processes, which provided high activity and selectivity with minimum energy consumption and minimum generation of byproducts.[1]

In drugs and also in natural product chemistry, one enantiomer has the desired properties whereas the opposite enantiomer is either inactive or has undesirable side-effects. The discovery of synthetic routes for obtaining enantiomerically pure compounds is therefore one of the most pursued goals in chemistry. Particularly, asymmetric catalysis is one of the most attractive approach because it can provide very high reactivity and selectivity.[1] Usually, with this strategy, a transition-metal complex containing a chiral ligand catalyzes the transformation of a prochiral substrate to one enantiomer as major product. The importance of asymmetric catalysis is reflected by the many publications in this field and the Nobel Prize award in 2001 to W. S. Knowles, K. B. Sharpless and R. Noyori and in 2010 to E. Negishi, R. F. Heck and A. Suzuki.[1]

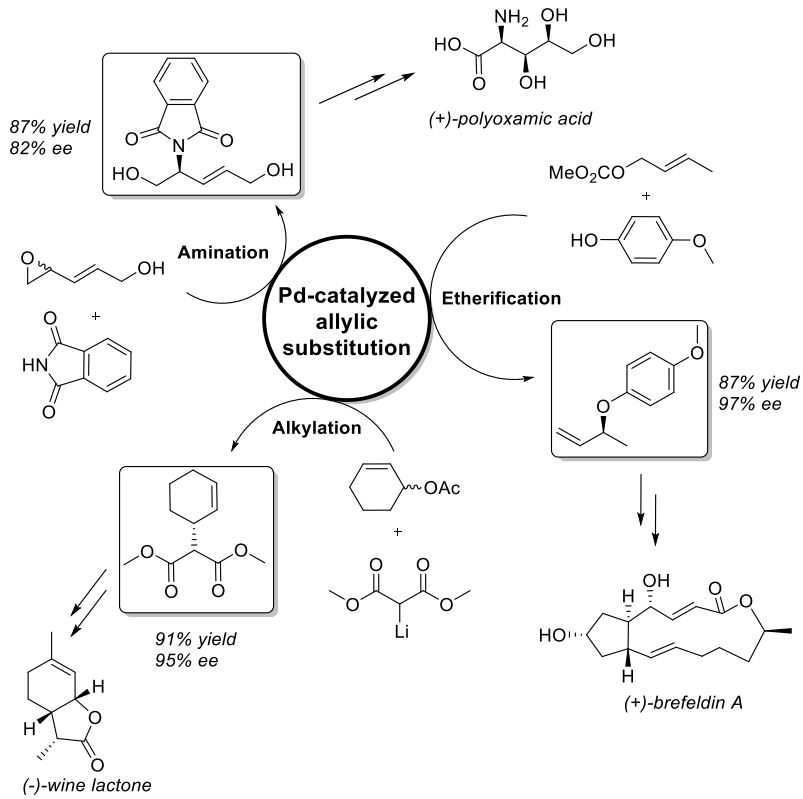
To reach high levels of reactivity and selectivity, several reaction parameters need to be optimized. The design of a chiral ligand is perhaps one of the most crucial step. In this respect, the use of highly modular ligand scaffolds is desirable, because it facilitates the synthesis and screening of series of chiral ligands, known as ligand libraries, in the search for high activities and selectivities for each particular asymmetric reaction. One of the simplest way to obtain chiral ligands is to transform or derivatize natural chiral compounds (chiral pool), thus making tedious optical-resolution procedures unnecessary.[1]

In this context, this thesis focuses on the development of new chiral ligand libraries, the synthesis of new chiral catalysts and their application in the Pd- and Cu-catalyzed asymmetric allylic substitution, Pd-catalyzed decarboxylative protonation of oxindoles, Ir-catalyzed asymmetric hydrogenation, Ir-catalyzed asymmetric hydroboration and Ni-1,2-addition of organoaluminum to aldehydes. In following sections, we describe the background of each asymmetric catalytic reaction studied in this thesis.

1.1. Asymmetric allylic substitution reactions

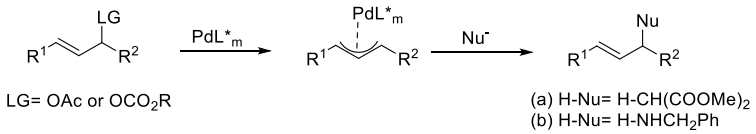
1.1.1. Pd-catalyzed asymmetric allylic substitution

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 (Scheme 1.1).[1,2]



Scheme 1.1. Pd-catalyzed allylic substitution for the synthesis of natural products.

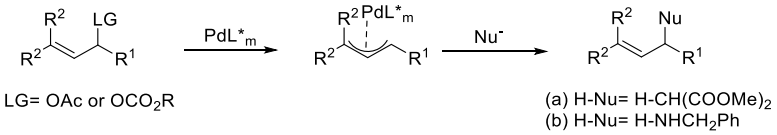
The Pd-catalyzed allylic substitution consists in the reaction between an allylic racemic substrate which contains a leaving group (such as acetate or carbonate) and a nucleophile (usually carbanion or amine). Then, a nucleophilic substitution takes place and an either new carbon-carbon or carbon-nitrogen bond is generated (Scheme 1.2).[2]



Scheme 1.2. Asymmetric allylic substitution reaction when symmetrical substrates are used: (a) dimethyl malonate (alkylation) and (b) benzylamine (amination).

When symmetric substrate is employed (Scheme 1.2), the reaction proceeds via symmetrical π-allyl intermediate. In this case, the enantioselectivity will be determined by the regioselectivity of the nucleophilic attack and therefore, depends on the ability of the chiral ligand (chiral Pd-complex) to differentiate between the two allyl termini.[2]

When racemic or prochiral substrate with two identical germinal substituents at one of the allyl termini (Scheme 1.3) reacts via the π-ally intermediate, it can isomerize via the well-established π–σ–π mechanism.[2] In this case, enantioselection can occur either in the ionization step, leading to the allyl intermediate, or in the nucleophilic addition. For these kind of substrates, not only the enantioselectivity of the process needs to be controlled, but also the regioselectivity is a problem because a mixture of regioisomers may be obtained.[2]



Scheme 1.3. Asymmetric allylic substitution reaction when unsymmetrical substrates are used: (a) dimethyl malonate (alkylation) and (b) benzylamine (amination).

In this context, most Pd-catalysts developed to date favor the nucleophilic attack towards the less substituted carbon, attaining the linear product. Therefore, the synthesis of highly regio- and enantioselective Pd-catalysts is still a challenge. In contrast to Pd, there are other metal-based catalysts such as Ir-, Ru-, W-, Mo-catalysts that provide very high selectivity towards the attack at the most substituted carbon, giving the desired branched product.[2]

The allylic substrates tested in this process can be linear or cyclic although *rac*-1,3-diphenylprop-1-enyl acetate **S1** is considered as the benchmark substrate for testing the new catalytic systems (Figure 1.1).

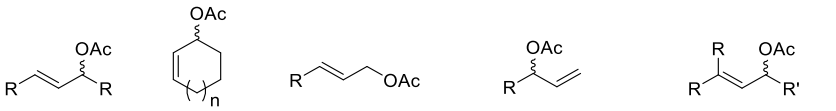


Figure 1.1. The most representative substrates for enantioselective allylic substitution.

Regarding the metal source, Pd is the most extensively used transition metal. A wide range of carbon soft nucleophiles (those derived from conjugate acids with pka <25) have been employed in this process. Besides dimethyl malonate, which has become the standard nucleophile for testing proposes, many other stabilized carbanions bearing carbonyl, sulfone, nitrile or nitro groups have been also used.[2] Amination has been also extensively studied (being benzylamine the benchmark N-nucleophile) but Pd-catalyzed allylic etherification, which has been less studied (mostly using benzylic alcohols as O-nucleophiles), is still a challenge. There are less examples of enantioselective reactions

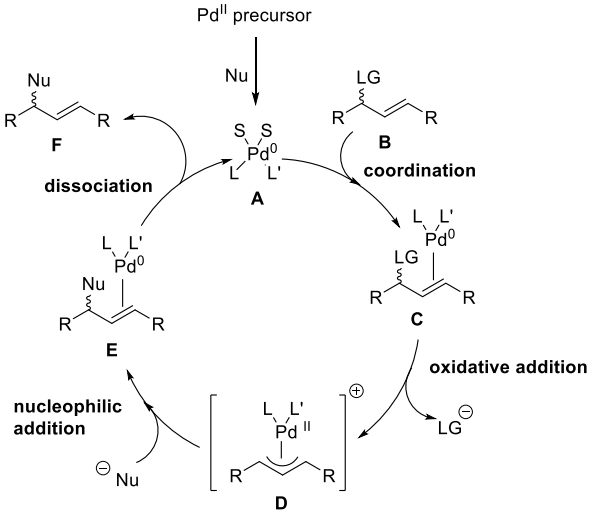
with non-stabilized nucleophiles such as diorganozinc or Grignard reagents and those are mainly limited to the use of Cu-catalysts[3] (Section 1.1.2).

1.1.1.1. The 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**.[2] The mechanism for palladium-catalyzed allylic substitution involves 4 steps (Scheme 1.4). 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) species can be used as catalyst 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.[2] 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 to positions that are susceptible to nucleophilic attack (two terminal carbons of the allyl system). This attack will be controlled by the 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.[2]

As it has been mentioned before, 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 1.2).



Scheme 1.4. Catalytic cycle for Pd-catalyzed allylic substitution reaction.

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

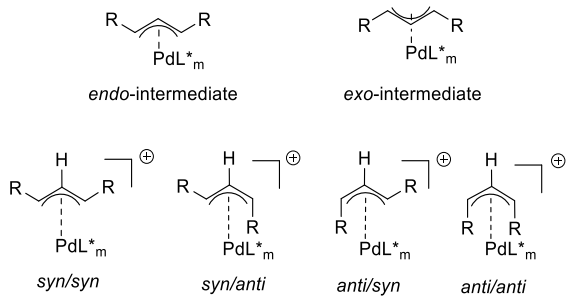


Figure 1.2. Possible isomers adopted by π-allyl palladium complex **D**.

Both oxidative addition and nucleophilic attack take place stereoselectively with inversion of configuration. In that case, if the intermediate **D** does not undergo any isomerization 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.

1.1.1.2. Ligands

Most of the successful ligands developed for this process use either C_2-symmetrical scaffolds to restrict the number of diastereomeric transition states and/or the ability of

the ligand to direct the approach to one of the allylic terminal atoms, by means of either a secondary ligand-nucleophile interaction; or the use of heterodonor ligands to provide an electronic differentiation of the two allylic terminal carbons.

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 **1** (Figure 1.3). 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.[4]

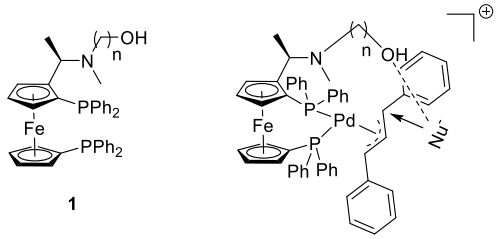


Figure 1.3. Ferrocene-based phosphine. Example of a directing group ligand.

In 2009, P.-O. Norrby in conjunction with G. C. Lloyd-Jones[5] reported a DFT calculation analysis which determined that the 13-membered chelate ring of Pd-**2** not only makes a chiral pocked where the substrate is embedded but also a secondary interaction which directs the nucleophilic attack (Figure 1.4).[6] 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 selectivity. This hydrogen-bond directed delivery of the nucleophile has precedent in the elegant design of chiral ferrocene ligand **1** developed by Hayashi and Ito (Figure 1.3).

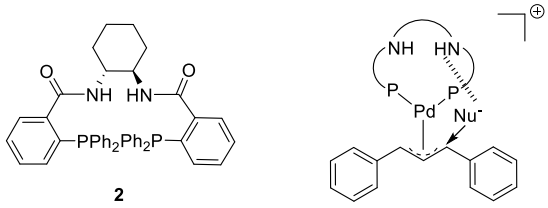


Figure 1.4. Secondary interections of Trost ligand **2** reported by Norrby and Loyd-Jones.

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.

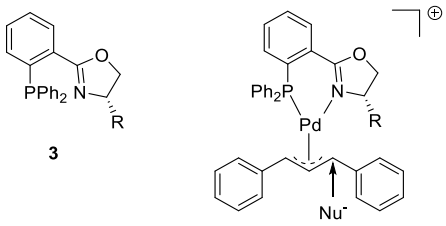


Figure 1.5. Example of electronic differentiation ligand. PHOX ligand.

The first ligand based on this strategy was the phosphine-oxazoline PHOX ligand **3**, developed by Pfaltz *et al.* (Figure 1.5).[7]

In this context, this project will be focused in the third strategy, the application of heterodonor ligands to create electronic differentiation between both allylic carbons, more precisely in the application of P,N ligand 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 [8] and phosphorus-sulfoxide[9] 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.[10] 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.[10]

The first successfully applied P,N-ligand to Pd-allylic substitution reaction was the phosphine-oxazoline PHOX ligand **3** (R= Me, Ph, ^{i}Pr, ^{t}Bu), developed simultaneously by Pfaltz, Helmchen and Williams.[7] Unfortunately, these kind of ligands only provided excellent enantioselectivities when bulky benchmark substrate **S1** was used. When less bulky dimethylated substrate **S2** or cyclic substrate **S3** were studied, enantioselectivities decreased up to 71% ee or to racemic mixtures. After that pioneering work, several modifications of that PHOX ligands have been made: replacing phosphine moiety by more electronically deficient phosphinite or phosphite and also replacing oxazolines by other sp^2- or sp^3-nitrogen donor groups. Next, some of the most successful P,N-ligands applied in the Pd-allylic substitution reaction will be summarized.

1.1.1.3. Phosphorus- sp^2-nitrogen ligands

The most widely used phosphorus-sp^2-nitrogen ligands have been phosphine-oxazoline. Inspired by work done by Pfaltz, Helmchen and Williams[7], almost all of them are

variations of that phosphine-oxazoline **3** and to lesser extend phosphinite- and phosphite-oxazoline ligands.

Phosphorus-oxazoline ligands

Phosphine-oxazoline ligands

In 1998, Kunz and coworkers developed phosphine-oxazoline **4** (Figure 1.6) derived from D-glucosamine.[11] Although high conversions and enantioselectivities were obtained with the benchmark substrate **S1** (ee's up to 98%) only moderate enantioselectivities were obtained for unhindered **S2** (ee's up to 69%). Ligand **4** was also tested in Pd-allylic alkylation of trisubstituted substrate **S8**, providing good enantioselectivities (ee's up to 88%).

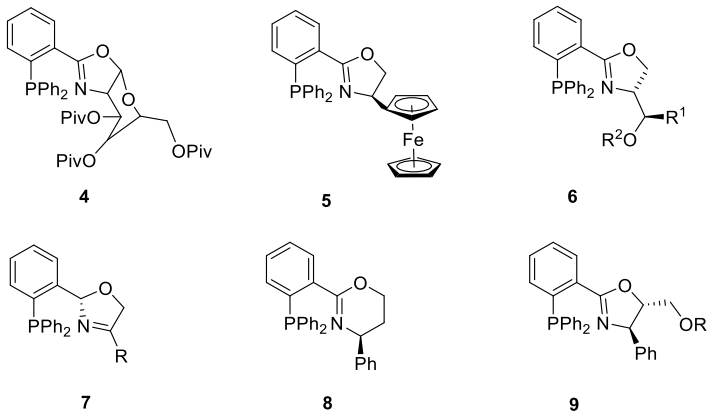
Moyano *et al.* introduced a ferrocenyl substituent on the oxazoline substituent of the PHOX ligand.[12] Ligand **5** provided comparable enantioselectivities to those obtained by PHOX ligands **3** but its activity was much lower (7 days for 63% yield). This ligand was also tested for unhindered **S2** and cyclic **S3** substrates but enantioselectivities were poor (44% ee and 12% ee respectively).

Moberg and coworkers[13] studied the effect of introducing a new stereogenic center on the oxazoline ring (ligand **6** R^1= Me, Ph; R^2= H, Me). Similar high enantioselectivities for model substrate **S1** were obtained compared to PHOX **3** results, but the allylic substitution of cyclic substrate **S3** were higher but still low (ee's up to 59%).

Conformationally rigid ligand **7**, developed by Zhang and coworkers in 2005, provided excellent results in terms of enantioselectivity (ee's up to 98%) for hindered **S1** but low enantioselectivities for unhindered **S3** (ee's up to 36%).[14]

Zehnder *et al.* studied the effect of replacing oxazoline by a oxazine ring (ligand **8**). The result for the model substrate **S1** were comparable to those using PHOX ligand **3** but activities were much lower.[15]

In 2007, Pericàs and Gómez groups[16] synthesized ligand **9** (R= Me, Bn, $CHPh_2$, CPh_3, CH_2CH_2OMe) which presents two stereocentres on the oxazoline moiety. Those ligands were successfully applied in the Pd-allylic alkylation of standard substrate **S1** in high enantioselectivity (97% ee). Less sterically hindered substrates **S2** and cyclic **S3** provided lower enantioselectivities (ee's up to 43 and 56% respectively). Ligand **9** provided excellent enantioinduction when trisubstituted substrate **S11** was studied (ee's up to 94%) as well as high regio- and enantioselectivity for monosubstituted substrate **S7** and **S9** (93% towards branched isomer and 82% ee).



4 **5** **6**

7 **8** **9**

Figure 1.6. Selected phosphine-oxazoline type ligands. Study of the effect of oxazoline ring.

A part from modifying oxazoline ring of PHOX-type ligands, the modification of the ligand backbone has also been studied (Figure 1.7).

Tieze *et al.* replaced the benzene ring by a benzothiophene or benzofuran moiety (ligand **10**, X= S, O)[17], but unfortunately these modifications provided somewhat lower enantioselectivities (ee's up to 97%) than PHOX ligand **3**. Later, Iamamoto's group replaced the benzene ring by a methylene bridge, introducing also a stereogenic phosphine with a wide range of alkyl- and aryl-substituents on the phosphine (ligand **11**, R^1= Cy, ^{t}Bu, Ph, 1-adamanthyl, CpFeCp; R^2= Me, Cy; R^3= H, Me, ^{i}Pr; R^4= H, Me, ^{i}Pr, tBu).[18] These modifications had a negative effect on both enantioselectivity (ee's up to 96%) and activity.

The next modification was introducing a ferrocene moiety (ligand **12**, R^1= H, Me, Bn; R^2= H, Me, ^{t}Bu, Bn).[19] This kind of ligands provided excellent enantioselectivities for alkylation of model substrate **S1** (ee's up to 99%).

Also the effect of variating the positions of the phosphine moiety has been studied (ligand **13**, R^1=^{i}Pr, ^{t}Bu; R^2= H, Me, Bn, $SiMe_3$). Results were similar to those provided by ligand **12**.[20] All authors agreed that planar chirality was decisive to control both absolute configuration and enantioselectivity.

Another ferrocenyl-based phosphine-oxazoline ligand **14** (Ar= *p*-MeO, *p*-CF_3, 3,5-CF_3, R= ^{i}Pr, ^{t}Bu) has been successfully applied in the allylic alkylation of cyclic substrates **S3**-**S5** providing excellent enantioselectivities (ee's up to 91%).

Dai *et al.* synthesized ferrocene phosphine-oxazoline ligand **15** (R= ^{i}Pr, Bn, Ph, ^{t}Bu) in the allylic alkylation and amination of monosubstituted substrates **S8**-**S9**. Excellent regio- and enantioselectivities were achieved (99% branched selectivity and 97% ee and 96% towards branched isomer and 97% ee, respectively).[21]

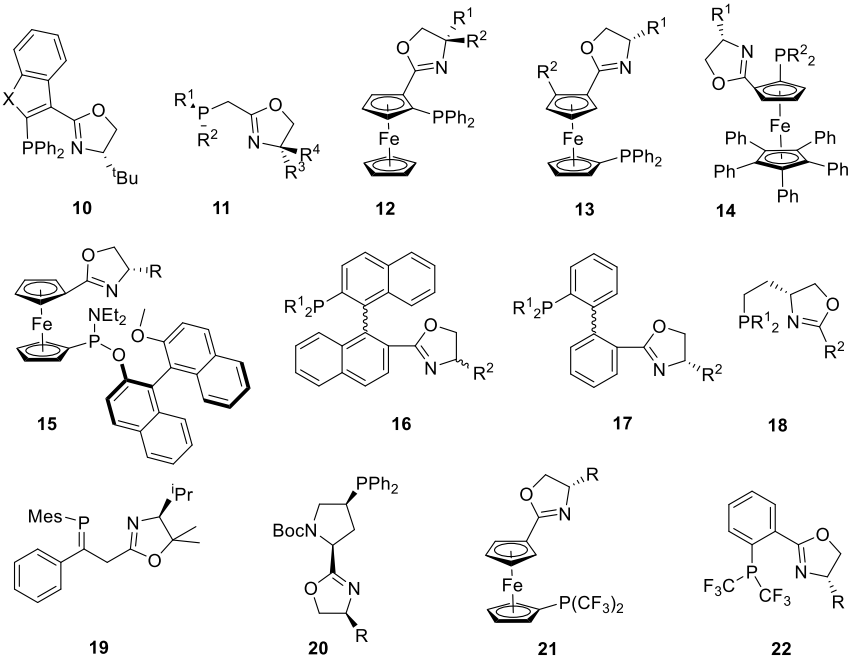


Figure 1.7. Selected phosphine-oxazoline type ligands. Study of the effect of ligand backbone.

Groups of Ikeda and Pregosin developed ligand **16** (R^1= Ph, 3,5-Me_2-Ph; R^2= ^{i}Pr, ^{t}Bu) by introducing a enantiomerically pure binaphthyl moiety.[22] This ligand provided lower enantioselectivities than PHOX **3** (ee's up to 97%). Absolut configuration of final product was determined by the configuration of the binaphthyl moiety.

Zang *et al.* developed phosphine-oxazoline **17**. This ligand presented an axial-unfixed biphenyl backbone. Once it coordinated to Pd, only (*S*)^{ax} conformer was present in solution. This ligand provided 92% ee for standard allylic alkylation using **S1** and dimethylmalonate as nucleophile.[23]

Burgess *et al.* reported the application of ligand **18** (R^1= Ph, *o*Tol; R^2= Me, ^{t}Bu, 1-adamantyl, CPh_3).[24] This kind of ligands provided excellent enantioselectivities for model substrate **S1** (ee's up to 98%) and also promising enantioselectivities for unhindered substrate **S2** (ee's up to 80%) and cyclic substrate **S3** (ee's up to 79%).

Another modification was carried by Gates *et al.* who applied phosphaalkene-oxazoline **19** in allylic alkylation of model substrate **S1** and wide range of different carbon nucleophiles, achieving enantioselectivities up to 92%.[25] Those enantiopure products were derivatized to cycloalkanes and other synthetically interesting products without losing enantioselectivity.

Gilberston *et al.* reported a series of proline-based phosphine-oxazoline **20** (R= Ph, ^{i}Pr, ^{t}Bu, Bn). Those ligands were successfully applied in the allylic alkylation of unhindered

cyclic substrates **S3**-**S5**. Enantioselectivities up to 96% were obtained for **S4** and the bigger the cycle was, the lower enantioselectivities were obtained.[26]

The last two interesting modifications (**21** and **22**) were performed in the phosphine moiety, by replacing arylphosphine by CF_3-phosphine. Those π–acceptor ligands were designed for monosubstituted substrates and they provided excellent regio- and enantioselectivities[27,28]. In this respect, You *et al.* synthesized **21** (R= ^{i}Pr, Bn, Ph, ^{t}Bu), based on a ferrocenyl backbone. It provided excellent regioselectivities (99% and 96% towards branched isomer) for **S9** and for less sterically hindered **S8**, respectively. In both cases good to excellent enantioselectivities were achieved (ee's up to 92% for **S9** and 88% for **S8**). [27] Shen *et al.* designed **22** (R= ^{t}Bu, Ph, Bn, ^{i}Pr), an electronic modification of PHOX ligand **3**. Those ligands provided excellent results in terms of regio- and enantioselectivity for monosubstituted substrate **S6** (96% towards branched product and 94% ee) and **S7** (92% towards branched isomer and 93% ee). [28]

Phosphinite-oxazoline ligands

Although numerous phosphine-oxazoline ligands have been successfully applied in several metal-catalyzed processes, only two families of phosphinite-oxazoline ligands have been successfully applied in the Pd-allylic alkylation (Figure 1.8).

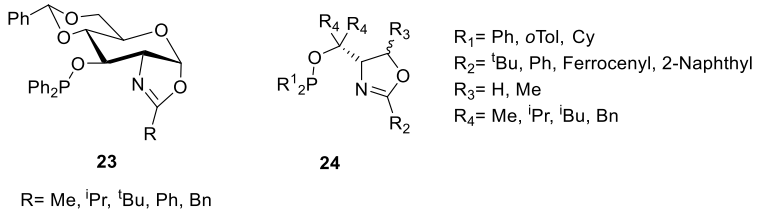


Figure 1.8. Phosphinite-oxazoline ligands **23** and **24** applied in Pd-allylic alkylation.

First, Uemura and coworkers [29] reported the synthesis of pyranoside phosphinite-oxazoline ligand **23**. These ligands provided high enantioselectivities for model substrate **S1** (ee's up to 96%) but discreet enantioselectivities for unhindered **S2** and cyclic **S3** substrates (ee's up to 57% and 74%, respectively).

The second family of phosphinite-oxazoline based ligands is **24**. These phosphinite-oxazoline **24** provided somewhat lower enantioselectivity than their phosphine analogues **18** (ee's up to 96%).[30]

Phosphite-oxazoline ligands

The first successful application of phosphite-oxazoline was achieved by Pfaltz *et al.* in 1997, who applied ligand **25** (Figure 1.9) in the Pd-allylic alkylation.[31] This ligand was

design to overcome the problem of regioselectivity in the allylic alkylation of monosubstituted linear substrates **S6**-**S9**. They found that both regio- and enantioselectivity were affected by the substituents on the oxazoline and by the substituents/configuration of the biaryl phosphite moiety.

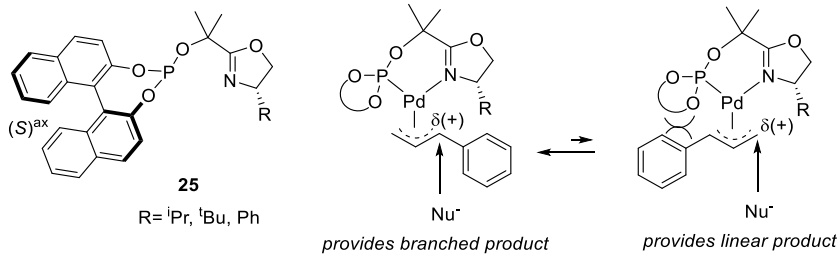


Figure 1.9. Phosphite-oxazoline **25** and its effect on regioselectivity.

An excellent regioselectivity (95% toward branched product) and enantioselectivities (up to 94%) were achieved. The success of this kind of ligand is due to the combination of two ligand parameters that direct the nucleophilic attack to the most substituted allyl carbon (Figure 1.9).[31] The first parameter is the π-acceptor ability of the phosphite moiety, which decreases the electron density of the allylic terminal carbon atom via *trans* influence, making the electrondensity difference between both allylic carbons higher. The second one is the introduction of a bulky biaryl-phosphite moiety which switches the equilibrium towards the desired Pd-π-allyl intermediate, which has the bulky substituent of the allyl substrate in the opposite side of the phosphite moiety, favoring the nucleophilic attack to the most substituted carbon *trans* to the phosphite moiety (Figure 1.9). Those factors made that phosphite-oxazoline **25** provided high levels of regioselectivity. Despite this success, low enantioselectivities were obtained for disubstituted hindered **S1** and unhindered **S2** substrates.

The same group also used TADDOL-based phosphite[32] **26** (R= ^{i}Pr, ^{t}Bu, Ph) and the same results were obtained: high regio- and enantioselectivities for monosubstituted substrates (>99% towards branched product and ee's up to 99%) but low enantioselectivities (ee's up to 56%) for disubstituted substrates **S1** and **S2**.

Gladiali *et al.* described the application of chiral (*S*)-binaphthalene-core ligands **28**. Unfortunately, moderate enantioselectivities were achieved using model substrate **S1** (ee's up to 43%).[33]

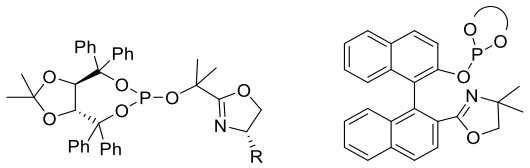


Figure 1.10. Phosphite-oxazolines **26** and **27** developed by Pfaltz and Gladiali, respectively.

In order to find a more versatile phosphite-oxazoline ligand, which could overcome problems of enantioselectivity for disubstituted substrates **S1**-**S2** while keeping high selectivities (both regio- and enantioselectivity) for monosubstituted substrates **S6**-**S9**, Diéguez *et al.* took phosphine-oxazoline PHOX **3** and replaced phosphine by a biaryl phosphite moiety (ligand **28**, R= Et, ^{i}Pr, ^{t}Bu, Ph). The introduction the cheap and simple biphenyl moieties has 3 main benefits:[34]

a) The activities increase thanks to the π-acceptor capacity of the biaryl phosphite moiety (TOF's > 2400).
b) High enantioselectivities (ee's up to 99%) for hindered **S1** and unhindered **S2** disubstituted, cyclic **S3**-**S5** and monosubstituted substrates **S6**-**S9** using dimethyl malonate as nucleophile were obtained.
c) Excellent regioselectivity, (up to 99% towards to the desired branched product), were obtained.

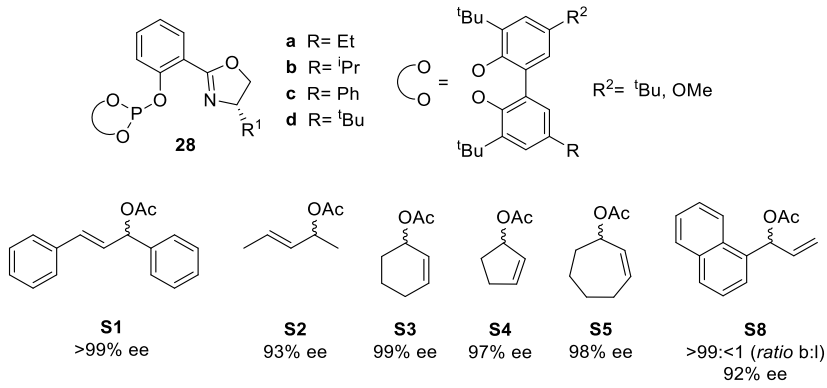


Figure 1.11. Pd-catalyzed allylic alkylation using phosphite-oxazoline **28**.

These ligands **28** showed higher versatility than their phosphine-oxazoline PHOX **3** analogues.[34] After these significant results, more phosphite-oxazoline have been developed (Figure 1.12).

Diéguez *et al.* applied pyranoside phosphite-oxazoline **29** (R= Me, ^{i}Pr, ^{t}Bu, Ph, Bn) a modification of Uemura's phosphinite-oxazoline **20** (Figure 1.8).[35] Replacing phosphinite

by phosphite moiety higher enantioselectivities were achieved: for hindered **S1** (ee's up to 99%), unhindered **S2** (ee's up to 81%) and cyclic **S3** (ee's up to 45%) and **S5** (ee's up to 95%). Also high regio- and enantioselectivities were achieved in monosubstituted substrates (80% regioselectivity and 90% ee).

The same group also applied ligand **30** (R^1= ^{t}Bu, Ph, *o*Tol, *p*Tol, 2,6-Me_2-Ph; R^2= H, Me, R^3= H, Me, Ph), a modification of **24** (Figure 1.8) by replacing phosphinite by a phosphite moiety. Excellent regio- and enantioselectivities were achieved for a wide range of disubstituted (**S1** and **S2** ee's up to 96%), cyclic (**S3** and **S5** ee's up to 83%) and monosubstituted substrates (>95% regioselectivity and 96% enantioselectivity).[36]

All these examples corroborate the fact that these Pd-phosphite-oxazoline Pd-**28**, Pd-**29** and Pd-**30** catalysts provide higher enantioselectivity than their phosphine/phosphinite analogues.[10]

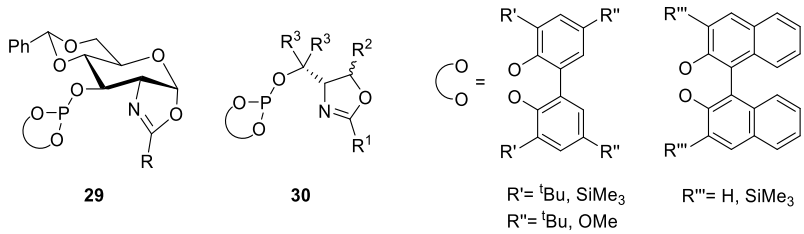


Figure 1.12. Representative phosphite-oxazoline ligands applied in Pd-allylic substitution.

Phosphorus-other sp^2-nitrogen ligands

Although most of P,N ligands applied in the palladium allylic substitution contain an oxazoline as nitrogen donor group, heterodonor ligands with other sp^2-nitrogen donor groups than oxazoline have been also applied. Next, the most important phosphorus-other sp^2-nitrogen ligands will be presented.

Phosphine-based ligands

Among other sp^2-nitrogen ligands, phosphine-imine based ligands are the most applied (Figure 1.13). In this context, Chung *et al*. reported ligand **31** (R^1= Me, Ph; R^2= H, Me, Ph; R^3= H, Me) which were successfully applied for the model substrate **S1** (ee's >98%).[37] Later, the same author developed a cyclopentadiene manganese ligands **32**[38] (R= ^{t}Bu, Ph, Bn, $CHPh_2$) and ferrocene derivatives **33** (R^1= Me, Cy, Ph; R^2= H, *p*-OMe, *p*-Cl, *p*-Me, *p*-NO_2, *m*-MeO, *m*-Cl, *m*-NO_2, *o*-NO_2).[39] Those ligands provided excellent results, which were comparable to those achieved with ligand **31**. Attar's group developed a second generation of ferrocene-imine ligands **34** obtaining somewhat lower enantioselectivities than previous ligands **31-33** (ee's up to 94%).[40]

Eycken *et al.* synthesized phosphine-imine **35** (R= H, *p*-Cl, *p*-Br) and they were applied in the allylic alkylation of benchmark substrate **S1**. Excellent enantioselectivities (ee's up to 99%) were achieved with a wide range of carbon nucleophiles. Less sterically hindered substrate **S2** and cyclic substrates **S3**-**S5** were also studied, achieving moderate to excellent enantioselectivities (74-90% ee). [41]

Iwao *et al.* reported the synthesis of ferrocenyl-based imino-phosphine ligand **36** and its application in the Pd-allylic alkylation, achieving enantioselectivities up to 97% for benchmark substrate **S1**. Using DFT calculations, authors could determine that *exo*-isomer was more stable than *endo*-isomer, predicting the absolute configuration of the outcome product.[42]

In 2012, Jiang *et al.* developed phosphine-imine **37** (R= Ph, ^{i}Pr) with Evan's auxiliary as chiral moiety. Moderate to good enantioselectivities (ee's up to 87%) were achieved using **S1** with wide range of carbon nucleophiles. [43]

Xu *et al.* applied phosphine-imine **38** with a binaphthol as chiral moiety. Excellent enantio- and diastereoselectivities were achieved with a wide range of cianoesters derived from dimethyl malonate (99:1 dr and 99% ee) with benchmark substrate **S1** and different electronic modifications. [44]

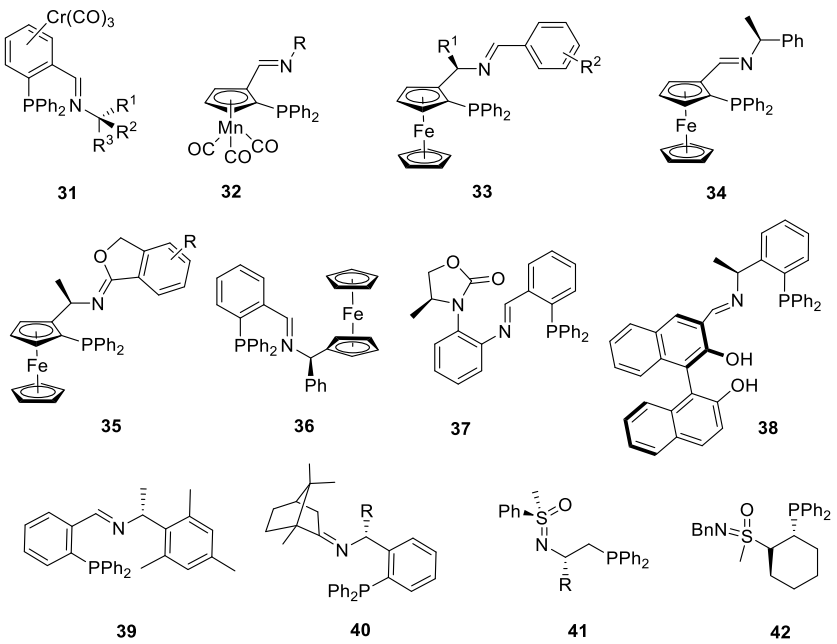


Figure 1.13. Representative phosphine-imine ligands.

Another successfully applied phosphine-other sp^2-nitrogen ligand is phosphine-imine **39** which provided excellent enantioselectivities (ee's up to 94%) for a wide range of α-substituted dimethyl malonate-based nucleophiles.[45]

Very recently, Chen and Xu applied a *D*-Camphor-based phosphine-imine **40** (R= Me, Et).[46] Authors found that the presence of *D*-Camphor as well as a methyl as substituent on the chiral imine were beneficial for the catalyst performance. Excellent enantioselectivities were achieved using **S1** and several modifications of that diphenylated substrate. Authors could alkylate a broad range of dialkyl malonates and also α-substituted dialkyl malonates, attaining enantioselectivities up to >99% ee. They were also able to extend the nucleophile scope, achieving excellent enantioselectivities (ee's up to >99%) for the allylic amination of a wide range of N-nucleophiles (aryl, benzyl- and alkyl-amines). Moreover, ligand **40** provided enantioselectivities up to >99% in a wide range of benzyl- and alkylalcohols, providing excellent results for the allylic etherification in terms of both enantioselectivities and nucleophile versatility.

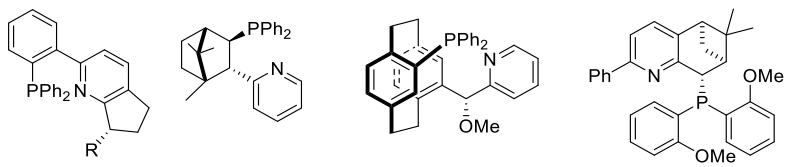
Reggelin *et al.*[47] designed phosphine-sulfoximine **41**. This ligand provided excellent enantioselectivities for **S1** (ee's up to 95%) but low enantioinduction for cyclic **S3** (ee's up to 35%). Regarding sulfoximine-based ligands, Gais *et al.* developed ligand **42** and its application in allylic alkylation of benchmark substrate **S1**, achieving enantioselectivities up to 97%.[48]

A part from phosphine-imine, phosphine-pyridine have emerged as an alternative to imines due to being more robust.[49] However, only good enantioselectivities have been achieved when benchmark substrate **S1** was used.

Ligands **43**[50] and **44**[51] (R= Me, ^{i}Pr, ^{t}Bu) provided ee's up to 96%.

Jiang *et al.* prepared a pyridine ligand **45** based on [2.2]Paracyclophane backbone. This ligand was applied in the allylic alkylation of model substrate **S1** and dimethylmalonate as nucleophile, achieving enantioselectivities up to 97%. [52]

Li *et al.* synthesized tetrahydroquinone-based phosphine-pyridine ligand **46** and it was successfully applied in the allylic alkylation of model substrate **S1**, attaining enantioselectivities up to 95% using a wide range of dialkyl malonates as nucleophiles.[53]



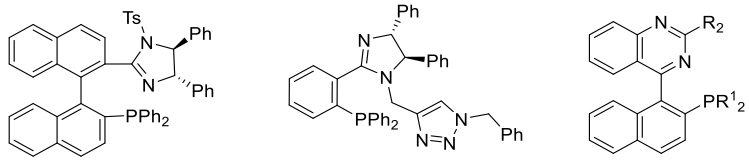
43 **44** **45** **46**

Figure 1.14. Representative phosphine-pyridine ligands.

Another sp^2-nitrogen donor group is imidazole, present as N-donor moiety in ligand **47**, providing excellent enantioselectivity using model substrate **S1** (ee's up to 98%).[54]

In 2011, Pericàs and Claver groups[55] presented a phosphine-remote triazole **48**. By DFT calculations they determined that the most stable Pd-**48** complex was the one in which the coordinative nitrogen moiety was not the imidazole but the triazole moiety. Ligand

48 provided excellent enantioselectivities for benchmark substrate **S1** in the alkylation using dimethylmalonate as nucleophile (ee's up to 99%) and in the allylic amination using a wide variety of N-nucleophiles, achieving excellent enantioselectivities in **S1** (ee's up to 99%).



47 48 49

Figure 1.15. Representative phosphine-other sp^2-nitrogen ligands.

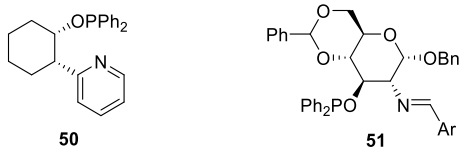
Guiry *et al.* designed a series of quinazolinap ligands **49** (R_1= Ph, 3,5-xylyl; R_2= Adm, *c*-Bu, ^{i}Pr). Authors found that the substituent on the 3-position of the quinazoline as well as the substituents on the phosphine moiety have an important role in tuning the reactivity in catalysis. They determined that enantioselectivity decreased when bulky substituents such as adamantly group were present in the quinazoline moiety. Excellent enantioselectivities were achieved when substituent in position 3 was an ^{i}Pr (ee's up to 92% using benchmark substrate **S1**).[56]

Phosphinite-based ligands

Only 2 phosphinite-other sp^2-nitrogen ligands have been successfully applied in the Pd-allylic alkylation.

Zhou *et al.* designed a cyclohexyl-based phosphinite-pyridine ligand **50**, achieving excellent enantioselectivities when standard substrate **S1** was studied (ee's up to 95%).[57]

In 2010, Zhang *et al.* reported a family of carbohydrate-based imino-phosphinite ligand **51** (Ar= Ph, *p*-Cl, *p*-OMe, *p*-NO_2, *o*-CF_3, *m*-Cl, *m*-NO_2), which were successfully applied in the Pd-allylic substitution of **S1** with different C- and N-nucleophiles, achieving enantioselectivities up to 92%.[58]



50 51

Figure 1.16. Phosphinite -based other sp^2-nitrogen ligands.

Phosphite-based ligands

Only three groups have successfully reported the application of phosphite-other sp^2-nitrogen ligands (Figure 1.17).

Gavrilov *et al.*[59] developed P-chiral ferroncenyl imino diaminophosphite ligand **52** and its application in Pd-allylic substitution reaction of model substrate **S1** achieving enantioselectivities up to 98%. The same group also applied phosphite-imine **53** in the allylic alkylation of model substrate **S1**, achieving enantioselectivities up to 94% ee.[60]

The second group which have successfully applied phosphite-based other sp^2-nitrogen ligands is Li *et al.* They applied phosphite-pyridine ligand **54** in the benchmark substrate **S1** achieving enantioselectivities up to 95% ee. They also applied this ligand in the allylic alkylation of cyclic **S3**, but enantioselectivities decreased up to 80% ee.[61]

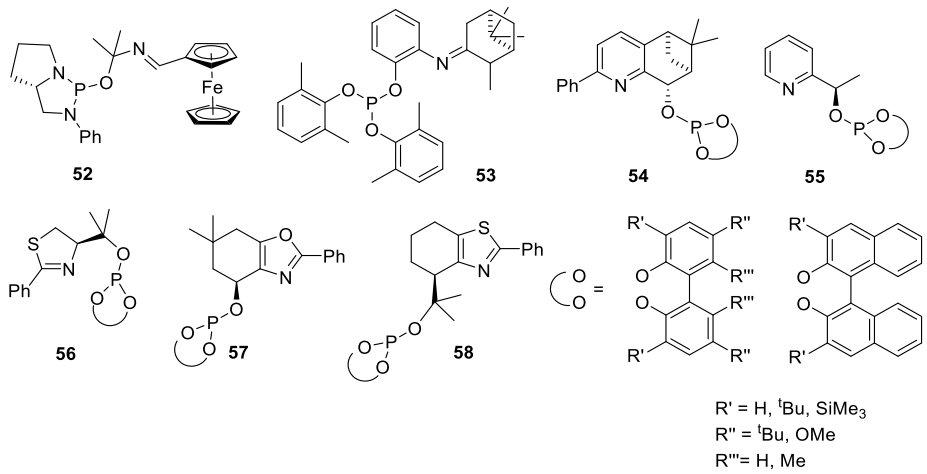


Figure 1.17. Representative phosphite-other sp^2-nitrogen ligands.

The other group who have reported the application of phosphite-other sp^2-nitrogen ligands is Diéguez *et al.* (ligands **55** -**58**).[62] They developed phosphite-pyridine **55**, phosphite-thiazoline **56**, phosphite-oxazole **57**, and phosphite-thiazole **58**. All were successfully applied in the Pd-allylic substitution reaction, achieving excellent enantioselectivities (up to 99%) 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.[62]

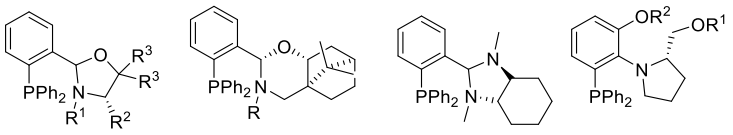
Phosphite-pyridine **55**[62b] provided excellent results for all kind of substrates and C-, N-, and O- nucleophiles, achieving enantioselectivities up to 99%. A particular note were the high enantioselectivities (ee's up to 99%) and activities for trisubstituted substrates **S10**-**S11**.

Phosphite-thiazoline **56**[62c] was designed to study the effect of replacing the oxazoline moiety (**30**, Figure 1.12) by a thiazoline. Results were complementary: whereas phosphite-oxazoline provided excellent results for linear substrates, phosphite-thiazoline **56** provided excellent results for cyclic substrates (**S3**-**S5**, ee's up to 94%). Both ligand families provided excellent regio- and enantioselectivities for monosubstituted substrates **S6**-**S9** (90% regio and 95% ee).
Phosphite-oxazole **57** provided excellent enantioselectivities for linear **S1** (ee's up to 92%) and trisubstituted **S10**-**S11** (ee's up to 95%), whereas phosphite-thiazole **58** were good for more challenging linear substrate **S2** (ee's up to 92%).[62a]

1.1.1.4. 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 in four families:
The first ligands are variations of PHOX **3** ligand, where oxazoline moiety has been replaced by sp^3-nitrogen heterocycles such as oxazolidines **59**[63] (R^1= Me, Bu; R^2= ^{i}Pr, Ph, R^3= H, Ph), oxazinanes **60**[64] (R= Et, Pr, Bu, Bn), imidazolidines **61**[65] and **62**[66] (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%).



59 **60** **61** **62**

Figure 1.18. PHOX-type phosphine-sp^3 nitrogen ligands.

In this second case, the enantioselectivity is provided from the axially chiral moieties: Azepine-type P,N ligands **63** and **64** have been successfully applied for the model substrate **S1** (ee's up to 97%) but poor results were obtained for unhindered substrate **S2**.[67]
Mino *et al.* developed amino-phosphine **65** (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.[68]

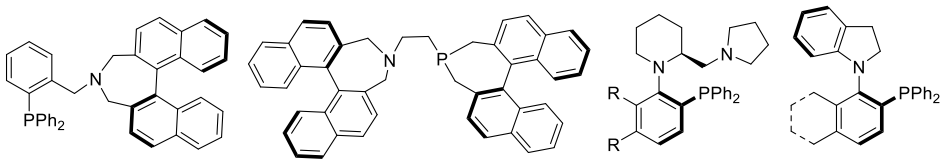


Figure 1.19. Axially chiral phosphine-amine ligands.

Amino-phosphine **66** 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.[69]

The third class of ligands are P,N with stereogenic N-donor secondary amines **67** (R= Me, ^{n}Bu, Ph). These ligands provided excellent enantioselectivities for model substrate **S1** (ee's 96%).

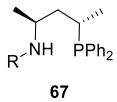


Figure 1.20. Phosphine-stereogenic sp^3-amine ligand.

Last ligand family has a planar chirality, which comes from ferroncenyl moiety. Fukuzawa *et al.* developed ferrocene-based phosphine-amine **68**. This ligand provided excellent enantioselectivities in the allylic alkylation and amination of standard substrate **S1** (ee's up to 96% and 90% respectively).[70]

Ligand **69**, developed by Kim and Jin[71], provided excellent enantioselectivities for the alkylation of model substrate **S1** (ee's up to >99%).

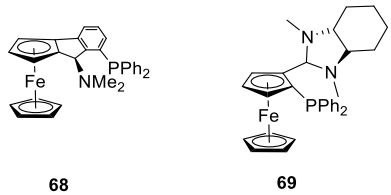
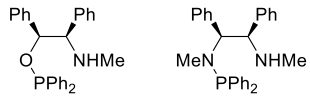


Figure 1.21. Selected ferrocene-based phosphine-sp^3-nitrogen ligands.

Phosphinite/N-phosphine-based ligands

Only two successful examples are reported in the literature. Ligand **70**, 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 that tertiary amine-based ligands.
N-phosphine **71**, 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%).[72]

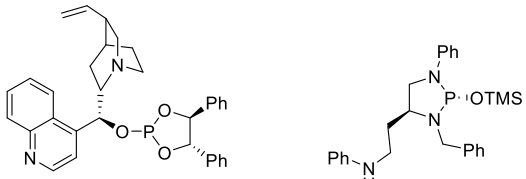


70 **71**

Figure 1.22. Selected phosphinite/aminophosphine-sp^3-nitrogen ligands.

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 **72** 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.[73]
The second example, developed by Nemoto and Hamada,[74] is a unique case. Diaphabox ligand **73** is peculiar as the actual active species binding to the palladium is generated in situ. Ligand **73** comes from the P(V) analogue, which is reduced to P^{III} by BSA, achieving P-steregenic phosphite-type ligand. This ligand provided excellent enantioselectivities for benchmark substrate **S1** (ee's up to 99%).

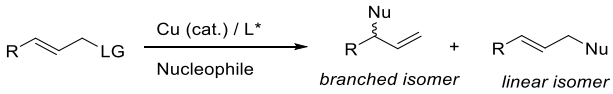


72 **73**

Figure 1.23. Phosphite-sp^3-nitrogen ligands.

1.1.2. Cu-catalyzed asymmetric allylic alkylation

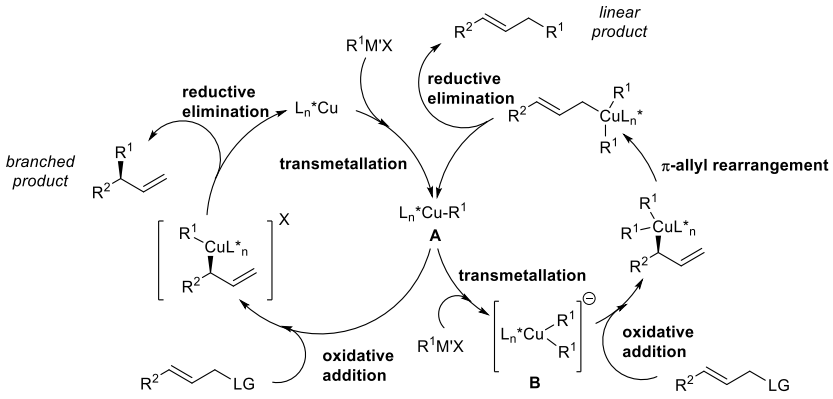
In contrast to other metals such as Pd, Mo and Ir, copper allows non-stabilized nucleophiles to be used (Scheme 1.5).[3] Grignard reagents are the most employed C-nucleophiles. Nevertheless, over the last years, the nucleophile scope has been expanded to include diorganozinc and triorganoaluminum species.



Scheme 1.5. Cu-catalyzed allylic alkylation (LG= leaving group)

Whereas stabilized nucleophiles such as malonates undergo direct attack to the most electrophilic carbon atom of the π-allylic system, non-stabilized nucleophiles undergo transmetallation with the copper to produce Cu-species **A** (Scheme 1.6).[3i-k] Then, oxidative addition of the substrate takes place, followed by reductive elimination, providing the new C-C bond formation. It is known that the nucleophile addition manner as well as the chiral ligand used have a strong influence on the regioselectivity.[3i-k]

Regarding nucleophile addition, a fast addition usually provides the formation of the species **B** via double transmetallation, which undergo oxidative addition with the substrate. Then, due to steric hindrance of the metal center and the substrate, the π-allyl rearrangement takes place, shifting the π-allyl complex equilibrium towards the γ-substituted allyl system. Finally, reductive elimination takes place, providing the undesired linear product.



Scheme 1.6. Catalytic cycle of Cu-catalyzed allylic alkylation reaction. (LG= leaving group, M' = Mg, Zn or Al).

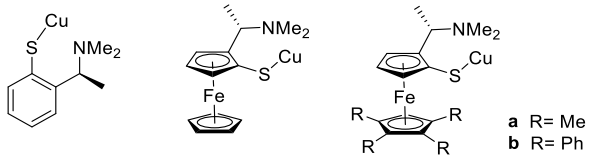
In this section, an overview of best catalytic systems, based on the ligands used, as well as the different non-stabilized nucleophiles used in this process will be disclosed.

1.1.2.1. Grignard reagents as nucleophiles

A review of the most successful catalytic systems developed to date using Grignard reagents as nucleophiles, reveals three main trends: thiolatocopper(I) compounds, phosphorus and carbene-based ligands.

Thiolatocopper (I) compounds

The use of Grignard reagents was first reported by Bäckvall and van Koten in 1995, using chiral copper thiolate **74** (Figure 1.24), yielding moderate enantioselectivities (ee's up to 42%) for alkyl allylic acetates. Later, Bäckvall *et al.* developed a second generation of thiolatocopper(I) compounds (**75** and **76**) with a ferrocene backbone. Ligands **75** and **76** provided enantioselectivities up to 64% ee. Results also indicated that enantioselectivity strongly depends on the reaction temperature, the coordination ability of the leaving group of the substrate as well as the nucleophile addition manner.[75]



74 **75** **76**

Figure 1.24. Thiolatocopper (I) chiral complexes developed by Bäckvall and van Koten.

Phosphorus-based ligands

Alexakis *et al.* were the first to study different type of phosphites and phosphoramidites (Figure 1.25).[76] TADDOL-based phosphite **77** was firstly studied, and both high levels of regio- and enantioselectivity could be obtained (94% towards branched isomer and 82% ee). Later, the same group discovered that phosphoramidite **78** performed better than previously developed TADDOL-based phosphite (91% regioselectivity and 86% ee). They also studied the effect of replacing the biphenyl group by a chiral binaphthyl moiety (leading to ligand **79**). The use of Cu-**79** catalytic system provided excellent regioselectivities (typically >99%) albeit with moderate enantioselectivities (up to 74% ee). They were able to increase ee's up to 96% when introducing methoxy groups at the *ortho* position of the aromatic ring on the amino group (ligand **80**) maintaining the excellent regioselectivities (>99% towards branched isomer).

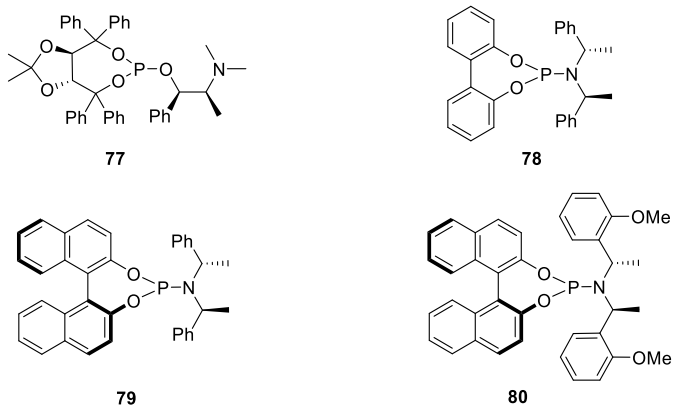


Figure 1.25. Phosphite- and phosphoramidite-based ligands for Cu-catalyzed allylic alkylation.

Feringa *et al.* have also reported successful results[77] by using ligands **81** and **82** (Figure 1.26). Whereas ligand **81** provided excellent results in terms of both regio- and enantioselectivity (85% towards branched product and 85% ee) in the Cu-catalyzed allylic alkylation of cinammyl-type substrate using MeMgBr. The use of other Grignard reagents let to lower enantioselectivities. Nevertheless, ligand **81** has been also successfully applied in the allylic alkylation of non-traditional substrates such as hetero-allylic substrates providing excellent regio- and enantioselectivities (regio's up to 99% and ee's up to 98%).[77b] The use of ligand **82** provided not only higher regio- and enantioselectivities for a range of cinammyl-type substrates than those with ligand **81**, but also showed a much higher nucleophile scope. Thus, a range of Grignard reagents could be successfully used.

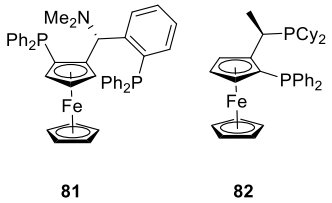
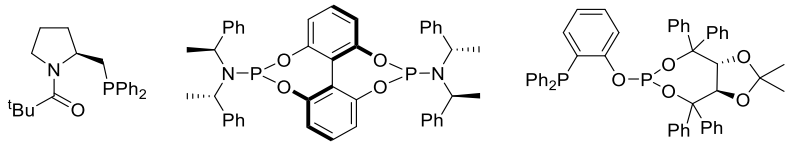


Figure 1.26. Ferrocene-based diphosphine ligands developed by Feringa *et al*.

Since then, great efforts have been carried out to expand Grignard reagents and substrate versatility. In this context, Tomioka *et al*. applied chiral amidophosphane **83** (Figure 1.27) in the Cu-catalyzed allylic alkylation of cinammyl-type substrates.[78] High enantioselectivities (up to 91% ee) were achieved with EtMgBr albeit with poor regioselectivity (62% towards branched product).

Later, in 2010 two successful applications of phosphorus ligands were reported. Zhang *et al.* applied chiral biphenyl-based diphosphoramidite **84** (Figure 1.27), which provided good levels of regio- and enantioselectivity (92% towards branched isomer and ee's up to 88%).[79] At the same time, Schmalz *et al.* reported the successful application of TADDOL-based phosphite-phosphine **85** (Figure 1.27), providing similar levels of regio- and enantioselectivity than Zhang's diphosphoramidite **84**.[80]

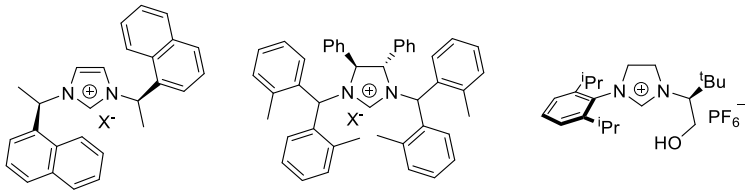


83 **84** **85**

Figure 1.27. Other successfully applied phosphorus-based ligands.

Carbene-based ligands

The third class of ligands employed in the Cu-AAA using Grignard reagents are carbenes (Figure 1.28). The first report by Okamoto *et al.* showed that the use of N-heterocyclic carbene **86** provided enantioselectivities up to 70% ee in the Cu-catalyzed allylic alkylation for difunctionalized substrates with *Z* double-bond geometry. It should be pointed out that the use of substrates with *E*-geometry provided the opposite enantiomer but in somehow lower enantioselectivity (up to 60% ee).[81] In 2009, Tomioka *et al.* improved their previous studied using phosphorus-based ligands, by employing chiral NHC ligand **87**.[82] The new Cu-**87** catalytic system could catalyze the reaction between cinammyl bromide and PhMgBr, furnishing diarylalkenes in excellent regioselectivity towards branched product (95%) and almost perfect enantioselectivity (98% ee).
In 2013, Mauduit *et al.* investigated the use of NHC **88** in the Cu-AAA of cinammyl phosphates with alkyl Grignard reagents, with high regio- (98% towards branched product) and enantioselectivities (ee's up to 90%).[83]



86 **87** **88**

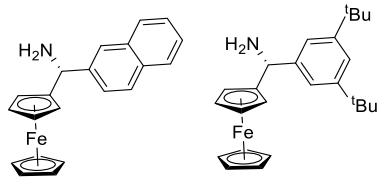
Figure 1.28. N-hererocyclic carbenes (NHC)-based ligands applied in the Cu-AAA.

1.1.2.2. Diorganozinc reagents as nucleophiles

Diorganozinc reagents have been also widely used but with less extension than Grignard reagents. A review of the most successful catalytic systems developed to date using diorganozinc compounds as C-nucleophiles, reveals four main trends: amine-based ligands, phosphorus-based ligands, imine-containing ligands and carbene-based ligands.

Amine-based ligands

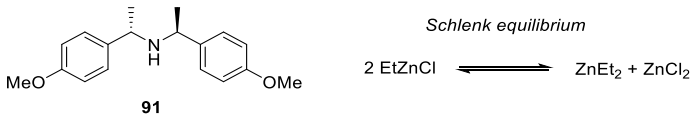
In 1999, Dubner and Knochel reported the first allylic alkylation using diorganozinc compounds with ligand **89** (Figure 1.29). To attain high enantioselectivities, the system required a high ratio of ligand to copper, very low temperatures and the presence of bulky alkyl groups on the diorganozinc (ee's up to 82%). Later, ligand **90**, containing bulky *tert*-butyl groups, was found to be more effective than **89** (ee's up to 96%).[84]



89 **90**

Figure 1.29. First successfully applied ligands in the Cu-AAA using diorganozinc reagents.

Later, Woodward *et al.* identified ligand **91**, from a series of amines, that provided enantioselectivities up to 90% ee in the reaction of electron-deficient allylic halides with $ZnEt_2$.[85] They also found that the enantioselectivity was higher at the beginning of the reaction, decreasing while the reaction was ongoing. They attributed that phenomena to the formation of $ZnCl_2$ during the reaction, shifting the Schlenk equilibrium towards EtZnCl, a non-selective reagent. To solve this problem, they added polymeric methylaluminum oxide (MAO) which was able to shift the equilibrium back to selective $ZnEt_2$ (Scheme 1.7).

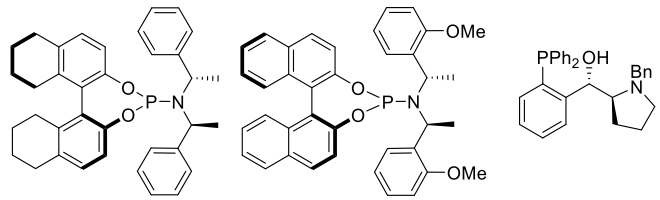


91

Scheme 1.7. Amine-based ligands applied by Woodward *et al*.

Phosphorus-based ligands

Feringa *et al.* screened a series of phosphoramidite-based ligands and they observed that ligand **92** (Figure 1.30), H8-analogue of previously mentioned ligand **79**, provided the best enantioselectivities (up to 88% ee) in the Cu-catalyzed allylic alkylation on cinammyl-type substrates. [86] Similarly, Alexakis *et al.* [87] reported higher enantioselectivities in that reaction using privileged binaphthol-based phosphoramidite **80** (ee's up to 91%). In 2009, Nakamura *et al*. reported the use of phosphine-based ligand **93**. The authors suggested that the multiple chelating sites on the ligand (P-, O-, N-) permitted the formation of a Cu/Zn bimetallic species, being the transition state a multichelating allyl system, promoting the anti-SN_2' oxidative addition, providing enantioselectivities up to 96% ee. [88]

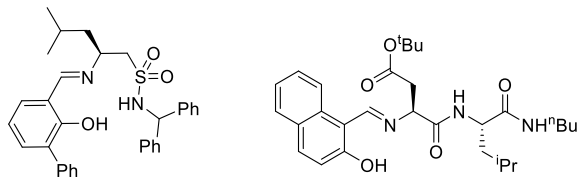


92 **80** **93**

Figure 1.30. Phosphine-based ligands applied in the Cu-AAA using diorganozinc compounds.

Imine-containing ligands

Another group of successfully applied ligands are imine-sulfonamides and imine-based peptide ligands. Gennari *et al.* tested a combinatorial library of 125 chiral imine-sulfonamides. Ligand **94** (Figure 1.31) provided lower enantioselectivities for cinammyl-type substrates (ee's up to 30%) but surprisingly this ligand provided excellent results (ee's up to 94%) in the desymmetrization of *meso* cyclic allylic bis(diethylphosphate). [89]



94 **95**

Figure 1.31. Sulfonamides and peptides as chiral ligand for the Cu-AAA.

Hoveyda *et al.* reported a series of imine-based peptide ligands bearing a hydroxynaphthimine core. Using a combinatorial approach, they found that ligand **95** could be successfully applied to the allylic alkylation of aryl-, alkyl- and vinyl-phosphates

and trisubstituted allylic systems, which allowed the formation of chiral quaternary centers. [90]

Carbene-based ligands

Hoveyda *et al.* also disclosed new chiral bidentate carbenes **96** and **97** (Figure 1.32). The best results were obtained with carbene **97**, which provided excellent enantioselectivities (up to 98% ee) with trisubstituted allylic phosphonates.[91]
Mauduit *et al*. revealed that hydroxyalkyl NHC **88** provided excellent results in both regio- and enantioselectivities (up to 96% ee) in the Cu-catalyzed allylic alkylation of cinammyl-phosphates.[92]

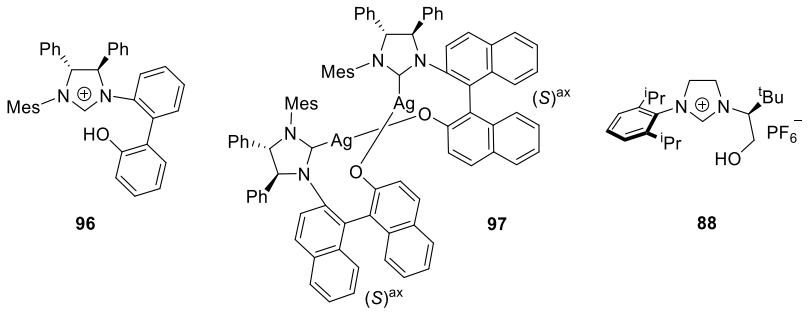


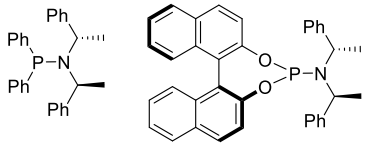
Figure 1.32. NHC-based ligands for the Cu-AAA using diorganozinc reagents as nucleophiles.

1.1.2.3. Triorganoaluminum regents as nucleophiles

Only few examples on the successful application of triorganoaluminum reagents in Cu-catalyzed allylic alkylation have been reported to date (Figure 1.34).[3] A review of the most successful catalytic systems developed to date using trialkylaluminum compounds as C-nucleophiles, reveals two main trends.

Phosphorus-based ligands

Aminophosphine **98** and phosphoramidite **79** have been successfully applied in Cu-catalyzed nucleophilic ring opening of bicyclic hydrazines using trialkylaluminum, achieving enantioselectivities up to 94% ee.[93]



98 **79**

Figure 1.33. Phosphorus-based ligands for Cu-AAA using triorganoaluminum reagents.

Carbene-based ligands

In 2008, Hoveyda *et al.* showed that Cu-complexes can catalyze the alkylation of allylic phosphates by vinylaluminum compounds. Those vinylaluminum reagents were prepared *in situ* by hydroalumination of alkynes and DIBAL-H (diisobutylaluminum hydride). NHC **99** was unique on delivering both high regio- and enantioselectivities (93% yield and 98% ee).[94] Following their success using vinylaluminum reagents, the same authors investigated if phenylaluminum reagents could undergo allylic alkylation. Excellent results in terms of yields, regio- and enantioselectivities were obtained using ligand **100** (yields up to 93%, regio's up to 99% and ee's up to 98%).[95]

In 2011, the same authors discovered that ligand **100** could also catalyzed the Cu-catalyzed allylic alkylation of alkynylaluminum reagents with allylic phosphates to form all-carbon quaternary stereocentres (yields up to 96%, regio's up to 99% and ee's up to 92%).[96]

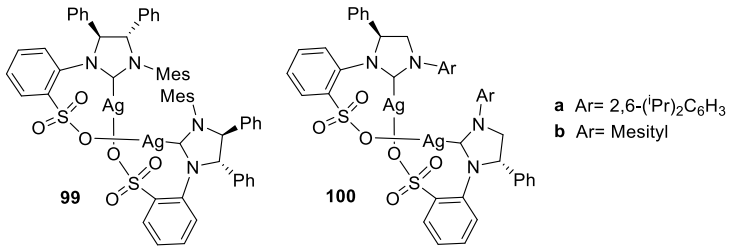


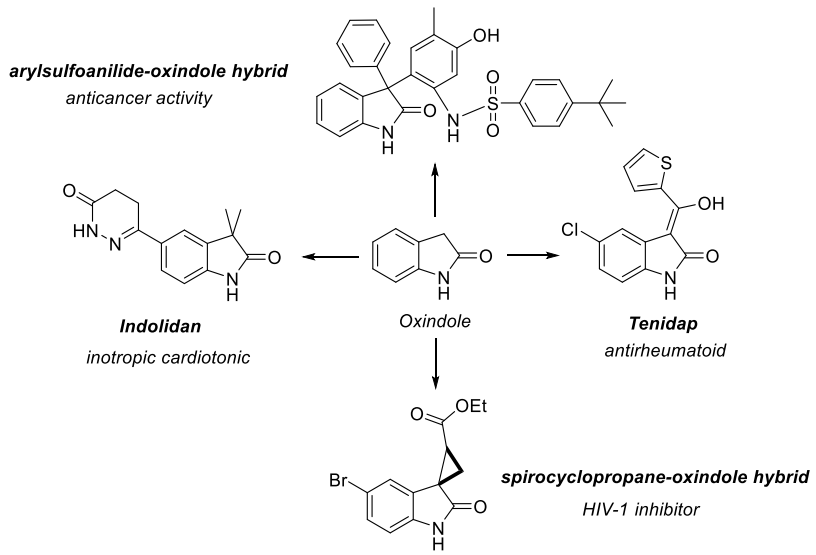
Figure 1.34. Chiral NHC-based ligands developed by Hoveyda *et al*.

1.2. Enantioselective synthesis of α-aryl oxindoles *via* Pd-decarboxylative protonation

One of the most challenging problems in organic chemistry which needs to be overcame is the formation of stereoselective C-C bond between an aromatic carbon and a carbon α to a carbonyl group. Transition metal catalyzed α-arylation has attracted considerable attention due to its versatility and utility of many medicinal targets. [97]

1.2.1. α-Substituted oxindoles

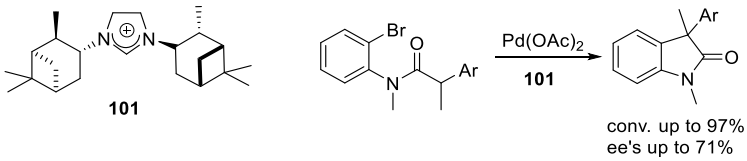
Oxindoles are endogenous aromatic organic compounds that are found in the tissues and body fluids of mammals. Oxindoles skeleton is also present in some natural products which present a wide range of properties and are reported to exhibit an extensive range of biological effects such as antiviral, antibacterial and anticancer activities (Scheme 1.8).[97] As C-3 substituted oxindoles present biological activity, many efforts have been made to prepare enantioselective α-substituted oxindoles.



Scheme 1.8. Oxindole-based biologically active products.

Among α-substituted oxindoles, α-aryl oxindoles has been less developed and many efforts have to be made for their obtaining.

First enantioselective approach was presented in 2001 by Hartwig *et al.* who reported the application of chiral carbene **101** in the palladium catalyzed asymmetric intramolecular cyclization for preparation of 3,3-disubstituted oxindoles (Scheme 1.9). Excellent conversions and promising enantioselectivities were achieved.[98]

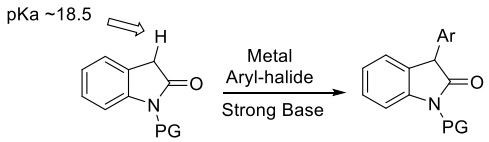


Scheme 1.9. Synthesis of 3,3'-disubstituted oxindoles via Pd-intramolecular cyclization.

However, such protocol[99] is unsuitable if onxindole core is already present in the substrate. For that reason, direct α-arylation of carbonyl compounds have emerged as an alternative to cyclization method.

1.2.2. α-Arylation of oxindoles

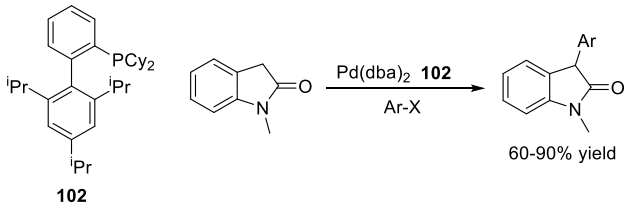
Metal-catalyzed α-arylation of carbonyl compounds and related compounds have been achieved with a wide range of nucleophiles such as enolates of ketones, esters, nitriles and amides. The α-arylation of amide enolates (Scheme 1.10) represents one of the most challenging chemical transformation due to the high pKa of the substrates, necessitating the use of strong bases which can limit the substrate scope. In addition, due to the strong basic media, the asymmetric α-arylation of oxindoles has not been reported yet because of the easy racemization of that tertiary stereocentre in α-position of the amide group.



Scheme 1.10. Standard α-arylation of oxindoles.

1.2.2.1. Synthesis of 3-aryl oxindoles

First palladium-catalyzed α-arylation of oxindoles was reported by Willis'[100] and Buchwald's[101] groups independently in 2008. They reported the application of Pd-phosphine **102** complexes which could catalyze α-arylation of oxindoles. Good to excellent yields were obtained with a wide range of aryl halides.

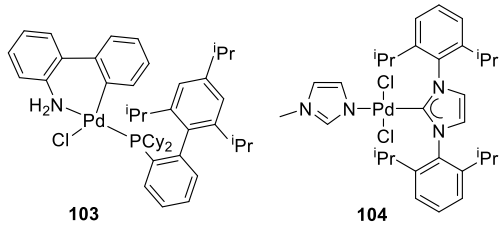


102

Scheme 1.11. Pd-catalyzed α-arylation of oxindoles reported by Willis and Buchwald.

Also Buchwald in 2011 reported the application of Pd-complex **103** (Figure 1.35) in the α-arylation of oxindoles in continuous flow.[102] Using this methodology, excellent conversions could be obtained (up to 95%).

Despite Pd-phosphine has been widely used as metal catalyst for α-arylation of oxindoles, also Pd-carbene complexes **104** proved to be efficient[103] (Figure 1.35). Excellent conversions were obtained (up to 98%) using Pd-complex **104**.



103 **104**

Figure 1.35. Successfully applied Pd-complexes for the α-arylation of oxindoles.

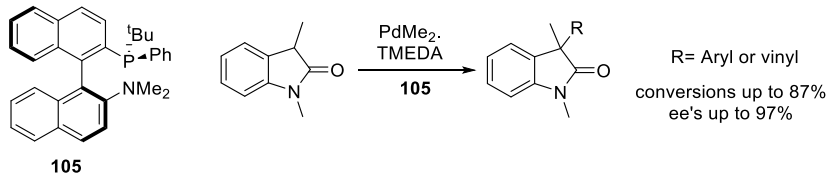
1.2.2.2. Synthesis of 3,3-disubstituted oxindoles

Metal-catalyzed synthesis of 3,3'-disubstituted oxindoles has been more widely explored than analogous monoarylated products and great and outstanding examples of asymmetric 3,3-disubtituted oxindoles have been reported.[104-107]

Two strategies have been applied for their preparation, such as: metal-catalyzed direct α-arylation, and phase transfer α-arylation.

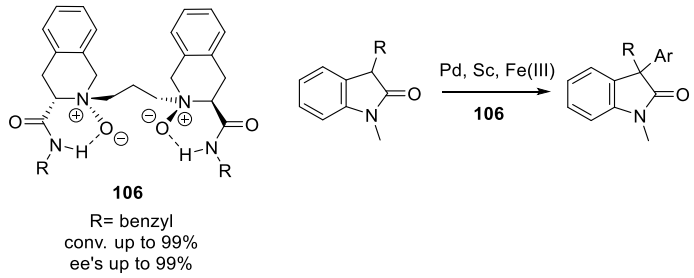
For the first strategy, palladium, scandium and iron have been the most successfully applied metal-complexes.

Buchwald *et al.*[104] reported the synthesis of 3,3-disubstituted oxindoles in high conversions and excellent enantioselectivities using chiral P-sterogenic-amine ligand **105** (Scheme 1.12).



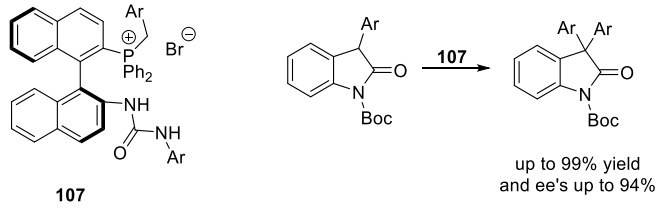
Scheme 1.12. Application of P-stereogenic phosphine-amine ligand for the formation of 3,3-disubstituted oxindoles.

Feng *et al.*[105] designed ligand **106** that was applied to the enantioselective Sc-catalyzed arylation of 3-benzyl oxindoles achieving excellent results in terms of both conversion and enantioselectivity (up to 99% in both cases). Iron (III) has also proved to catalyze this reaction, as Li and Liu *et al.* reported recently[106], achieving excellent yields up to 97% with a wide range of aryl and alkyl substituents.



Scheme 1.13. Successful α-arylation of 3-substituted oxindoles.

Last approach to the synthesis of 3,3-disubstituted oxindoles has been reported by Maruoka *et al.*[107] It consists on the synthesis of 3,3'-diaryloxindoles by phase-transfer catalysis (Scheme 1.14). They applied chiral phosphonium-bromide salts **107** achieving excellent results in terms of both activity and enantioselectivity.

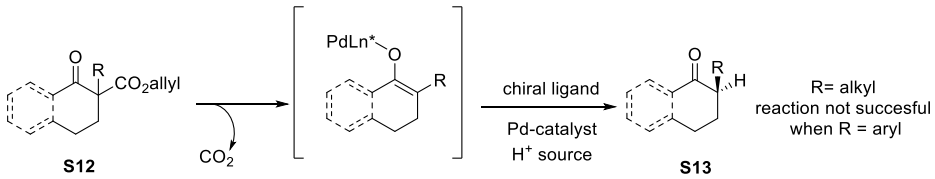


Scheme 1.14. Synthesis of 3,3'-diaryloxindoles by phase-transfer catalysis.

1.2.3. Asymmetric Pd-catalyzed decarboxylative protonation

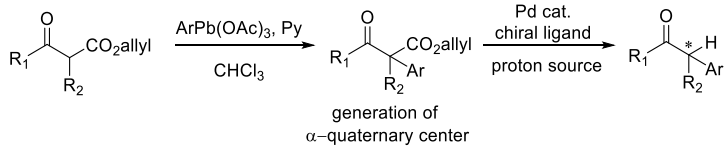
Since the presence of high enantiopure tertiary α-aryl carbonyls are prevalent structural motifs in many biologically active molecules and pharmaceuticals, the enantioselective protonation of achiral metal enolates or enol equivalents involving chiral proton sources is an efficient route to access carbonyl compounds with tertiary carbon stereocenters at α-position. However, most of the reported methods are limited in substrate scope, few are catalytic, and they do not provide a general solution for the enantioselective protonation of enolates.[108]

Pd-catalyzed decarboxylative protonation was first introduced by Stoltz *et. al.*[109] where a prochiral enolate formed from the decarboxylation of **S12**-type substrates was intercepted by a proton source, leading tertiary α-substituted ketones (Scheme 1.15). In that case, the reaction was only successful when the α-substituent was an alkyl group.



Scheme 1.15. Enantioselective protonation of racemic β-ketoesters.

Due to the Pd-decarboxylative protonation developed by Stoltz et al. was not successful when an aryl group was present at α-position to the carbonyl group, Guiry *et al.* developed an alternative. Their methodology was having the aryl group already introduced in the α-position of carbonyl compound and, by Pd-catalyzed asymmetric decarboxylative protonation, generating the chiral steroecenter (Scheme 1.16).[110, 111, 112]



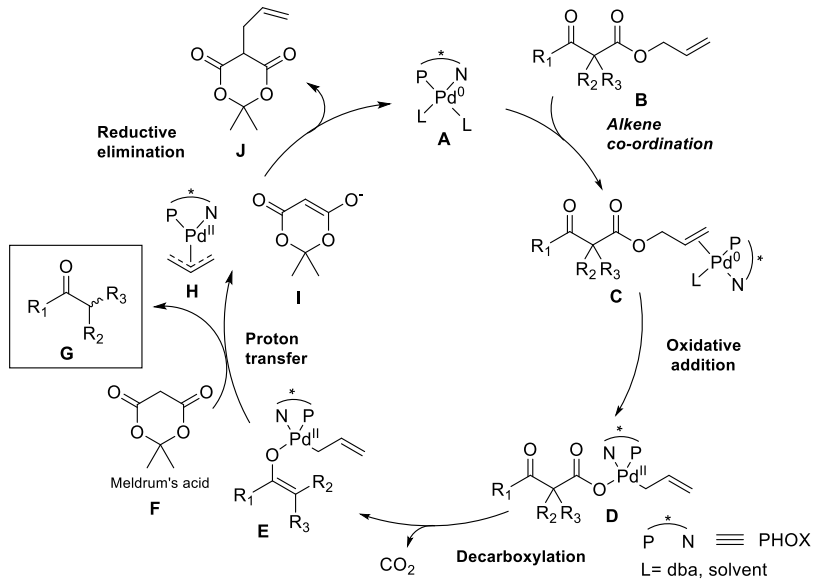
Scheme 1.16. Pd-catalyzed asymmetric decarboxylative protonation of β–ketoesters.

These aryllead triacetates have shown an important ability to α-arylate β-ketoesters, even introducing sterically bulky aryl groups, generating a quaternary center in high yields.[113,114] Despite its toxicity, the use of aryllead triacetates as arylating agents, allows the introduction of electronrich aryl groups whereas the use of non-toxic aryliodonium salts do not.[115]

1.2.3.1. The mechanism

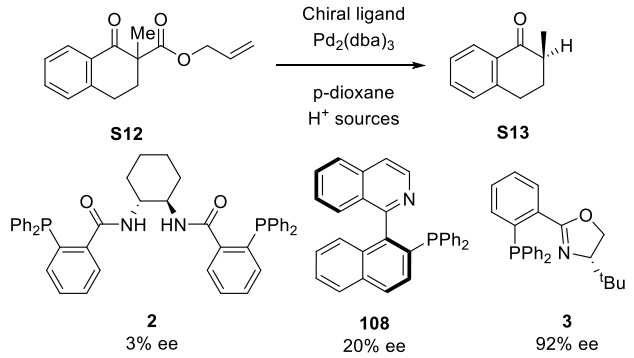
Although the mechanism for the asymmetric decarboxylative allylation of allyl β-ketoesters by Pd catalyst has been investigated both experimentally and computationally, the mechanism for the decarboxylative protonation is still not understood. The current mechanism proposal for decarboxylative protonation mainly relies on some preliminary kinetic experiments developed by Stoltz *et al.*[116,117]

In this proposed catalytic cycle (Scheme 1.17), the Pd(0) active species **A** is obtained by the complexation of P,N-based ligand to Pd catalyst precursor. Then, alkene coordination takes place and this new Pd(0) complex **C** undergoes an oxidative addition forming an alkoxy intermediate **D**. Then, decarboxylation occurs leading the formation of a prochiral enolate **E**. This prochiral enolate **E** will attack to the acid proton of the proton source **F** by a proton transfer step providing the α-substituted compound **G**. A reductive elimination will lead the regeneration of the active specie **A** and the formation of the side product monoarylated-H^+ source **J**. By kinetics studies, Stoltz *et al.* determined that the amount of allyl ketoester **B**, over time, displayed a zero-order decay, suggesting that ketoester **B** reacts very fast generating the Pd-carboxylate **D** which undergoes further reaction in a slowest step.[117] Although these results give some information regarding the first steps of the mechanism, further studies are required to elucidate the mechanism and the origin of the enanioselectivity.[116]



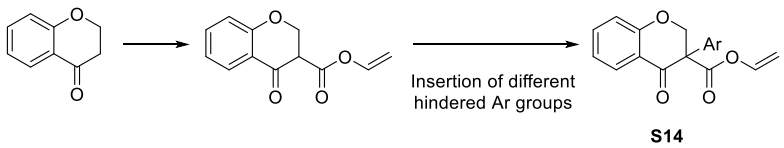
Scheme 1.17. Catalytic cycle for the enantioselective Pd-catalyzed decarboxylative protonation of β-ketoesters.

In 2006, Stoltz *et. al.* achieved the successful enantioselective protonation of a wide scope of racemic β-ketoesters to produce chiral α-tertiary cyclic ketones with high enantioselectivities (up to 92% ee) using PHOX-derived ligand **3** (Scheme 1.18).[109]
A variety of achiral organic proton sources were tested and the commercially available meldrum's acid was the proton source which provided better results.
Bulky substituents on the oxazoline provided the best enantioselectivities for the decarboxylative protonation (92% ee), whereas diphosphine ligands provided almost racemic product (Scheme 1.18).



Scheme 1.18. Ligand screening in asymmetric decarboxylative protonation.

While these transformations were able to generate α-tertiary ketones with a range of alkyl groups in excellent enantioselectivities and yields, only two examples have been described when the α-substituent was an aryl group, all reported by Guiry *et al*.
They reported the catalytic synthesis of isoflavanones from α-aryl-β-ketoesters **S14** achieving high enantioselectivities (up to 97% ee) for a wide range of sterically hindered aryl groups, such as mono-*ortho*-substituted and di-*ortho*-substituted.



Scheme 1.19. Synthesis of isoflavanone precursors.

They applied the P,N-ligands **3** and **109** in the decarboxylative protonation of α–aryl-β-ketoesters **S14** for the formation of tertiary stereocenters to the first catalytic asymmetric synthesis of isoflavanones **S15** (Scheme 1.20). Comparing ^{t}BuPHOX **3** and electron-deficient (*S)*-CF_3-^{t}BuPHOX ligand **109** (Figure 1.36), they found that electron deficient phosphines provided better enantioselectivities (78% ee compared to 92% ee respectively).

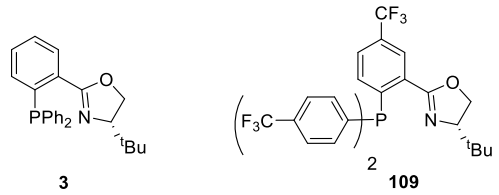
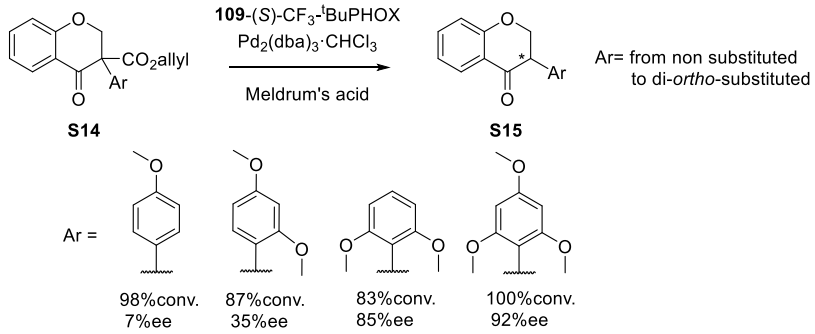


Figure 1.36. PHOX **3** and electron-deficient (*S*)-CF_3-^{t}Bu-PHOX **109**.

Different aromatic substituted-moieties were studied to determine the influence on the enantioselectivity (Scheme 1.20). Authors found that bulky substituents on the aryl group, and also on the oxazoline moiety, play an important role in the enantioselectivity of the reaction.



Scheme 1.20. Asymmetric catalyzed decarboxylative protonation of isoflavanones.

Based on the catalytic results, they were able to propose that the key intermediate in this reaction consists, probably, in a prochiral palladium enolate. One of the *ortho*-methoxy groups and the ^{t}Bu group on the oxazoline combine to block the *Re*-face of the enolate and ensuring protonation by the *Si*-face. (Figure 1.37).

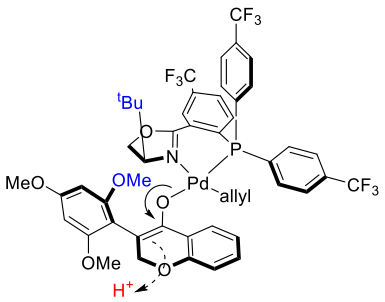


Figure 1.37. Proposed transition state in asymmetric protonation.

Working on the synthesis of *Sativanone* (Figure 1.38),[111] Guiry *et al.* found that changing the proton source, using formic acid instead of Meldrum's acid, restores excellent enantioselectivity, but leading the opposite enantiomer. This phenomenon leads to think that the enantiodetermining step could be the proton transfer, and changing the proton source, the key intermediate would be different, and so will allow the switch of the enantioselectivity of the reaction (Scheme 1.21).[111]

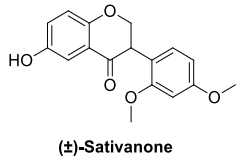
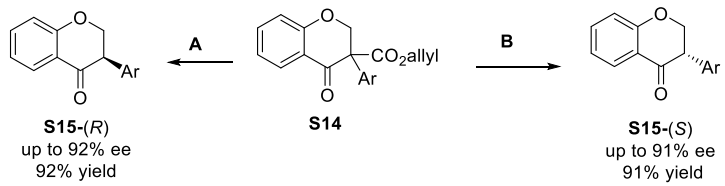


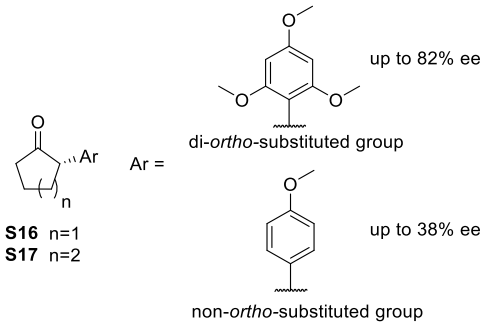
Figure 1.38. Sativanone.



Scheme 1.21. Enantiodivergence observed with different proton sources. **A**: Meldrum's acid used as proton source. **B**: Formic acid used as proton source.

The ability to obtain both enantiomers of a particular chiral molecule using the same chiral ligand is a valuable methodology in organic synthesis and represents a significant challenge. Previously, dual stereocontrol has been achieved by variation of catalyst substituents, and changing the metal center or precursor. In this instance they have shown that these factors are not the cause of the observed switch in enantioselectivity. Interestingly, the rates of the reactions are significantly different; such that the Meldrum's acid reaction is complete in 30 min, whereas the formic acid reaction takes up to 10 h. This may suggest the necessity for a carbopalladation to occur, which is subsequently quenched by formic acid. Alternatively, some pre-coordination of formic acid to the chiral Pd–enolate complex may result in an inner-sphere-type protonation to a different face of the enolate than with Meldrum's acid. That should explain the reason why this switch in the enantioselectivity occurs.

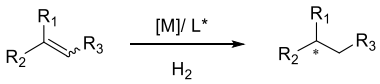
In 2014, Guiry and co-workers were able to generate enantiomerically enriched α-aryl tertiary stereocenters in cyclic ketones **S16**-**S17** via Pd-decarboxylative protonation approach using the same methodology as for the synthesis of isoflavanones (Scheme 1.22).[112] They could also see the influence of the substituents in the aryl group on the enantioselectivity: the more sterically hindered, the highest enantiodiscrimination is obtained.



Scheme 1.22. Asymmetric Pd-decarboxylative protonation. Generation of α-tertiary stereocenters in cyclic ketones.

1.3. Asymmetric hydrogenation of olefins

Due to its high efficiency, atom economy and operational simplicity, the asymmetric hydrogenation of olefins can be a sustainable and direct synthetic tool for preparing enantiomerically pure compounds.[1,118] Usually in this strategy, a chiral metal-complex catalyzes the addition of hydrogen to a prochiral substrate containing a double bound giving rise to a new chiral C-H bond.



Scheme 1.23. Asymmetric M-catalyzed hydrogenation of olefins

The first advances in asymmetric hydrogenation of olefins arose in the decade of 1970s with the use of rhodium and ruthenium catalysts modified with chiral diphosphine ligands.[1,118] The manufacturing process of L-Dopa, which is used in the clinical treatment of Parkinson's disease developed by Montsanto,[119] showed that these catalysts can be applied on an industrial scale. Since then, the hydrogenation has become a dominant methodology in asymmetric catalysis at both industrial and academic levels.

1.3.1. Asymmetric hydrogenation of minimally functionalized olefins

The reduction of minimally functionalized olefins represents one of the major challenges in the field of chemistry. Iridium complexes modified with heterodonor P,N ligands have become efficient catalysts for asymmetric hydrogenation of minimally functionalized olefins, as a complement of rhodium and ruthenium catalysts.[120] The asymmetric hydrogenation of alkenes by Rh(I) and Ru(II) complexes bearing diphosphine ligands

rely on the presence of a coordinating group in close proximity to the double bond (*i.e.* dehydroamino acids). This additional functional group is of particular importance because it works as a secondary complexation function in addition to the alkene functionality forming a chelate which limits the set of available conformations thus making easier to achieve high stereoselectivity.[118] In contrast, iridium catalysts do not require the presence of an extra coordinating group to achieve high levels of enantioselectivity.[120]

1.3.1.1. The mechanism

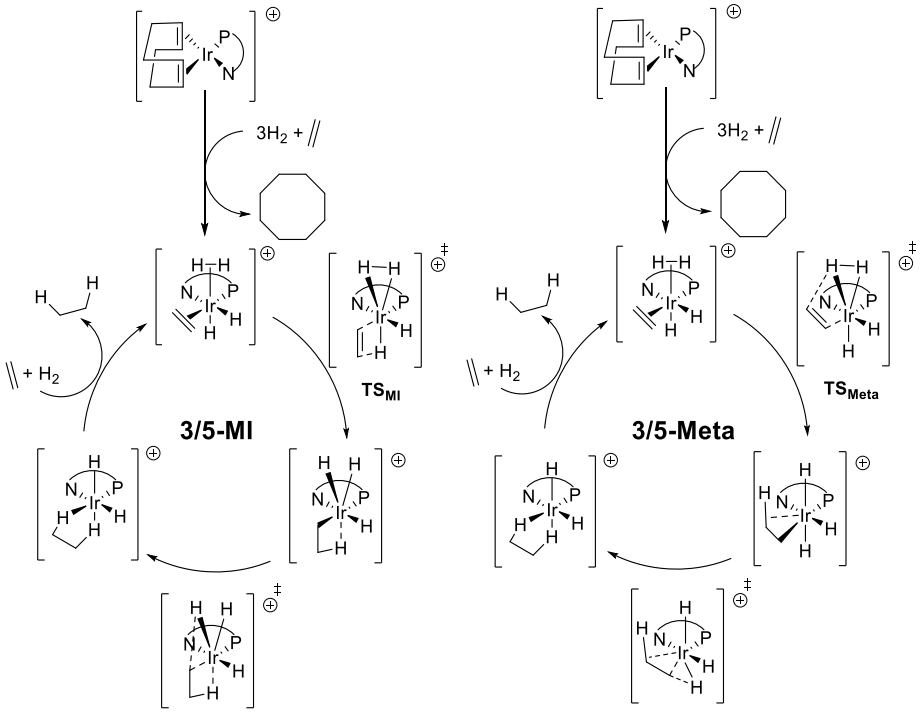
Whereas the mechanism for the Rh-catalyzed asymmetric hydrogenation of olefins containing an adjacent coordinating polar group is well understood[121], the mechanism for the Ir-catalyzed hydrogenation of minimally functionalized olefins has been less studied. In the case of Rh-catalyzed asymmetric hydrogenation, there are evidences that support a Rh(I)/Rh(III) mechanism where the rate of the reaction is determined by the oxidative addition of H_2 and the stereochemistry of the product is provided by the coordination face of the olefin, controlled by the adjacent polar group.[121]

Andersson *et al.* have used DFT (Density Functional Theory) calculations and a full experimentally tested combination of ligands and substrates to find that the catalytic cycle passed through Ir(III)/Ir(V) intermediates, but they failed to distinguish between the two Ir(III)/Ir(V) mechanisms.[122] One of the mechanisms includes the migratory insertion of one hydride onto the olefin followed by a reductive elimination (mechanism 3/5-MI, Scheme 1.24) whereas the second mechanism involves a σ-metathesis also followed by a reductive elimination (mechanism 3/5-Meta, Scheme 1.24).

In 2011, Hopmann *et al.* performed a computational study using a PHOX-based iridium catalysts, corroborating Andersson's results.[123] At the same time our group in collaboration with Norrby's and Andersson's groups performed a study with DFT calculations using iridium catalysts with phosphite-oxazoline ligand.[124] Both studies confirm that the hydrogenation of minimally functionalized olefins follows the 3/5-MI pathway, but energetic barriers between both catalytic cycles do not differ a lot to discriminate directly 3/5-Meta.

Recently in 2014, Pfaltz *et al.* has been able to characterize by NMR the elusive catalytically competent intermediates [Ir(P-N)$(H)_2(H_2)$(alkene)], which further supports the Ir(III)/Ir(V) mechanism because an extra molecule of H_2 was needed to hydrogenate the alkene.[125] They found that there are two dihydride-alkene intermediates in equilibrium via a dissociation/association process, differing by the coordinating face of the alkene. The configuration of the product obtained from the hydrogenation had the absolute configuration which requires coordination of the alkene, determined as the minor isomer. Thus, the pathway leading to the major enantiomer seems to proceed via a minor intermediate, similar to the mechanism of the Rh-catalyzed asymmetric hydrogenation. Also phosphite-thioether ligands have been used as models for DFT

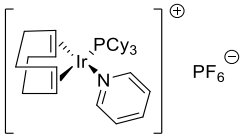
calculations and HP-NMR, both cases, carried out by Diéguez *et al.* [126] Their results also confirmed the expected 3/5 catalytic cycle and the catalytic active species dihydride-hydrogen-alkene that Pfaltz and co-workers[125] also observed.



Scheme 1.24. Proposed catalytic cycles 3/5-MI and 3/5-Meta for asymmetric hydrogenation of minimally functionalized olefins.

1.3.1.2. Ligands

During the 1970s, Crabtree *et al.* studied the properties of metal complexes of the type $[M(cod)L_2]X$ (M = Rh or Ir, (cod = 1,5-cyclooctadiene), L = phosphine ligand, X = Cl, BF_4 or PF_6) in alkene hydrogenation. After careful ligand-screening experiments, they discovered that replacing one of the phosphine ligands by a pyridine lead to a significant improvement of the catalytic properties of the Ir-catalysts. Thus, $[Ir(cod)(Py)PCy_3]PF_6$ catalytic precursor **110** (so-called Crabtree's catalysts; Figure 1.39) is faster than the corresponding diphosphine catalyst and able to reduce tri- and tetrasubstituted non-functionalized olefins efficiently.[127]



110

Figure 1.39. Crabtree's catalyst **110**.

A breakthrough in this field occurred in 1998 when Pfaltz *et al.* used phosphine-oxazoline ligands PHOX **3** (Figure 1.40) to design [Ir(COD)(**3**)]PF_6[128], a chiral mimic of the Crabtree's catalyst widely used in the not enantioselective hydrogenation of non-functionalized olefins.

Although this catalyst hydrogenated with high enantioselectivity *E*-trisubstituted olefins, it was unstable under the reaction conditions. Pfaltz overcame this problem by replacing the catalyst anion hexafluorophosphate to tetraquis[3,5-bis(trifluoromethyl)phenyl] borate, $[3,5\text{-}(F_3C)_2\text{-}(C_6H_3)_4B]^-$ (BAr_F), which is less coordinative. The result was [Ir(cod)(**3**)]BAr_F **111** (Figure 1.40) an active, enantioselective and stable catalyst, for the hydrogenation of minimally functionalized olefins, albeit with relative moderate scope.[128, 129, 130]

Since this discovery, the research has been mainly focused in the synthesis of new chiral P,N ligands.[120] Therefore, the phosphine moiety has also been replaced by a phosphinite or phosphite group and the oxazoline moiety by other *N*-donor groups (such as pyridine, imidazole, thiazoline, oxazole and thiazole). The backbone of the ligand has been also modified. More recently, the nature of the *N*-donor group has been replaced for S-,[126,131] and O-donor[132] groups as well as the phosphorus moiety has been replaced by strongly σ-donor carbene moieties.[133] These modifications have led to the discovery of new ligands that have increased the scope of the hydrogenation of minimally functionalized olefins.

In the next sections we summarized the most relevant catalytic systems reported for asymmetric hydrogenation of minimally functionalized olefins with phosphorus-nitrogen donor ligands.

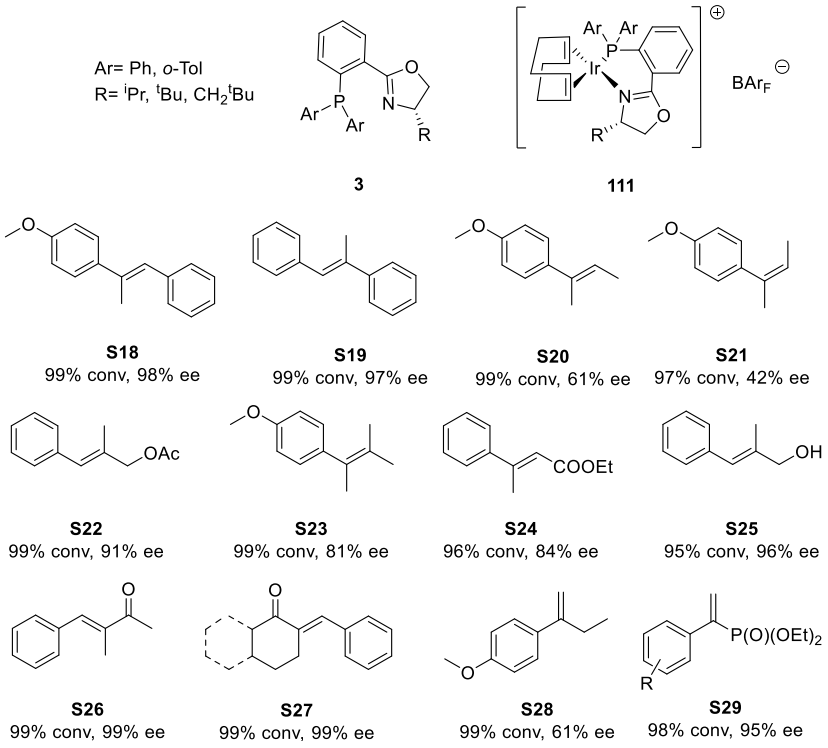


Figure 1.40. PHOX ligands and the structure of developed catalyst precursor.

Phosphorus-oxazoline ligands

Phosphine-oxazoline ligands

Soon, after the success of the PHOX ligands in this process, Kündig *et al.* reported a modification in the oxazoline moiety with the development of phosphine-benzoxazine analogues **112** (R= ^{t}Bu, ^{i}Pr).[134] The presence of bulky substituents such as *tert*-butyl at the oxazine group provided high enantioselectivities (ee's up to 89% for **S19** and 55% ee for **S20**) but these enantioselectivities were lower than those obtained with PHOX ligand **3**.

The rest of new phosphine-oxazoline ligands developed for the Ir-catalyzed hydrogenation were based on modifications of the ligand backbone.

Previously mentioned ligands **18** (R^1= Ph, *o*-Tol and R^2= Me, ^{t}Bu, 1-Ad, CPh_3)[135], developed by Burgess *et al.*, were applied in the hydrogenation of several aryl-alkyl alkenes. These ligands proved to be more efficient than the PHOX ligands **3** in the hydrogenation of *Z*-trisubstituted alkenes (ee's up to 75% for **S21**) while ee's for the reduction of *E*-trisubstituted alkenes were lower (ee's up to 72% and 67% for **S22** and **S25** respectively). This development promoted a further modification of ligands **13** by

introducing again the *ortho*-phenylene motif of the PHOX ligands. In this respect, the previously mentioned ligands **7** (R^1= Ph, Cy and R^2 = ^{t}Bu, 1-Ad, $CHPh_2$, 3,5-^{t}Bu$_2$-Ph), developed in Zhang's group, proved to be excellent in the hydrogenation of *trans*-α-methyl stilbene derivatives **S18** (ee's up to 99%) and higher enantioselectivity for **S24**, bearing an ester group (ee's up to 99%).[136]

In 2003, Cozzi *et al.* reported the development of ligands **113**, in which the phenyl ring of the PHOX ligands was replaced by a thiophene group (R^1= Ph, *o*-Tol, Cy and R^2= ^{i}Pr, ^{t}Bu).[137] The application of ligands **115** indicated that this modification also led to high enantioselectivities in the hydrogenation of **S19** (ee's up to 99%) and also for **S25** (ee's up to 94%). These ligands were also applied in the hydrogenation of imines, giving promising enantioselectivities up to 86%.

Then, in 2007 Pfaltz *et al.* synthesized a series of simple and readily accessible phosphine-oxazoline ligands **114** which formed a 5-membered chelate ring when coordinated to iridium (R^1= Ph, *o*-Tol, Cy, ^{t}Bu and R^2= ^{i}Pr, ^{t}Bu, Ph, Bn).[138] Interestingly, this family of ligands has proved to be the most efficient catalyst system in the hydrogenation of challenging tetrasubstituted alkenes. Excellent conversions and enantioselectivities were achieved in model substrate **S23** (99% conv. and 97% ee) as well as in a wide range of tetrasubstituted alkenes with different electronic and steric properties.

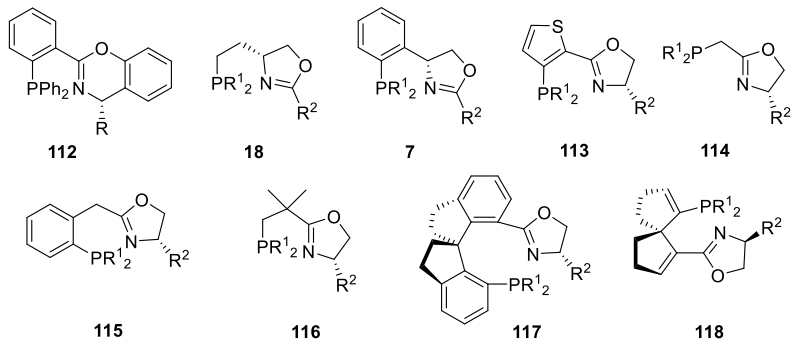


Figure 1.41. Most relevant phosphine-oxazoline ligands.

In 2008, on the basis of PHOX ligands, Hou *et al.* developed new phosphine oxazoline ligands **115** in which the flat *ortho*-phenylene group was replaced by benzylic type group (R^1= Ph, *o*-Tol, *p*-Tol and R^2= Me, ^{i}Pr, ^{t}Bu).[139] These ligands were successfully applied in the Ir-catalyzed asymmetric hydrogenation of a wide range of *E*-trisubstituted aryl/alkyl alkenes **S18**-**S20**, α,β–unsaturated esters **S24**, allylic alcohols **S25**, ketones **S26** and **S27**, providing excellent enantioselectivities up to 99% ee.

Pfaltz *et al.* also further modified PHOX ligands by replacing the *ortho*-phenylene tether by a branched alkyl chain (ligands **116**, R^1= Ph, *o*-Tol, Xyl and R^2= ^{i}Pr, ^{t}Bu, Bn).[140] These ligands provided higher enantioselectivities in the hydrogenation of trisubstituted *E*- and

Z-aryl alkenes (**S19**-**S21**) than the PHOX ligands (ee's up to 98%) as well as for 1,1'-disubstituted alkenes **S28** (ee's up to 66%) and allylic alcohols **S15** and α,β–unsaturated esters **S14** (ee's up to 96%). The authors demonstrated the potential of ligands **118** with the synthesis of (*R*)-7-demethyl-2-methoxycalamenene an antitumor natural product, achieving this natural product in 96% ee.

Zhou *et al.* reported a new family of *spiro* phosphine-oxazoline ligands **117** (R^1= Ph, 3,5-Me_2-Ph, 3,5-$^tBu_2$-Ph and R^2= Bn, Ph, Me, H).[141] These ligands were extremely effective in the hydrogenation of both α-aryloxy and α-alkoxy-α,β-unsaturated carboxylic acids, achieving enantioselectivities up to >99% ee. Other *spiro*cyclic phosphine-oxazoline ligands **118** (R^1= *o*-Tol, Ph and R^2= Ph, Bn), developed by Zhang and Ding, were used in the asymmetric hydrogenation of α-aryl-substituted unsaturated carboxylates, providing excellent results in terms of both conversion and enantioselectivity (99% conv. and 96% ee).[142] These latter *spiro* phosphine-oxazoline ligands were also successfully applied in the hydrogenation of α,β-unsaturated Weinreib amides [143] and α,β-disubstituted enones, [144] achieving in both cases excellent enantioselectivities (ee's up to 97% and >99%, respectively).

N-phosphines/phosphinite-oxazoline ligands

Also N-phosphine-oxazoline ligands have been reported to be successful for Ir-catalyzed hydrogenation of minimally functionalized olefins.

In 2001, the Pfaltz *et al.* modified the PHOX ligands by replacing the *ortho*-phenylene group by a pyrrole as linker to the phosphorus, leading to ligands **119** (R^1= Ph, *o*-Tol, Cy and R^2= ^{i}Pr, ^{t}Bu).[145] Enantiomeric excesses surpassed those previously obtained with the PHOX ligands **3** in all kind of substrates **S19**, **S20** and **S24**. Nevertheless, the enantioselectivities for *Z*-trisubstituted olefins **S15** were not above 80% ee, even achieving higher enantioselectivity than PHOX ligand **3**.

Later, Gilberston *et al.* developed the proline-based *N*-phosphine-oxazoline ligands **120** (R^1= Ph, *o*-Tol and R^2= ^{i}Pr, ^{t}Bu) that provided lower enantioselectivities than previous pyrrole-based ligands **119**.[146]

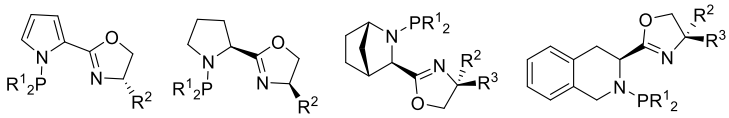
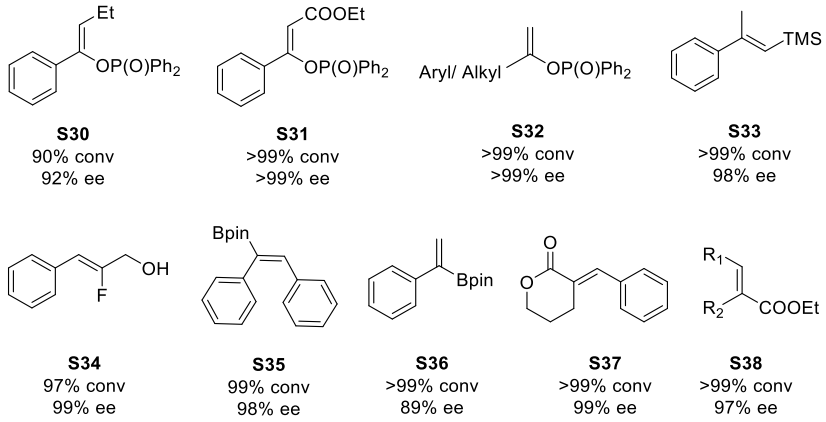


Figure 1.42. The most relevant N-phosphine-oxazoline ligands.

Andersson *et al.* developed ligands **121** and **122** for this process (**121**; R^1= Ph, *o*-Tol, Cy; R^2= H, ^{t}Bu, Ph and R^3= H, Ph; and **122**; R^1= Ph; R^2= H, ^{i}Pr, Ph and R^3= H, ^{i}Pr, Ph).[147,148] Ligands **121**[147], which are based on a rigid bicyclic backbone, provided higher

enantioselectivities than **122**[148], with a more flexible backbone. [Ir(**121**)(cod)]BAr_F catalyst precursors afforded high enantioselectivities in the hydrogenation of enol phosphinates **S30**-**S32**[147b,c], vinyl silanes **S33**[147d], fluorinated olefins **S34**[147e], and vinyl boronates **S35-S36**[147f] as well as α,β-unsaturated lactones **S37** and α,β-unsaturated acrylic esters **S38**[147g] (Figure 1.43).



S30 90% conv 92% ee
S31 >99% conv >99% ee
S32 >99% conv >99% ee
S33 >99% conv 98% ee
S34 97% conv 99% ee
S35 99% conv 98% ee
S36 >99% conv 89% ee
S37 >99% conv 99% ee
S38 >99% conv 97% ee

Figure 1.43. Representative challenging substrates hydrogenated by Ir-**121** complex, developed by Andersson *et al.*

Only three families of phosphinite-oxazoline ligands have been successfully developed for the Ir-asymmetric hydrogenation (Figure 1.39).[149,150,151]

The first family of phosphinite-oxazoline ligands (ligands **24**) was reported by Pfaltz *et al*.[149] Ligands **24** (R^1= Ph, *o*-Tol, Cy; R^2= ^{t}Bu, Ph, ferrocenyl, 2-Naph; R^3= H, Me, 3,5-Me_2-Ph and R^4= Me, ^{i}Pr, ^{t}Bu, Bn) constitute one of the most privileged ligands for this process. These ligands therefore provided excellent enantioselectivities in the hydrogenation of a broad range of both *E*- and *Z*-trisubstituted olefins **S19** (99% ee), **S20** (99% ee) and **S21** (92%ee), including α,β-unsaturated esters **S24** (94% ee) and a limited range of more challenging terminal olefins **S28** (ee's up to 94%) as well as 1,1'-disubstituted enamines with enantioselectivities up to 93% ee. Very recently, Pfaltz *et al.* have successfully applied Ir-**24** complexes in the hydrogenation of α,β–unsaturated nitriles with excellent enantioselectivities (ee's up to 99%).[149e]

The second family of phosphinite-oxazoline are ligands **123** (R^1= Ph, *o*-Tol and R^2= ^{i}Pr, ^{t}Bu). It is based in the previous **24** in which the alkyl chain is bonded in the carbon 2 instead of the carbon 4 of the oxazoline moiety, shifting the chirality from the alkyl chain to the oxazoline moiety.[150] The scope of these ligands is narrower in comparison with the privileged phosphinite-oxazoline ligands **24**, however, they are complementary. Therefore, ligands **123** provided high enantioselectivities for allylic alcohols **S25** (97% ee) and alkenes bearing heteroaromatic substituents and terminal boronic esters with enantioselectivities up to 96% ee.

Last successful phosphinite-oxazoline has been developed by Kazmeier *et al.* Ligand **124** have provided excellent enantioselectivities for linear and cyclic α,β–unsaturated ketones **S26** and **S27**, achieving excellent enantioselectivities up to >99%.[151]

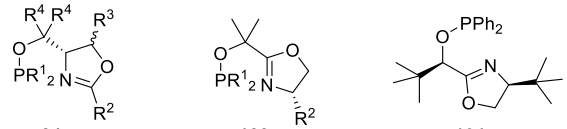


Figure 1.44. The most relevant phosphinite-oxazoline ligands.

Phosphite/phosphoramidite-oxazoline ligands

Despite the advantages of phosphite/phosphoramidite ligands in asymmetric catalysis[120,152] only few families of phosphite/phosphoramidite-oxazoline ligands have been applied in Ir-catalyzed asymmetric hydrogenation of minimally functionalized olefins. Ligands **125** (R^1= Ph, *o*-Tol, Cy, 3,5-Xyl-$(CH_2)_4$; R^2= SO_2-Ph, 3-OMe-Ph, 4-OMe-Ph, 4-^{t}Bu-Ph, 4-Ph-Ph, 2-Naph and R^3= ^{t}Bu, Ph) provided lower enantioselectivities and activities than their related phosphinite/phosphine-oxazoline ligands.[153] They also required a higher catalyst loading (4 mol%) and higher pressures (100 bar) to achieve full conversions.

In 2008, Diéguez *et al.* reported the first successful application of phosphite-oxazoline ligands for this process. Previously described pyranoside phosphite-oxazoline ligands **29** (R^1= Me, ^{i}Pr, ^{t}Bu, Ph, Bn) provided excellent enantioselectivities in the hydrogenation of a wide range of *E*- and *Z*-trisubstituted olefins, including triaryl-substituted alkenes and 4-methyl-1,2-dihydronaphthalenes (ee's up to >99%).[124,154]Moreover, ligands **29** also provided excellent enantioselectivities for the more challenging 1,1'-disubstituted olefins and also to α,β-unsaturated ketones and esters, allylic alcohols and vinyl silanes (ee's up to >99%).

Biaryl phosphite-oxazoline ligands **30** (R^1= Ph, 4-Me-Ph, 4-CF_3-Ph; R^2= H, Me and R^3= H, Me), which are based on privileged phosphinite-oxazoline ligands **16**, have been successfully applied in the hydrogenation of a wide range of *E*- and *Z*-trisubstituted olefins **S18**-**S21**, 1,1'-disubstituted alkenes **S28**, and alkenes containing a neighboring polar group (ee's up to >99%).[155] These results clearly indicated that introducing a biaryl phosphite moiety in the ligand design was highly advantageous in terms of substrate versatility.

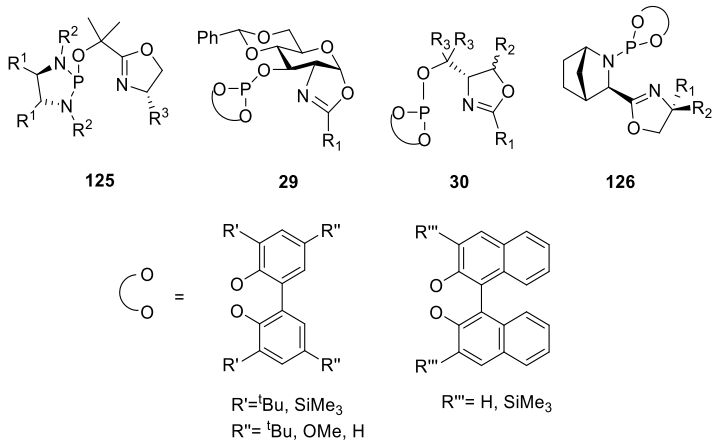


Figure 1.45. Successfully applied phosphite/phosphoramidite-oxazoline ligands.

In 2014, Diéguez in collaboration with Andersson, designed a modification of the previously described **121** by replacing the N-phosphine by a phosphoramidite moiety. This phosphoramidite-oxazoline **126** provided excellent results in terms of both, conversions and enantioselectivities, achieving excellent results even with the more challenging *Z*-alkenes **S21** (ee's up to 96%).[156]

Phosphorus-other-sp^2-nitrogen donor ligands

As mentioned previously, phosphorus-oxazoline ligands have played a dominant role in the iridium-catalyzed hydrogenation of minimally functionalized olefins. However, in the recent years, the research has focused on the design of ligands containing other nitrogen donor groups more robust than oxazolines. In this section, a collection of the most representative phosphorus/other nitrogen donor ligands will be presented.

Phosphorus-pyridine ligands

In this respect, the use of pyridine-containing ligands as an alternative to oxazolines is of interest due to the robustness and the easy incorporation of the pyridine group. Only few pyridine-containing ligands have provided outstanding results in terms of enantioselectivity and substrate versatility.

To mimic the coordination sphere of Crabtree's catalyst, Knochel *et al.* designed a new kind of chiral P,N ligands that incorporated a pyridine moiety as N-donor group. They prepared phosphine-pyridine ligand **127**[157] (R^1= Ph, Cy,; R_2= H, Ph; R_3= H; R_2-R_3= CH-CH=CH-CH) for the hydrogenation of trisubstituted olefins and obtained moderate-to-high enantioselectivities in the reduction of *E*-stilbenes derivatives (ee's up to 96%).

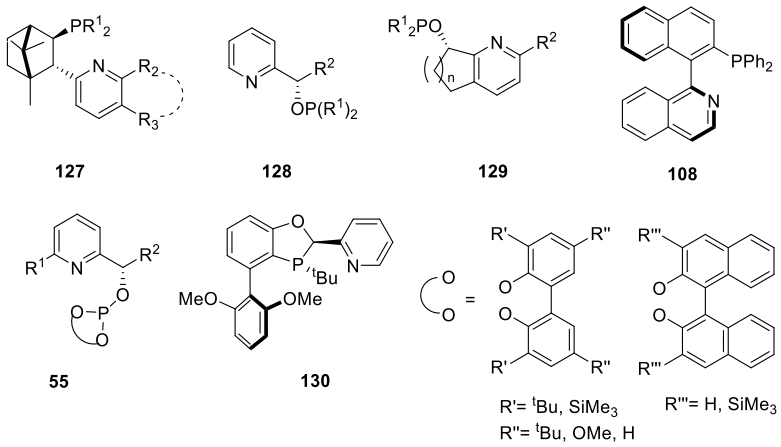


Figure 1.46. Representative example of phosphorus-pyridine donor ligands.

Pfaltz *et al.* developed the first generation of phosphinite-pyridine ligands **128**[158] (R^1= Ph, *o*-Tol, Cy, ^{t}Bu and R^2= Me, ^{t}Bu, Ph, CPh_3), which was successfully applied in the hydrogenation of trisubstituted olefins **S19**-**S21** (ee's up to 96%, 87% and 90%, respectively), and olefins containing a neighboring polar group such as **S24** and **S25**, achieving enantioselectivities up to 96% ee. Moreover, tetrasubstituted olefins **S17** could be hydrogenated in full conversion and 81% ee. Although good enantioselectivities were obtained, the substrate versatility was not broad.

In order to increase the rigidity in the alkyl bridge moiety, ligands **129** were developed (R^1= Ph, *o*-Tol, Cy, ^{t}Bu; R^2= H, Ph, Me and R^3= H, Me).[159] This ligand family has become one of the most powerful pyridine-containing ligand for Ir-hydrogenation of minimally functionalized olefins. These ligands have efficiently hydrogenated all kind of trisubstituted olefins, including furans and benzofurans derivatives **S40-S43** and pure alkyl trisubstituted alkenes **S44**-**S46** in high enantioselectivities as well as trisubstituted pinacol derived boronic esters **S47-S48**, α,β-unsaturated lactones **S37** and N-protected indoles **S49-S50** (Figure 1.47).

In 2007, phosphine-quinoline ligand **108** was developed by Li *et al.*[160] That ligand presented axial chirality and was applied in the Ir-hydrogenation of trisubstituted olefins with promising results (ee's up to 95% for both *E*- and *Z*-isomers **S20**-**S21**).

In 2013, Diéguez *et al.* reported a modular library of readily available phosphite-pyridine ligands **55** (R^1= H, Me, Br, Ph, Quin and R^2= Me, ^{t}Bu, Ph).[161] Ligands **55** showed higher substrate versatility than related phosphinite-based ligands **128**. Excellent enantioselectivities (ee's up to 99%) have been therefore obtained in a wide range of *E*- and *Z*-trisubstituted alkenes, including more demanding triaryl-substituted olefins and dihydronaphthalenes **S39**. Moreover, this phosphite-pyridine family extends its good

performance to the very challenging class of terminal disubstituted olefins **S28**, and to olefins containing neighboring polar groups.

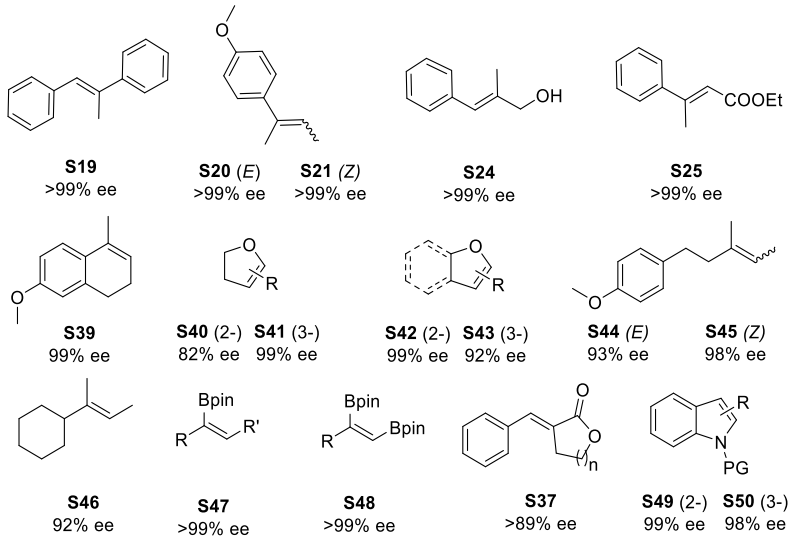


Figure 1.47. Substrate scope for the hydrogenation of olefins using Ir**-129**.

Recently, in 2014, group of Qu[162] presented P-stereogenic phosphine-pyridine ligand **130**. This ligand was successfully applied in the hydrogenation of tetrasubstituted olefins, providing full conversion and enantioselectivities up to 80% ee. Moreover, this Ir-**130** catalytic system could also enantioselectively hydrogenate susbtarte **S19** (90% ee), dihydronaphthalenes **S39** (76% ee) and allylic alcohols **S24** (86% ee).
Another interesting approach is the replacement of oxazoline by imidazole, oxazole or thiazole and thiazoline groups (Figure 1.48).

Imidazole/Oxazole/Thiazole/Thiazoline-phosphorus ligands

The first application of this type of ligands was reported by Pfaltz *et al.* using phosphine-imidazole ligands **131** (R^1= Ph, *o*-Tol; R^2= ^{i}Pr, ^{t}Bu; R^3= ^{i}Pr, ^{t}Bu, Cy, Ph, Bn, *p*-Tol).[163] The advantage that this kind of ligands present is the introduction of an extra substituent at the nitrogen of the N-donor group. Ligand **131** provided better enantioselectivities in Z-alkenes **S21** compared to PHOX **3** (ee's up to 88 compared to those ee's up to 42% obtained using PHOX **3**). The same group also replaced the substituent in the nitrogen of the imidazole group by an anionic substituent, achieving zwitterionic iridium complexes. Unfortunately, that derivatization had a negative effect on the enantioselectivity.[164] Andersson *et al*. developed phosphine-imidazole **132** (R^1= Ph, o-Tol, 3,5-diMe-Ph), which provided enantioselectivities up to 98% ee in the hydrogenation of unfunctionalized alkenes.[165] Also Andersson reported a family of phosphinite-oxazole

ligands **133** (R= Ph, *o*-Tol, 3,5-diMe-Ph)[166] and phosphine-thiazole ligands **134** (R^1= Ph, *o*-Tol, R^2 = H, Ph).[167] Both families of ligands provided high enantioselectivities in the hydrogenation of both *E*- and *Z*-aryl/alkyl trisubstituted olefins becoming valuables ligands in the hydrogenation of minimally functionalized olefins. Ligands **134** have also proved to be optimal for the hydrogenation of cyclic alkenes, dienes, 1,1'-diaryl trisubstituted olefins, trifluoromethyl-containing olefins and vinyl silanes.[167]

The same authors also developed N-phosphine thiazole **135** and **136**. N-phosphine-thiazole **135**[168] allowed to expand the substrate versatility of the catalytic system. Therefore, high enantioselectivities were achieved in the hydrogenation of fluorinated olefins, diphenylphosphine oxides and vinyl phosphonates, becoming one of the most privileged ligands for the Ir-hydrogenation of minimally functionalized olefins. N-phosphine-thiazole **136** (R^1= Ph, *o*-Tol and R^2= Me, ^{t}Bu, Ph)[169] has a rigid bicyclic backbone and allows achieving high enantioselectivities in the reduction of *E*-trisubstituted olefins (ee's up to 97%) but enantioselectivities for *Z*-olefins decreased to 83%. Interestingly, Ir-**136** catalytic system provided excellent enantioselectivities for the hydrogenation of vinyl boronates. Those results complement perfectly with the N-phosphine-oxazoline **121** (Figure 1.42), which could enantioselectively hydrogenate monoborated substrates. Recently, Andersson *et al.* have demonstrated that N-phosphine-thiazoline **136** are able to hydrogenate vinylic, allylic and homoallylic sulfones with enantioselectivities up to 99%.

Ellman *et al.* developed chiral sulfonyl imine ligands **137**[170] (R_1= Ph, *o*-Tol, Mes; R_2= ^{t}Bu, 1-adamanthyl, *p*-Tol). These ligands were only able to hydrogenate standard trisubstituted alkene **S19** in high enantioselectivity (ee's up to 94%).

In 2010, Diéguez in collaboration with Andersson's group reported a library of phosphite-oxazole/thiazole ligands – **57** and **58**- for this process (**57**; R= Ph, 4-CH_3-Ph, 4-CF_3-Ph, ^{t}Bu and **58**; R= H, Me).[171] Enantioselectivities were excellent (ee's up to 99%) for a wide range of *E*- and *Z*-trisubstituted and 1,1'-disubstituted terminal alkenes.

Another successful collaboration between Diéguez and Andersson group drove into the synthesis of phosphoramidite-thiazole **138**, a modification of the previously reported **136** by Andersson *et al.* These phosphoramidite-thiazole **138** provided excellent results in terms of conversion and enantioselectivity. It is needed to point out that those ligands, as well as phosphoramidite-oxazoline **126** (Figure 1.45) provided excellent enantioselectivities for *Z*-alkenes (ee's up to 90%).[156]

Diéguez *et al.*[172] also applied ligand **56** and they achieved excellent enantioselectivities in the hydrogenation of a wide range of *E*- and *Z*-trisubstituted **S19-S21** and 1,1-disubstituted terminal olefins **S28**, which included examples with neighboring polar groups. They found that replacing the oxazoline **30** with a thiazoline moiety in the ligand design is beneficial in terms of the substrate scope. Thus, the range of substrates that can be hydrogenated with excellent enantioselectivities with the new Ir phosphite–thiazoline catalysts was extended because more challenging *Z*-trisubstituted olefins, α,β-

unsaturated ketones **S26-S28**, and trifluoromethyl olefins were included. These results opened up a new class of ligands for the highly enantioselective Ir-catalyzed hydrogenation of a wide range of substrates, which competes favorably with the best reported in the literature[172]

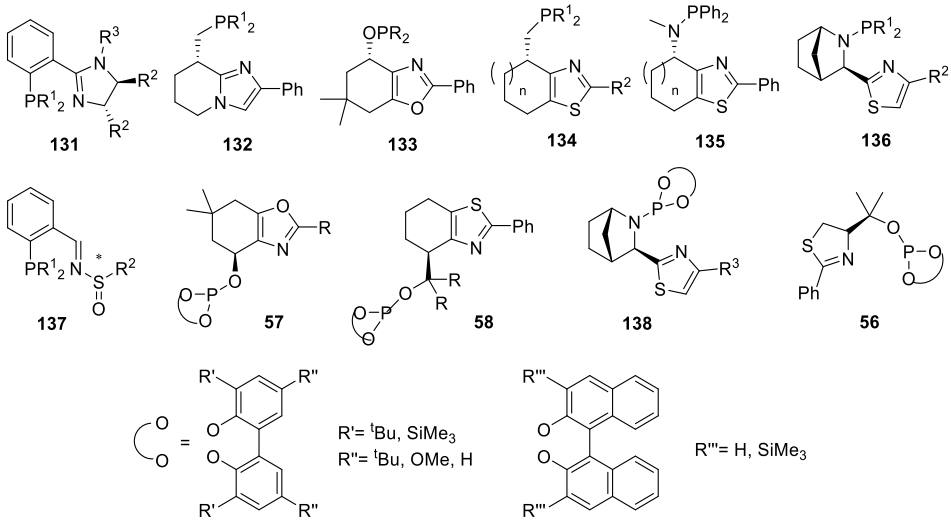


Figure 1.48. Phosphorus-imidazole/oxazole/thiazole ligands.

Phosphorus-sp^3-nitrogen-donor ligands

Also phosphorus sp^3-nitrogen containing ligands have been developed and successfully applied in the hydrogenation of alkenes.

Zhou *et al.* developed a modification of *spiro* ligand **117** (Figure 1.41), leading to ligand **139** (R^1= Ph, 3,5-Me_2-Ph, 3,5-$^t Bu_2$-Ph; R^2= H, Me), in which the oxazoline moiety has been replaced by an amino group.[173] They determined that secondary amines were better than primary amines if enantioselectivity want to be high. Those ligands were successfully applied in the iridium hydrogenation of a wide range of α-substituted acrylic acids **S51**-**S55**, achieving excellent enantioselectivities up to 99% ee (Figure 1.49).

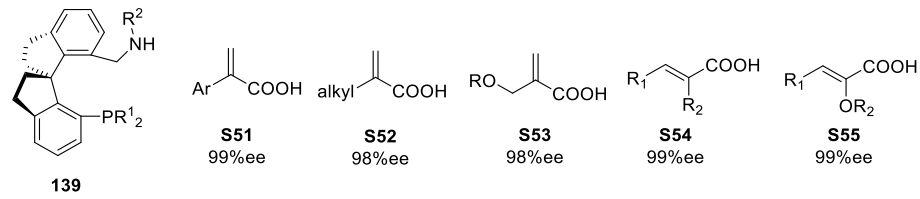


Figure 1.49. Spiro phosphine-amine ligand **139** developed by Zhou *et al.*

1.3.2. Asymmetric hydrogenation of cyclic β-enamides

As previously mentioned, several efficient catalytic systems based on Ru, Rh and Ir have emerged for hydrogenation of olefins. However, there is still a lack of substrate versatility in terms of enantioselectivity. Such substrates include cyclic enamides derived from β-tetralones and derivatives. The asymmetric hydrogenation of these substrates is highly persuaded due to the therapeutic properties that chiral amines present (Figure 1.50).[174]

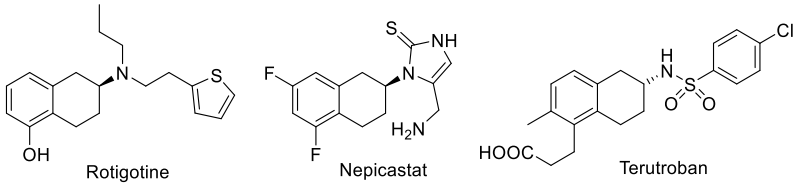


Figure 1.50. Therapeutic products derived from the hydrogenation of cyclic β-enamides.

Until few years ago, the asymmetric hydrogenation of cyclic enamides has been mainly focused on α-enamides, and to less extension, β-enamides.

The use of Rh-, Ru- and Ir-catalyst have emerged as powerful catalyst for hydrogenation of challenging cyclic β-enamides. However, complete control of stereoselectivity of this transformation has remained elusive. With Ru-based systems, Burneau *et al*.[175] and Ratovelomanona-Vidal *et al.*[176] successfully applied ligands **140** and **141** respectively, achieving ee's up to 95%. In the field of Rh-catalytic systems, Pizzano *et al.* developed a P-stereogenic phosphine-phosphite **142** achieving excellent enantioselectivities (up to 93% ee).[177] Also the groups of Reek and Tang have developed Rh-hydrogenation of cyclic β-enamides, using ligands **143** [178] and **144** [179] respectively, achieving enantioselectivities up to 96% ee.

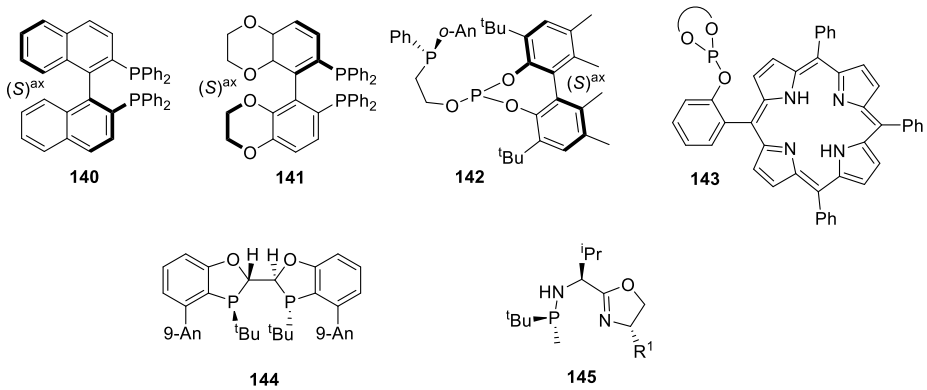


Figure 1.51. Successfully applied ligands in the hydrogenation of cyclic β-enamides.

Finally, in the field of Ir-catalysts, Verdaguer *et al.* recently published a successful application of P-stereogenic phosphine-oxazoline ligands **145** (R^1= ^{i}Pr, ^{t}Bu), achieving excellent enantioselectivities (ee's up to 99%) for a wide range of cyclic α- and β-enamides.[180]

1.3.2.1. The mechanism

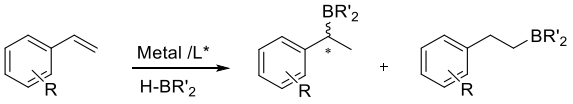
The challenging nature of these kind of substrates to be hydrogenated in high enantioselectivities as well as the few successful examples in the literature, exemplifies the lack of mechanistic information. Only attempts to get further information have been presented using Rh-catalytic systems.

In 2013, Pizzano *et al.* reported an investigation of several fundamental features of these kind of substrates with their hydrogenation process catalyzed by Rh-**142** catalytic system.[177] They analyzed the catalytic species formed from the mixture of catalyst precursor and cyclic β-enamide and they found the presence of two species in a *ca.* 3:1 ratio. After characterization by NMR the authors suggest that those species were η6-arene coordination to Rh, differing from the coordination of the substrate by each of its diastereotopic faces. It is remarkable to note that this coordination mode was unusual for an N-acyl enamide, which typically shows a O,C,C chelating mode in Rh(I) complexes. Due to the relatively low rates shown for these kind of substrates, they could suggest that these unreactive η^6-arene-Rh complex, under hydrogenation conditions, is in equilibrium with the Rh-O,C,C species, more shifted to the η6-arene-Rh species.

These results obtained, however, did not show a distinctive feature of the hydrogenation of these kind of substrates, responsible for the rather difficult control of enantioselectivity.

1.4. Asymmetric hydroboration of 1,1-disubstituted olefins

Metal-catalyzed hydroboration of olefins has emerged as a powerful synthetic tool for organic chemists (Scheme 1.25). The contribution of organoboron species to organic chemistry, recognized already by one Nobel prize, continues unabated.[181]



Scheme 1.25. Metal-catalyzed hydroboration of olefins.

Considering that the introduction of main-group organometallics such as boron into organic compounds is rarely the ultimate goal of a hydroboration reaction, methods for

transformation of the newly introduced carbon-boron bond with retention of stereoselectivity are crucial.[181]

The organoboranes produced are important intermediates in many natural product and drug synthesis. They serve as synthons for numerous functional groups and are often subject to a consecutive carbon-oxygen, carbon-carbon, carbon-nitrogen bond-forming reactions (Figure 1.52).[181]

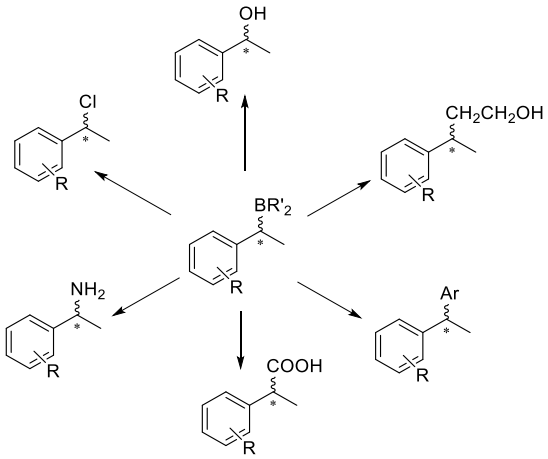
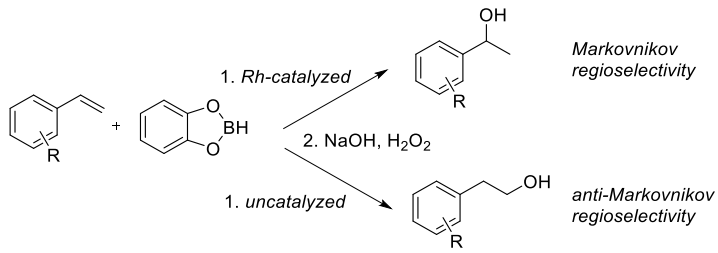


Figure 1.52. Transformations of the carbon-boron bond.

Whether the process mediated or catalyzed, in most asymmetric transformations involving olefins as prochiral reagents, 1,1-disubstituted olefins stand out as a particularly more challenging substrates.[182] This can be attributed to the difficulty of a chiral auxiliary or chiral catalyst to discriminate between two relatively similar substituents at a germinal position and therefore, discriminate between the two faces of the olefin. For that reason, enantioselectivities for these substrates are usually lower than those obtained for the corresponding 1,2-disubstituted, trisubstituted or even tetrasubstituted analogues.[181,182,183] In addition, in asymmetric hydroboration the un-catalyzed hydroboration-oxidation of an alkene usually affords the anti-Markovnikov product, while the catalyzed version can be induced to provide either Markovnikov or anti-Markovnikov products (Scheme 1.26).[181]

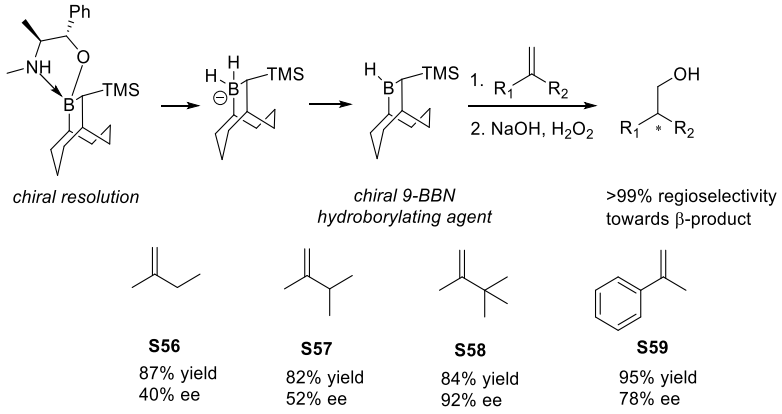
The strongly favored Markovnikov regioselectivity observed with most chiral transition metal catalyst investigated to date has certainly precluded the development of a catalytic asymmetric hydroboration of terminal olefins.[181,184] Suzuki, Burgess and Ito and Hayashi have independently demonstrated the difficulty of obtaining specific hydroboration at terminal position (β) rather than at the more substituted (α) using chiral rhodium catalyst (Scheme 1.26).[185] Moderate regioselectivities and low enantioselectivities were obtained in the best cases. For that reason, almost all studies have been focused on the α-hydroboration of styrene derivatives.



Scheme 1.26. Regioselectivity in metal-catalyzed and uncatalyzed hydroboration.

1.4.1. Uncatalyzed asymmetric hydroboration of 1,1-disubstituted olefins

A first successful procedure for hydroboration of 1,1-disubstituted olefins was carried out by Soderquits *et al.* who designed chiral variants of 9-borabicyclononane (9-BBN) that mediated the hydroboration of four different terminal olefins, displaying an unprecedented enantioselectivities for the most basic substrates **S56**-**S59** (Scheme 1.27).[186]



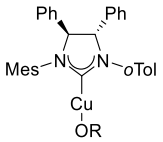
Scheme 1.27. First successful hydroboration of 1,1-disubstitued olefins.

As previously mentioned, uncatalyzed hydroboration of alkenes always afford *anti*-Markovnikov regioisomer. Soderquits' work provided excellent yields, total regioselectivity and moderate-to-excellent enantioselectivities (Scheme 1.27).

1.4.2. Metal-catalyzed asymmetric hydroboration of 1,1-disubstituted olefins

Subsequently, two important breakthroughs in asymmetric hydroboration of 1,1-disubstituted olefins were reported.[187,188] They both included metal-catalyzed processes instead of expensive and sacrificial stoichiometric chiral auxiliaries.

First breakthrough on metal-catalyzed hydroboration of terminal olefins was carried out by Hoveyda *et al.* They reported a NHC-Cu-catalyzed enantioselective hydroboration of acyclic and exocyclic 1,1-disubstituted alkenes (Scheme 1.28).[187]



146

Scheme 1.28. NHC-Cu-catalyzed asymmetric hydroboration of alkenes.

Hoveyda et al. were able to hydroborate sterically and electronically different 1,1-disubstituted alkenes providing organoboranes in high conversions and in a wide range of enantioselectivities (ee's from 61% to 92%) using Cu-**146** catalytic system. They could also hydroborate exocyclic alkenes, a kind of substrates which had never been hydroborated before (Figure 1.53a). Despite this important advance, high catalyst loadings (7.5 mol%), long reaction times (48h), low temperature (ranging from -15 ºC to -50 ºC) and the presence of an almost equimolar amount of base were required.
After such excellent results they tried to hydroborate α-CF_3 styrene derivative **S60**, due to its importance in biologically active products, but unfortunately authors obtained difluoroallylboronated instead of expected hydroborated product (Figure 1.53b).

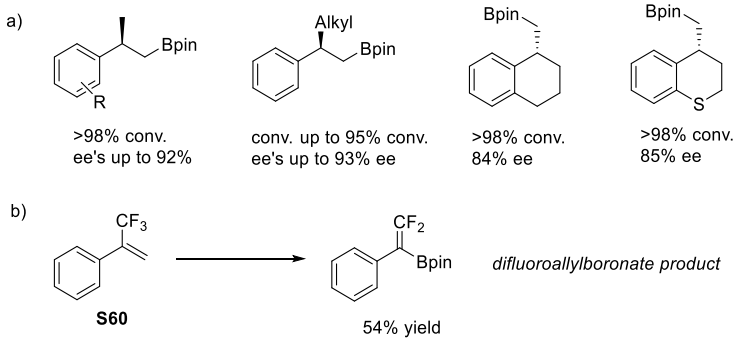
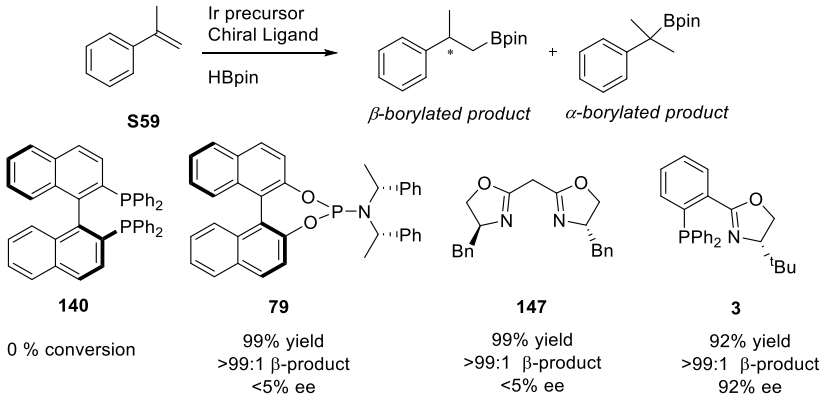


Figure 1.53. Selected results for NHC-Cu-catalyzed asymmetric hydroboration.

The second breakthrough in metal-catalyzed hydroboration of 1,1-disubstituted olefins was carried out by Mazet *et al.*[188] They presented a highly regio- and enantioselective catalytic hydroboration of α-substituted styrene derivatives.
They used phosphine-oxazoline (PHOX **3**) iridium catalyst to afford high regioselectivities towards β-borylated product. As Marder and Baker, Crudden and Miyaura stablished, iridium catalysts display a complementary regioselectivity that of rhodium catalysts in the hydroboration of styrene derivatives.[189] They screened different kind of chiral ligands

(Scheme 1.29). They found out that only C_1-symmetric PHOX **3** ligands provided excellent enantioselectivity (92% ee) in the hydroboration of α-methyl styrene.



Scheme 1.29. Screening of four ligands carried out by Mazet *et al.*

Authors applied this *in situ* generated Ir-PHOX complex to the hydroboration of a wide range of α-substituted styrene substrates, achieving promising enantioselectivities while excellent conversions and regioselectivities were attained. (Figure 1.54). They found that the introduction of electron-withdrawing substituents on the *para*-position decreased slightly the enantioselectivity compared to the model substrate.

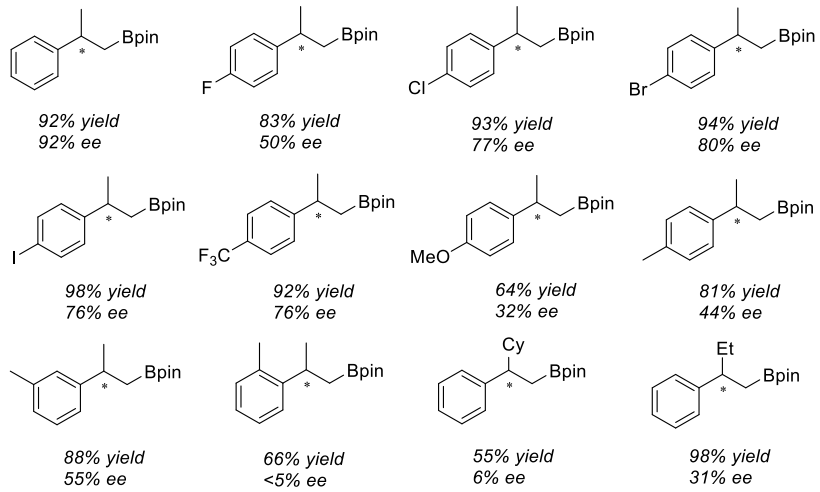


Figure 1.54. Iridium catalyzed asymmetric hydroboration performed by Mazet *et al.*

Also increasing the steric demand at the vicinity of the benzylic position by using a larger substituent compared to methyl such as cyclohexyl or ethyl substituents or also replacing the phenyl by a *ortho*-tolyl, drastically reduced the enantioselectivities (Figure 1.54).

1.5. Asymmetric Ni-catalyzed 1,2-addition of organoaluminum reagents to aldehydes

Among C-C bond forming reactions, the addition of carbon nucleophiles to carbonyl compounds such as aldehydes, is one of the most fundamental transformation for organic synthesis. The formed secondary alcohols, which contains a new stereogenic center, has let to great efforts to control stereochemistry of these additions.[190]

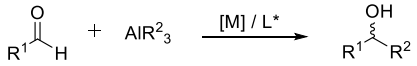
The typical reagents for racemic additions, such as lithium and magnesium organyls, are less suitable for this reaction because of their high reactivity and therefore, less chemoselectivity. In contrast, diorganozinc reagents, which are less reactive and its addition is catalyzed by a metal and could be asymmetrically added to carbonyl compounds, is rather attractive due to economic reasons. Moreover, $ZnMe_2$, a valuable organozinc reagent because of the importance of introducing methyl groups in synthetic strategy, is not very reactive.[191]

The reactivity of triorganoaluminum reagents is found between those two organometallic groups explained above. On one hand, trialkylaluminum reagents slowly react with carbonyl groups[192] and on the other hand, they show a higher functional groups tolerance than their magnesium and lithium analogues.[193] An additional advantage is the low price of unfunctionalized trialkylaluminum reagents (AlR_3, R= Me, Et, ^{n}Pr, ^{n}Bu and ^{i}Bu), which are produced on an industrial scale as they are easily synthesized by reaction of aluminum hydride and olefins.[194]

Another attractive venue is offered by hydroalumination of different unsaturated C-C bonds, which provides a wide range of different and highly potential triorganoaluminum compounds. They have shown to react easily, not only in 1,2-addition to carbonyl compounds, but also to cross-coupling and 1,4-additions reactions.[195]

Despite all advantages that triorganoaluminum reagents offer, only few examples of 1,2-addition of organoaluminum compounds to carbonyls have been reported in the literature.[196-200]

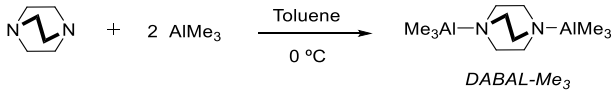
In this respect, the few successful catalysts developed to date for the enantioselective addition of trialkylaluminum reagents to aldehydes (Scheme 1.30) can be grouped in 2 types, depending on the metal that catalyzes this addition.



Scheme 1.30. Metal-catalyzed 1,2-addition of trialkylaluminum to aldehydes.

The first group is based on titanium complexes which usually provide high enantioselectivities, but the high catalyst loadings (10-20 mol%) as well as the slow turnover rate, hamper their potential utility.[196] The second group is based on nickel complexes, which were introduced by Woodward *et al.*, and they provide similar enantioselectivities to those using Ti-complexes but with low catalyst loadings (1 mol%).[197,196] Several aldehydes, such as aryl-, alkyl- and vinyl aldehydes have been tested. However, benzaldehyde have been used as benchmark substrate for testing the potential of the new ligands. Another important parameter which one has to take into account is the aluminum source, which has an important effect on the activity as well as in the enantioselectivity. Traditionally, commercially available trialkyl aluminum reagents have been mostly used. However, as these reagents are air- and moisture sensitive, they can be contaminated and their reactivity can be modified.

Woodward *et al.* have reported the preparation of DABAL-Me_3 (Scheme 1.31) as new air-stable solid $AlMe_3$ adduct that is easily prepared and also scaled-up from the reaction of neat $AlMe_3$ and DABCO (1,4-diazobicyclo[2,2,2]octane).[201]

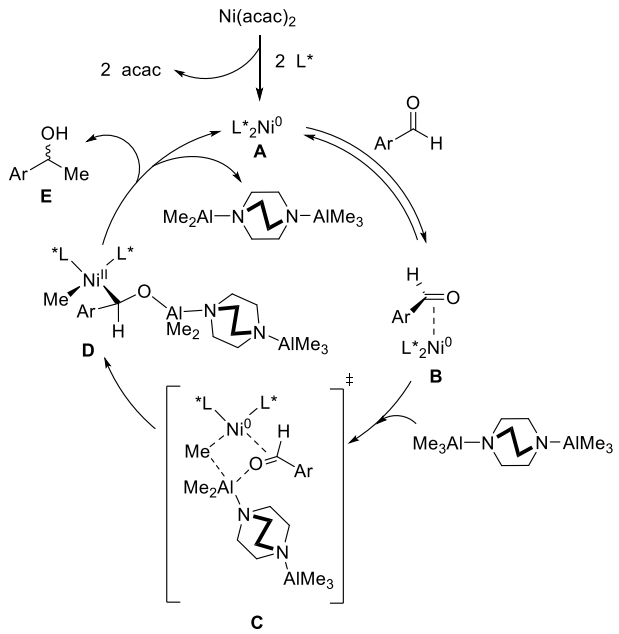


Scheme 1.31. Synthesis of DABAL-Me_3, developed by Woodward *et al.*

1.5.1. The Mechanism

The tentative mechanism proposed by Woodward *et al.* for the Ni-catalyzed 1,2-addition of DABCO-trimethylaluminum reagents to aryl aldehydes is shown in Scheme 1.32.

The reductive generation of the active specie Ni^0 **A** proceeds from the corresponding ligand complexation with Ni precursor (usually $Ni(acac)_2$). This reductive generation of the active catalyst **A** is followed by the formation of a η-aldehyde complex **B**, as showed possible by the work of Walther who was able to crystalize $Ni(\eta^2\text{-}O{=}CHAr)(PCy_3)_2$ (Ar= Ph and 2,4-$(OMe)_2C_6H_3$). [202] Then, the triorganoaluminum prompted the oxidative addition promoted by the formation of an extremely strong Al-O bond, furnishing Ni^{II} species **D** through transition state **C**. Finally, reductive elimination provided the corresponding alcohol **E** and the regeneration of the active catalyst **A**.



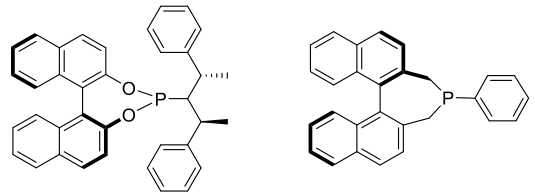
Scheme 1.32. Proposed catalytic cycle for the Ni-catalyzed 1,2-addition of DABAL-Me_3 to aromatic aldehydes.

1.5.2. The Ligands

As previously mentioned, only few catalytic systems based on Ni-catalyst have been successfully applied in the 1,2-addition of trialkylaluminum reagents to aldehydes.

Monodentate Ligands: phosphoramidite and phosphite ligands

A first breakthrough in this field was presented in 2005 by Woodward *et al.* who applied phosphoramidite **79** and phosphine **148** - based Ni catalyst to the 1,2-addition of trialkylaluminum reagents to aldehydes (Figure 1.55).[197] Authors applied ligand **79** in the Ni-catalyzed 1,2-addition of trialkylaluminum reagents to aldehydes. Their results were pioneering on this field. Using benzaldehyde as benchmark substrate, they found that using either AlR_3 or the air stable analogue DABAL-Me_3, enantioselectivities did not dramatically changed (88% ee for $AlMe_3$ and 92% for DABAL-Me_3 adduct), but yields were, in some cases, lower using non-stable organoaluminum reagents. They also studied the electronic effects of the substrate on the catalysis. They were further gratified to find that the range of substrates for that reaction using DABAL-Me_3 was wider than that of the original Fujisawa reaction[203], which had a narrower range, as only electronrich aldehydes reacted quickly. Excellent conversions and enantioselectivities (81-95% ee) were obtained either with electron-rich or electron-deficient benzaldehyde derivatives.



79 148

Figure 1.55. Phosphoramidite and monophosphine-based ligands applied by Woodward *et al.* in the Ni-1,2-addition of AlR_3 to aldehydes.

Using other alky- and cinnamaldehydes enantioselectivities were lower (ee's up to 77%). These poor enantioselectivities were improved using monophosphine **148**, which provided higher enantioselectivities for cinnamaldehyde (66% ee using **79** and 80% ee using **148**). It is worth to mention that sterically demanding aldehydes such as 1-naphthylaldehyde or 2-naphthylaldehyde could not be alkylated in high enantioselectivity, meaning that this Ni-**79** catalyst has apparently some steric limitations on the substrates that may be overcome. However, for the more challenging substrates such as enones and aliphatic aldehydes, enantioselectivities attained using **79** where excellent (ee's up to 94% for cyclic aliphatic aldehydes and 89% ee for lineal aliphatic aldehydes).

The other catalytic systems which have been successfully applied in the Ni-1,2-addition arose from a collaboration between Diéguez and Woodward groups in 2006.[198a] They applied a modular sugar-based phosphite ligand library **149**-**153** for studying the important structure features of the ligand (such as configuration of C-3 and C-4, ring size of the ligand scaffold and the presence of the phosphite function on a primary carbon) and to determine the scope of the phosphite ligand. They found that configuration of both C-3 and C-4 have a huge influence on the catalytic performance as well as the ring size, being ligand **149** the one which provided highest enantioselectivity (ee's up to 91%).

They determined that changing from $AlMe_3$ to $AlEt_3$ and DABAL-Me_3 there was no change on the catalytic performance, maintaining both activities and enantioselectivities. Regarding substrate scope, authors found that no matter the electronics of the substrate, enantioselectivity was always kept, having enantioselectivities of 94% ee and 93% ee for electron-rich and electron-poor benzaldehyde derivatives. For more flexible substrates such as cinnamaldehyde and aliphatic aldehydes, enantioselectivities decreased up to 25%.

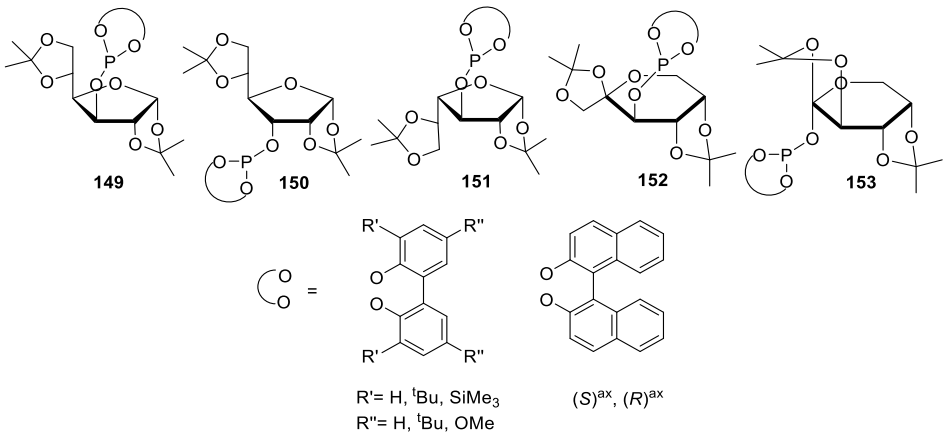


Figure 1.56. Sugar-based monophosphite ligands developed by Diéguez and Woodward groups.

In 2009 the same authors decided to replace phosphite moiety by a phosphoramidite, but unfortunately enantioselectivities were lower (ee's up to 78%) than their phosphite analogues **149**-**153**.[198b]

To fully understand the behavior of privileged phosphites **149**, in 2011 Diéguez *et al.* decided to modify C-3 by introducing alkyl substituents (**152** and **153** R= Me, Et, ^{i}Pr, Bn, Ph). The introduction of a substituent on the C-3 of the ligand backbone had a negative effect on the catalytic performance, decreasing enantioselectivities from 90% to 76% (using benzaldehyde and other derivatives). Interestingly, this monophosphite ligand provided good to excellent enantioselectivities (ee's up to 84%) when bulky 2-naphthaldehyde was used as a substrate and DABAL-Me_3 as alkylating agent.[199]

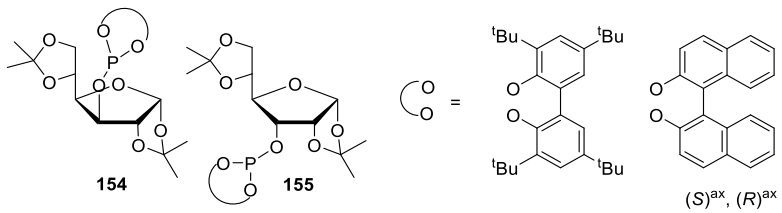


Figure 1.57. Modifications for privileged sugar-based monophosphite ligands **154**-**155**.

Bidentate ligands: P-P' and P-N ligands

In 2008, Diéguez and coworkers applied phosphite-oxazoline ligand **26** and phosphite-phosphoramidite ligand **156** in the Ni-catalyzed 1,2-addition to aldehydes with limited success. Systematically varying the electronic and steric properties of the oxazoline and

the biaryl substituents and the functional groups attached to the ligand backbone, they found a strong influence of the oxazoline substituents.

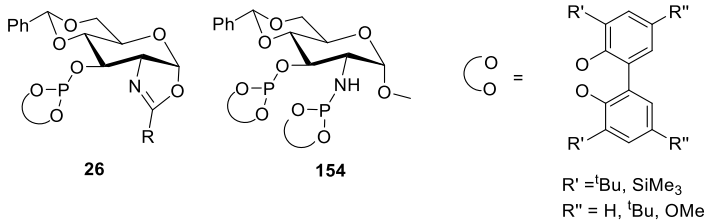


Figure 1.58. Bidentated phosphite-oxazoline and phosphite-phosphoramidite ligands.

Best enantioselectivities were achieved using phosphite-phosphoramidite **156** providing ee's up to 59%.[200b]

The same authors also have successfully applied furanoside phosphite-phosphoramidite and diphosphoramidite ligands **157**-**161**.[200a]

That work represented the first successful application of bidentate ligands for Ni-1,2-addition to aldehydes. Ligand **161** provided the best enantioselectivity (ee's up to 84% for benchmark benzaldehyde).

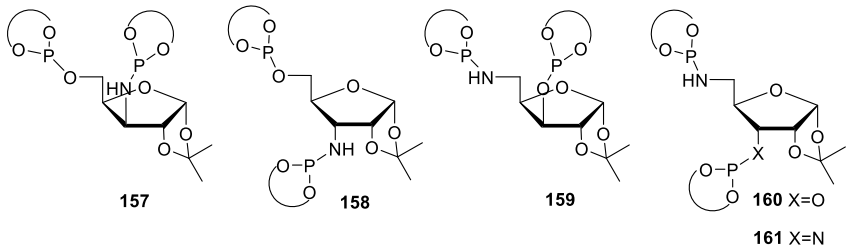


Figure 1.59. First successfully applied bidentate ligands in Ni-1,2-addition to aldehydes by Diéguez and coworkers.

1.6. References

1 a) *Asymmetric Catalysis in Industrial Scale: Challenges, Approaches and Solutions*; Blaser, H.U., Schmidt, E., Eds.; Wiley: Weinheim, **2003**. b) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N, Pfaltz, A., Yamamoto,H., Eds.; Springer-Verlag: Berlin, **1999**. c) *Asymmetric Catalysis in Organic Synthesis*; Noyori, R., Ed.; Wiley: New York, **1994**. d) *Applied Homogeneous Catalysis with Organometallic Compounds*, 2nd ed.; Cornils, B., Hermann, W. A., Eds.; Wiley-VCH: Wienhein, **2002**. e) *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; Wiley: New Jersey, **2010**.

2 a) *Palladium Reagents and Catalysis, Innovations in Organic Synthesis*; Tsuji, J., Ed.; Wiley: New York, **1995**. b) Trost, B. M.; van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395.

c) Johansen, M.; Jorgensen, K. A. *Chem. Rev.* **1998**,*98*, 1689. d) Trost, B. M.; Crawley,M. L. *Chem Rev.* **2003**, *103*, 2921. e) Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000**, *33*, 336. f) Lu, Z.; Ma, S. *Angew. Chem. Int. Ed.* **2008**, *47*, 258.

[3] For selected reviews and books, see: a) Yorimitsu, H.; Oshima, K. *Angew. Chem. Int. Ed.* **2005**, *44*, 4435. b) Alexakis, A.; Bäckvall, J.-E; Krause, N.; Pàmies, O.; Diéguez, M. *Chem. Rev.* **2008**, *108*, 2796. c) Karlström, A. S. E.; Bäckvall ,J.-E. in *Modern Organocopper Chemistry*; Krause, N., Ed.; Wiley-VCH: Weinheim, **2002**. d) *Copper-Catalyzed Asymmetric Synthesis*; Alexakis, A.; Krause, N.; Woodward, S.; Ed. Wiley-VCH: Weinheim, **2014**. e) Harutyunyan, S. R.; den Hartog, T.; Geurts, K.; Minaard, A. J.; Feringa, B. L. *Chem. Rev.* **2008**, *108*, 2842. f) Faciola, C. A.; Alexakis, A. *Eur. J. Org. Chem.* **2008**, 3765. g) Cherney, A. H.; Kadunce, N. T.; Reisman, S. E. *Chem. Rev.* **2015**, *115*, 9587. For selected publications of mechanistic studies, see: h) Bäckvall, J.-E.; Sellén, M.; Grant, M. *J. Am. Chem. Soc.* **1990**, *112*, 6615. i) Sofia, A.; Karlström, E.; Bäckvall, J.-E. *Chem. Eur. J.* **2001**, *7*, 1981. j) Yamanaka, M.; Kato, S.; Nakamura, E. *J. Am. Chem. Soc.* **2004**, *126*, 6287, k) You, H.; Rideau, E.; Sidera, M.; Fletcher, S. P. *Nature*, **2015**, *571*, 351.

[4] Hayashi, T.; Yamamoto, A.; Ito, Y.; Nishioka, E.; Miura, H.; Yanagi, K. *J. Am. Chem. Soc.* **1989**, *111*, 6301.

[5] Butts, C. P.; Fiali, E.; Lloyd-Jones, G. C.; Norrby, P.-O.; Sale, D. A.; Schramm, Y. *J. Am. Chem. Soc.* **2009**, *131*, 9945.

[6] a) Trost, B. M.; van Vranken, D. L.; Bingel, C. *J. Am. Chem. Soc.* **1992**, *114*, 9327. b) Trost, B. M. *Acc. Chem. Res.* **1996**, *29*, 355.

[7] a) Von Matt, P.; Pfaltz, A. *Angew. Chem. Int. Ed.* **1993**, *32*, 566. b) Sprinz, J.; Helmchen, G. *Tetrahedron Lett.* **1993**, *34*, 1769. C) Dawson, G. J.; Frost, C. G.; Williams, J. M.; Coote, S. J. *Tetrahedron Lett.* **1993**, *34*, 3149.

[8] For selected reviews: a) Martin, E.; Diéguez, M. *C. R. Chimie* **2007**, *10*, 188. b) Gomez, R.; Carretero, J. C. *Chem. Commun.* **2011**, *47*, 2207. For selected results see: c) Evans, D. A; Campos, K. R.; Tedrow, J. S.; Michael, F. E.; Gagné, M. R. *J. Org. Chem.* **1999**, *64*, 2994. d) Evans, D. A; Campos, K. R.; Tedrow, J. S.; Michael, F. E.; Gagné, M. R. *J. Am. Chem. Soc.* **2000**, *122*, 7905. e) Caldentey, X.; Pericàs, M. A. *J. Org. Chem.* **2011**, *75*, 2628. f) Priego, J.; García Macheño, O.; Cabrera, S.; Gómez Arrayás, R.; Llamas, T.; Carretero, J. C. *Chem. Commun.* **2002**, 2512. g) García Mancheño, O.; Priego, J.; Cabrera, S.; Gómez Arrayás, R.; Llamas, T.; Carretero, J. C. *J. Org. Chem.* **2003**, *68*, 3679. For selected results on etherification reactions: h) Coll, M.; Pàmies, O.; Diéguez, M. *Org. Lett.* **2014**, *16*, 1892. i) Lam, F. L.; Au-Yeung, T. T.-L.; Kwong, F. Y.; Zhou, Z.; Wong, K. Y.; Chan, A. S. C. *Angew. Chem. Int. Ed.* **2008**, *47*, 1280.

[9] a) Cheng, H.-G.; Feng, B.; Chen, L.-Y.; Guo, W.; Yu, X.-Y.; Lu, L.-Q.; Chen, J.-R.; Xiao, W.-J. *Chem. Commun.* **2014**, *50*, 2873. b) Feng, B.; Cheng, H.-G.; Chen, J.-R.; Deng, Q.-L.; Lu, L.-Q.; Xiao, W.-J. *Chem. Commun.* **2014**, *50*, 9550.

[10] Diéguez, M.; Pàmies, O. *Acc. Chem. Res.* **2010**, *43*, 312.

[11] Gläser, B.; Kunz, H. *Synlett.* **1998**, 53.

[12] Moreno, R. M.; Bueno, A.; Moyano, A. J. *Organometal. Chem.* **2002**, *660*, 62.

[13] Frölander, A.; Lutsenko, S.; Privalov, T.; Moberg, C. *J. Org. Chem.* **2005**, *70*, 9882

[14] Liu, D.; Dai, Q.; Zhang, X. *Tetrahedron* **2005**, *61*, 6460.

[15] Liu, S.; Müller, J. F. K.; Neuburger, M.; Schaffner, S.; Zehnder, M. *Helv. Chem. Acta.* **2000**, *83*, 1256.

[16] Popa, D.; Puigjaner, C.; Gómez, M.; Benet-Buchholz, J.; Vidal-Ferran, A.; Pericàs, M. A. *Adv. Synth. Catal.* **2007**, *349*, 2265.

[17] Tietze, L. F.; Lohmann, J. K. Synlett, 2002, 2083.

[18] Danjo, H.; Higuchi, M.; Yada, M.; Imamotot, T. *Tetrahedron Lett.* **2004**, *45*, 603.

[19] a) Ahn, K. H.; Cho, C.-W.; Park, J.; Lee, S. *Tetrahedron: Asymmetry* **1997**, *8*, 1179. b) You, S.-L.; Hou, X.-L-; Dai, L.-X; Yu, Y-H.; Xia, W. J. Org. Chem. 2002, 67, 4684.

[20] a) Zhang, W.; Yoneda, Y.-I.; Kida, T.; Nakatsiju, Y.; Ikeda, I. *Tetrahedron: Asymmetry* **1998**, *9*, 3371. b) Park, J.; Quan, Z.; Lee, S.; Ahn, K. H.; Cho, C.-W. *J. Organometal. Chem.* **1999**, *584*, 140. c) Deng, W.-P.; You, S.-L.; Hou, X.-L.; Dai, L.-X.; Yu, Y.-H.; Xia, W.; Sun, J. *J. Am. Chem. Soc.* **2001**, *123*, 6508.

[21] You, S.-L.; Zhu, X.-Z.; Luo, Y.-M.; Hou, X.-L.; Dai, L.-X. *J. Am. Chem. Soc.* **2001**, *123*, 7471.

[22] a) Imai, Y.; Zhang, W.; Kida, T.; Nakatsuji, Y.; Ikeda,I. *Tetrahedron Lett.* **1998**, *39*, 4343. b) Selvkumar, K.; Valentini, M.; Pregosin, P.S. *Organometallics* **2000**, *19*, 1299.

[23] Tian, F.; Yao, D.; Zhang, Y. J.; Zhang, W. *Tetrahedron* **2009**, *65*, 9609.

[24] a) Hou, D.-R.; Burgess, K. *Org. Lett.* **1999**, *1*, 1745. b) Hou, D.-R.; Reibenspies, J. H.; Burgess, K. *J. Org. Chem.* **2001**, *66*, 206.

[25] Dugal-Tessier, J.; Dake, G. R.; Gates, D. *Org. Lett.* **2010**, *12*, 4667.

[26] a) Gilbertson, S. R.; Xie, D.; Fu, Z. *Angew. Chem. Int. Ed.* **1999**, *38*, 2750. b) Gilbertson, S. R.; Xie, D.; Fu, Z. *J. Org. Chem.* **2001**, *66*, 7240.

[27] Lai, Z.-W.; Yang, R.-F.; Ye, K.-Y.; Sun, H.; You, S.-L. *Beilstein J. Org. Chem.* **2014**, *10*, 1261.

[28] Hu, Z.; Li, Y.; Liu, K.; Shen, Q. *J. Org. Chem.* **2012**, *77*, 7957.

[29] a) Yonehara, K.; Hashizume, T.; Mori, K.; Ohe, K.; Uemura, S. *Chem. Commun.* **1999**, 415. b) Yonehara, K.; Hashizume,T.; Mori, K.; Ohe, K.; Uemura, S. *J. Org. Chem.* **1999**,*64*, 9374.

[30] a) Jones, G.; Richards, C. J. *Tetrahedron Lett.* **2011**, *42*, 5553. b) Jones, G.; Richards, C. J. *Tetrahedron: Asymmetry* **2004**, *15*, 653.

[31] a) Prétôt, R.; Pfaltz, A. *Angew. Chem. Int. Ed.* **1998**, *37*, 323. b) Prétôt, R.; Loyd-Jones, G. C.; Pfaltz, A. *Pure Appl. Chem.* **1998**, *70*, 1035.

[32] Hilgraf, R.; Pfaltz, A. *Adv. Synth. Catal.* **2005**, *347*, 61.

[33] Gladiali, S.; Loriga,G.; Medici, S.; Taras, R. *J. Mol. Cat. A: Chem.* **2003**, *196*, 27.

[34] Pàmies, O.; Diéguez, M.; Claver, C. *J. Am. Chem. Soc.* **2005**, *127*, 3646.

[35] a) Mata, Y.; Diéguez, M.; Pàmies, O.; Claver, C. *Adv. Synth. Catal.* **2005**, *347*, 1943. b) Mata, Y.; Pàmies, O.; Diéguez, M. *Adv. Synth. Catal.* **2009**, *351*, 3217.

[36] Diéguez, M.; Pàmies, O. *Chem. Eur. J.* **2008**, *14*, 3653.

[37] Jang, H.-Y.; Seo, H.; Han, J. W.; Chung, Y. K. *Tetrahedron Lett.* **2000**, *41*, 5083.

[38] Lee, J. H.; Son, S. U.; Chung, Y. K. *Tetrahedron: Asymmetry* **2003**, *14*, 2109.

[39] a) Hu, X.; Dai, H.; Hu, X.; Chen, H.; Wang, J.; Bai, C.; Zheng, Z. *Tetrahedron: Asymmetry* **2002**, *13*, 1687. b) Hu, X.; Dai, H.; Chen, H.; Wang, J.; Bai, C.; Zheng, Z. *Tetrahedron: Asymmetry* **2004**, *15*, 1065.

[40] Thiesen, K. E.; Maitra, K.; Olmstead, M. M.; Attar, S. *Organometallics* **2010**, *29*, 6334.

[41] Noël, T.; Bert, K.; Van der Eycken, E.; Van der Eycken, J. *Eur. J. Org. Chem.* **2010**, 4056.

[42] Fukuda, T.; Takehara, A.; Iwao, M. *Tetrathedron: Asymmetry* **2001**, *12*, 2793.

[43] Li, Y.; Liang, F.; Wu, R.; Li, Q.; Wang, Q.-R.; Xu, Y.-C.; Jiang, L. *Synlett* **2012**, 23, 1805.

[44] Deng, W.-H.; Ye, F.; Bai, X.-F.; Zheng, Z.-J.; Cui, Y.-M.; Xu, L. W. *ChemCatChem* **2015**, *7*, 75.

[45] Kohara, T.; Hashimoto, Y.; Saigo, K. *Synlett* **2000**, 517.

[46] Liu, Q.-L.; Chen, W.; Jiang, Q.-Y.; Bai, X.-F.; Li, Z.; Xu, Z.; Xu, L.-W. *ChemCatChem* **2016**, *8*, 1495.

[47] Spohr, V.; Kaiser, J. P.; Reggelin, M. *Tetrahedron: Asymmetry* **2006**, *17*, 500.

[48] Lemasson, F.; Gais, H.-J.; Raabe, G. *Tetrahedron Lett.* **2007**, *48*, 8752.

[49] For other recent applications, see: a) Godolfuss, B.; Löschmann, T.; Rominger, F. *Chem. Eur. J.* **2004**, *10*, 5422. b) Liu. Q.-B.; Zhou, Y.-G. *Tetrahedron Lett.* **2007**, *48*, 2101. c) Meng, X.; Gao, Y.; Li, X.; Xu. D. *Cat. Commun.* **2009**, *10*, 950. d) Leca, F.; Fernandez, F.; Muller, G.; Lescop, C.; Réau, R.; Gómez, M. *Eur. J. Inorg. Chem.* **2009**, 5583.

[50] Bunlaksananusorn, T.; Luna, A. P.; Bonin, M.; Micouin, L.; Knochel, P. *Synlett* **2003**, 2240.

[51] Ito, K.; Kashiwagi, R.; Iwasaki, K.; Katsuki, T. *Synlett* **1999**, 1563.

[52] Jiang, B.; Lei, Y.; Zhao, X. L. *J. Org. Chem.* **2008**, *73*, 7833.

[53] Meng, X.; Li, X.; Xu, D. *Tetrahedron: Asymmetry* **2009**, *20*, 1402.

[54] Mei, L.-Y.; Yuan, Z.-L.; Shi, M. *Organometallics* **2011**, *30*, 6466.

[55] De la Fuente, V.; Marcos, R.; Cambeiro, X. C.; Castillón, S.; Claver, C.; Pericàs, M. A. *Adv. Synth. Catal.* **2011**, *353*, 3255

[56] a) Fekner, T.; Müller-Bunz, H.; Guiry, P. J. *Eur. J. Org. Chem.* **2008**, *30*, 5055. b) Maxwell, A. C.; Franc, C.; Pouchain, L.; Müller-Bunz, H.; Guiry, P. *J. Org. Biomol. Chem.* **2008**, *6*, 3848.

[57] Liu, Q.-B.; Zhou, Y.-G. *Tetrahedron Lett.* **2007**, *48*, 2101.

[58] Shen, C.; Xia, H.; Zheng, H.; Zhang, P.; Chen, X. *Tetrahedron: Asymmetry* **2010**, *21*, 1936.

[59] Tsarev, V. N.; Lyubimov, S. E.; Bondarev, O. G.; Korlyukov, A.; Antipin, M. Y.; Prestovskii, P. V; Davankov, V. A.; Shiryaev, A. A.; Benetsky, E. B.; Vologzhani, P. A.; Gavrilov, K. N. *Eur. J. Org. Chem.* **2005**, 2097.

[60] Gavrilov, K. N.; Tsarev, V.; Zheglov, S.; Korlyukov, A.; Antipin, M.; Davankov, V. *Synthesis* **2007**, 1717.

[61] Meng, X.; Gao, Y.; Li, X.; Xu, D. *Catalysis Communications* **2009**, *10*, 950.

[62] a) Mazuela, J.; Paptchikhine, A., Tolstoy, P.; Pàmies, O.; Diéguez, M.; Andresson, P. G. *Chem. Eur. J.* **2010**, *16*, 620. b) Mazuela, J.; Pàmies, O.; Diéguez, M. *Chem. Eur. J.* **2013**, *19*, 2416. c) Mazuela, J.; Pàmies, O.; Diéguez, M. *ChemCatChem* **2013**, *5*, 1504. d) Lega, M.; Margalef, J.; Ruffo, F.; Pàmies, O.; Diéguez, M. *Tetrahedron Asymmetry* **2013**, *24*, 995.

[63] a) Jin, M.-J.; Jung, J.-A.; Kim, S.-H. *Tetrahedron Lett.* **1999**, *40*, 5197. b) Okuyama, Y.; Nakano, H.; Hongo, H. *Tetrahedron: Asymmetry* **2000**, *11*, 1193.

[64] a) Mino, T.; Tanaka, Y.; Akita, K.; Sakamoto, M.; Fujita, T. *Heterocycles* **2003**, *60*, 9. b) Mino, T.; Hata, S.; Ohataka, K.; Sakamoto, M.; Fujita, T. *Tetrahedron Lett.* **2001**, *42*, 4837.

[65] Jin, S.-H.; Jung, B.-H.; Ahn, W.-S.; Kim, G.-J. *Tetrahedron Lett.* **2003**, *44*, 1971.

[66] Tanaka, Y.; Mino, T.; Akita, K.; Sakamoto, M.; Fujita, T. *J. Org. Chem.* **2004**, *69*, 6679.

[67] a) Kubota, H.; Koga, K.; *Heterocycles* **1996**, *42*, 543. b) Wildhalm, M.; Nettekoven, U.; Kalchhauser, H.; Mereiter, K.; Calhorda, M. J.; Félix, V. *Organometallics* **2002**, *21*, 315.

[68] a) Mino, T.; Saito, A.; Tanak, Y.; Hasegawa, S.; Sato, Y.; Sakamoto, M.; Fujita, T. *Tetrahedron Letters* **2003**, *44*, 4667. b) Mino, T.; Saito, A.; Tanak, Y.; Hasegawa, S.; Sato, Y.; Sakamoto, M.; Fujita, T. *Tetrahedron* **2002**, *58*, 5209. c) Mino, T.; Saito, A.; Tanak, Y.; Hasegawa, S.; Sato, Y.; Sakamoto, M.; Fujita, T. *J. Org. Chem.* **2005**, *70*, 1937.

[69] Mino, T.; Wakui, K.; Oishi, S.; Hattori, Y.; Sakamoto, M.; Fujita, T. *Tetrahedron: Asymmetry* **2008**, *19*, 2711.

[70] Fukuzawa,S.-I.; Yamamoto, M.; Hosaka, M.; Kikuchi, S. *Eur. J. Org. Chem.* **2007**, *33*, 5540.

[71] Jin, M.-J.; Takale, V. B.; Sarkar, M. S.; Kim, Y. M. *Chem. Commun.* **2006**, 663.

[72] Schnitzler, V.; Nonglaton,G.; Roussière, H.; Maillet, C.; Evain, M.; Janvier, P.; Bujoli, B.; Petit, M. *Organometallics* **2008**, *27*, 5997.

[73] Wgang, Q.-F.; He, W.; Liu, X.-Y.; Chen, Y.; Qin, X.-Y.; Zhang, S.-Y. *Tetrahedron: Asymmetry* **2008**, *19*, 2447.

[74] Nemoto, T.; Hamada, Y. *Chem. Rec.* **2007**, *7*, 150.

[75] a) Van Klaveren, M.; Persson, E. S. M.; del Villar, A.; Grove, D. M.; Bäckvall, J. E. van Koten, G. *Tetrahedron Lett.* **1995**, *36*, 3059. b) Karlstrom, A. S. E.; Huerta, F. F.; Meuzelaar, G. J.; Bäckvall, J. E. *Synlett* **2001**, 923. c) Cotton, H. K.; Norinder, J.; Bäckvall, J. E. *Tetrahedron* **2006**, *62*, 5632.

[76] a) Alexakis, A.; Malan, C.; Lea, L.; Benhaim, C.; Fournioux, X. *Synlett* **2001**, 927. b) Alexakis, A.; Croset, K. *Org. Lett.* **2002**, *4*, 4147. c) Falciola, C. A.; Croset, K. T.; Alexakis, A. *Angew. Chem. Int. Ed*. **2006**, 45, 5995. d) Croset, K. T.; Alexakis, A. *Tetrahedron Lett.* **2004**, *45*, 7375. e) Falciola, C. A.; *Alexakis, A. Angew. Chem. Int. Ed.* **2007**, *46*, 2619. f) Li, H.; Alexakis, A. *Angew. Chem. Int. Ed.* **2012**, *51*, 1055. g) Giacomina, F.; Riat, D.; Alexakis, A. *Org. Lett.* **2010**, *12*, 1156. h) Langlois, J.-B.; Alexakis, A. *Chem. Commun.* **2009**, 3860. i) Langlois, J.-B.; Alexakis, A. *Adv. Synth. Catal.* **2010**, *352*, 447. j) Langlois, J.-B.; Emery, D.; Mareda, J.; Alexakis, A. *Chem. Sci.* **2012**, *3*, 1062. k) Langlois, J.-B.; Alexakis, A. *Angew. Chem. Int. Ed.* **2011**, *50*, 1877.

[77] a) van Zijl, A. W.; López, F.; Minnaard, A. J.; Feringa, B. L. *J. Org. Chem.* **2007**, *72*, 2558. b) Geurts, K.; Fletcher, S. P.; Feringa, B. L. *J. Am. Chem. Soc.* **2006**, *128*, 15572. c) López, F.; van Zijl, A. W.; Minnaard, A. J.; Feringa, B. L. *Chem. Commun.* **2006**, 409. d) den Hartog, T.; Macia, B.; Minnaard, A. J.; Feringa, B. *Adv. Synth. Catal.* **2010**, *352*, 999. e) Hornillos, V.; Perez, M.; Fañanas-Mastral, M.; Feringa, B. L. *Chem. Eur. J.* **2013**, *19*, 5432. f) Huang, Y.; Fañanas-Mastral, M.; Minnaard, A. J.; Feringa, B. L. *Chem. Commun.* **2013**, *49*, 3309. g) Fañanas-Mastral, M.; Feringa, B. L. *J. Am. Chem. Soc.* **2010**, *132*, 13152. h) Giannerini, M.; Fañanas-Mastral, M.; Feringa, B. L. *J. Am. Chem. Soc.* **2012**,

134, 4108. i) Hornillos, V.; Perez, M.; Fañanas-Mastral, M.; Feringa, B. L. *J. Am. Chem. Soc.* **2013**, *135*, 2140.

[78] Selim, K. B.; Yamada, K.; Tomioka, K. *Chem. Commun.* **2008**, 5140.

[79] Lölsberg, W.; Ye, S.; Schmalz, H.-G. *Adv. Synth. Catal.* **2010**, *352*, 2023.

[80] Fang, F.; Zhang, H.; Xie, F.; Yang, G.; Zhang, W. B. *Tetrahedron* **2010**, *66*, 3593.

[81] Tominaga, S.; Oi, Y.; Kato, T.; An, D. K.; Okamoto, S. *Tetrahedron Lett.* **2004**, *45*, 5585.

[82] Selim, K. B.; Matsumoto, Y.; Yamada, K.; Tomioka, K. *Angew. Chem. Int. Ed.* **2009**, *48*, 8733.

[83] Magrez, M.; Le Guen, Y.; Basle, O.; Crévisy, C.; Mauduit, M. *Chem. Eur. J.* **2013**, *19*, 1199.

[84] a) Dubner, F.; Knochel, P. *Angew. Chem. Int. Ed.* **1999**, *38*, 379. b) Dubner, F.; Knochel, P. *Tetrahedron Lett.* **2000**, *41*, 9233.

[85] Goldsmith, P. J.; Teat, S. J.; Woodward, S. *Angew. Chem. Int. Ed.* **2005**, *44*, 2235

[86] a) van Zijl, A. W.; Arnold, L. A.; Minnaard, A. J.; Feringa, B. L. *Adv. Synth. Catal.* **2004**, *346*, 413. b) Piarulli, U.; Daubos, P.; Claverie, C.; Monti, C.; Gennari, C. *Eur. J. Org. Chem.* **2005**, 895. c) Piarulli, U.; Claverie, C.; Daubos, P.; Gennari, C.; Minnaard, A. J.; Feringa, B. L. *Org. Lett.* **2003**, *5*, 4493. d) Shi, W. J.; Wang, L. X.; Fu, X.; Zhu, S. F.; Zhou, Q. L. *Tetrahedron: Asymmetry* **2003**, *14*, 3867. e) Badalassi, F.; Crotti, P.; Macchia, F.; Pineschi, M.; Arnold, A.; Feringa, B. L. *Tetrahedron Lett.* **1998**, *39*, 7795.

[87] Croset, K. T.; Polet, D.; Alexakis, A. *Angew. Chem. Int. Ed.* **2004**, *43*, 2426.

[88] Yoshikai, N.; Miura, K.; Nakamura, E. *Adv. Synth. Catal.* **2009**, *351*, 1014−1018.

[89] a) Ongeri, S.; Piarulli, U.; Roux, M.; Monti, C.; Gennari, C. *Helv. Chim. Acta* **2002**, *85*, 3388. b) Piarulli, U.; Daubos, P.; Claverie, C.; Roux, M.; Gennari, C. *Angew. Chem. Int. Ed.* **2003**, *42*, 234.

[90] a) Luchaco-Cullis, C. A.; Mizutani, H.; Murphy, K. E.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2001**, *40*, 1456. b) Murphy, K. E.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2003**, *125*, 4690. c) Kacprzynski, M. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2004**, *126*, 10676. d) Murphy, K. E.; Hoveyda, A. H. *Org. Lett.* **2005**, *7*, 1255.

[91] a) Larsen, A. O.; Leu, W.; Oberhuber, C. N.; Campbell, J. E.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2004**, *126*, 11130. b) van Veldhuisen, J. J.; Campbell, J. E.; Guidici, R. E.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2005**, *127*, 6877. c) Kacprzynski, M. A.; May, T. L.; Kazane, S. A.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2007**, *46*, 4554.

[92] Jennequin, T.; Wencel-Delord, J.; Rix, D.; Daubignard, J.; Crevisy, C.; Mauduit, M. *Synlett* **2010**, 1661.

[93] a) Bournaud, C.; Falciola, C.; Lecourt, T.; Rosset, S.; Alexakis, A.; Micouin, L. *Org. Lett.* **2006**, *8*, 3581. b) Pineschi, M.; Del Moro, F.; Crotti, P.; Macchia, F. *Org. Lett.* **2005**, *7*, 3605.

[94] Lee, Y.; Akiyama, K.; Gillingham, D. G.; Brown, M. K.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2008**, *130*, 446.

[95] a) Akiyama, K.; Gao, F.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2010**, *49*, 419. b) Gao, F.; McGrath, K. P.; Lee, Y.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2010**, *132*, 14315. c) Gao, F.; Lee, Y.; Mandai, K.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2010**, *49*, 8370.

[96] a) Dabrowski, J. A.; Gao, F.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2011**, *133*, 4778. b) Dabrowski, J. A.; Haeffner, F.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2013**, *52*, 7694.

[97] For recent reviews about a-arylation, see: a) Hartwig, J. F. *Synlett* **2006**, *9*, 1283. b) Culkin, D. A.; Hartwig, J. F. *Acc. Chem. Res.* **2003**, *36*, 234. c) Hartwig, J. F. *Pure Appl. Chem*. **2009**, *71*, 1417. d) Johansson, C. C. C.; Colacot, T. J. *Angew. Chem. Int. Ed.* **2010**, *49*, 676. e) Sivanandan, S. T.; Shaji, A.; Ibnusaun, I.; Johansson, C. C. C.; Colacot, T. J. *Eur. J. Org. Chem.* **2015**, *1*, 38. For selected examples of application of α-arylation in total synthesis, see: a) Carril, M.; SanMartin, R.; Churruca, F.; Tellitu, L.; Dominguez, E. *Org. Lett.* **2005**, *7*, 4787. b) Honda, T.; Namiki, H.; Satoh, F. *Org. Lett.* **2001**, *3*, 631. c) Honda, T.; Sakamaki, Y. *Tetrahedron Lett.* **2005**, *46*, 6823. d) Rudrangi, S. R. S.; Bontha, V. K.; Manda, V. R.; Bethi, S. *Asian J. Research Chem.* **2011**, *4*, 335.

[98] Lee, S.; Hartwig, J. F. *J. Org. Chem.* **2001**, *66*, 3402.

[99] For synthesis of oxindoles via cyclisation reactions, see: a) Jia, Y.-X.; Hillgre, J. M.; Watson, E. L.; Mardsen, S. P.; Kündig, E. P. *Chem. Commun.* **2008**, 4040 (ee's up to 99%). b) Luan, X.; Xu, L.; Drinkel, E.; Mariz, R.; Gatti, F.; Dorta, R. *Org. Lett.* **2010**, *12*, 1912 (ee's up to 94%). For intramolecular Pd-Heck reaction, see: c) Dounay, A. B.; Hatanaka, K.; Kodanko, J. K.; Ostereich, M.; Overman, L. E.; Pfeifer, L. A.; Weiss, M. W. *J. Am. Chem. Soc.* **2003**, *125*, 6261 (ee's up to 98%).

[100] Durbin, M. J.; Willis, M. C. *Org. Lett.* **2008**, *10*, 1413.

[101] Altman, R. A.; Hyde, A. M.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2008**, *130*, 9613.

[102] Li, P.; Buchwald, S. L. *Angew. Chem. Int. Ed*. **2011**, *50*, 6396.

[103] Xiao, Z.-K.; Yin, H.-Y., Shao, L.-X. *Org. Lett.* **2013**, *15*, 1254.

[104] Taylor, A. M.; Altman, R. A.; Buchwals, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 9900.

[105] Guo, J.; Dong, S.; Zhang, Y.; Kuang, Y.; Liu, X.; Lin, L.; Feng, Z. *Angew. Chem. Int. Ed.* **2013**, *52*, 10245.

[106] Wu, H.-R.; Huang, H.-Y.; Ren, C.-L.; Liu, L.; Wang, D.; Li, C.-J. *Chem, Eur. J.* **2015**, *21*, 1.

[107] Shirakawa, S.; Koga, K.; Tokuda, T.; Yamamoto, K.; Maruoka, K. *Angew. Chem. Int. Ed.* **2014**, *53*, 6220.

[108] a) Marinescu, S. C.; Nishimata, T.; Mohr, J. T.; Stoltz, B. M. *Org. Lett*., **2008**, *10*, 1039–1042. b) Nakamura, Y.; Takeuchi, S.; Ohgo, Y.; Yamaoka, M.; Yoshida, A.; Mikami, K. *Tetrahedron Lett*.,**1997**, *38*, 2709−2712. c) Nakamura, Y.; Takeuchi, S.; Ohgo, Y.; Yamaoka, M.; Yoshida, A.; Mikami, K. *Tetrahedron*, **1999**, *55*, 4595−4620. d) Yanagisawa, A.; Touge, T.; Arai, T. *Angew. Chem., Int. Ed*., **2005**, *44*, 1546−1548. e) Asensio, G.; Cuenca, A.; Rodriguez, N.; Medio-Simó, M. *Tetrahedron: Asymmetry* **2003**, *14*, 3851−3855; f) Asensio, G.; Cuenca, A.; Gaviña, P.; Medio-Simo, M. *Tetrahedron Lett*., **1999**, *40*, 3939−3940.

[109] Mohr, J. T.; Nishimata, T.; Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc*., **2006**, *128*, 11348–11349.

[110] Carroll, M. P.; Mueller-Bunz, H.; Guiry, P. J. *Chem. Commun.* **2012**, *48*, 11142.

[111] Doran, R.; Carroll, M. P.; Akula, R.; Hogan, B. F.; Martins, M.; Fanning, S.; Guiry, P. J. *Chem. Eur. J.* **2014**, *20*, 15354.

[112] Doran, R.; Guiry, P. J. *J. Org. Chem.* **2014**, *79*, 9112.

[113] a) Barton, D. H. R.; Donnelly, D. M. X.; Finet, J.-P.; Guiry, P. J. *Tetrahedron Lett.,* **1989**, *30*, 1539–1542; b) Barton, D. H. R.; Donnelly, D. M. X.; Finet, J.-P.; Guiry, P. J. *Tetrahedron Lett.,* **1990**, *31*, 7449–7452; c) Barton, D. H. R.; Donnelly, D. M. X.; Finet, J.-P.; Guiry, P. J.; Kielty, J. M. *Tetrahedron Lett.,* **1990**, *31*, 6637– 6640; d) Donnelly, D. M. X.; Finet, J.-P.; Guiry, P. J.; Hutchinson, R. M. *J. Chem. Soc*. *Perkin Trans. 1* **1990**, 2851–2852; e) Barton, D. H. R.; Donnelly, D. M. X.; Finet, J.-P.; Guiry, P. J. *J. Chem. Soc. Perkin Trans. 1,* **1992**, 1365–1375; f) Donnelly, D. M. X.; Finet, J.-P.; Rattigan, B. A. *J. Chem. Soc. Perkin Trans. 1,* **1995**, 1679– 1683; g) Donnelly, D. M. X.; Finet, J.-P.; Guiry, P. J.; Rea, M. D. *Synth. Commun*., **1999**, *29*, 2719–2730; h) Deng, H.; Konopelski, J. P. *Org. Lett*., **2001**, *3*, 3001– 3004; i) Harvey, M. J.; Banwell, M. G.; Lupton, D. W. *Tetrahedron Lett.,* **2008**, *49*, 4780–4783.

[114] Kozyrod, R. P.; Pinhey, J. T. *Org. Synth*., **1984**, *62*, 24–30

[115] For recent review see: a) Merritt, E. A.; Olofsson, B. *Synthesis* **2011**, *4*, 517. b) Merritt, E. A.; Olofsson, B. *Angew. Chem. Int. Ed.* **2009**, *48*, 9052. For selected publications see: c) Dey, C.; Lindstedt, E.; Olofsson, B. *Org. Lett.* **2015**, *17*, 4554. d) Malmgren, J.; Nagendiran, A.; Tai, C.-W.; Bäckvall, J.-E.; Olofsson, B. *Chem. Eur. J.* **2014**, *20*, 13531. e) Zhu, M.; Jalalian, N.; Olofsson, B. *Synlett* **2008**, *4*, 592. f) Bielawski, M.; Zhu, M.; Olofsson, B. *Adv. Synth. Catal.* **2007**, *349*, 2610.

[116] Keith, J. A.; Behenna, D. C.; Sherden, N.; Mohr, J. T.; Ma, S. C. Marinescu, R J. Nielsen, J. Oxgaard, B. M. Stoltz, W. A. Goddard, *J. Am. Chem. Soc.,* **2012**, *134*, 19050–19060.

[117] Marinescu, S. C.; Nishimata, T.; Mohr, J. T.; Stoltz, B. M. *Org. Lett.* **2008***, 10,* 1039.

[118] Tang, W. S.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029.

[119] Knowles, W. S. *Angew. Chem. Int. Ed.* **2002**, *41*, 1998.

[120] a) Roseblade, S. J.; Pfaltz, A. *Acc. Chem. Res*. **2007**, *40*, 1402. b) Cui, X.; Burgess, K. *Chem. Rev.* **2005**, *105*, 3272. c) Woodmansee, D. H.; Pfaltz, *A. Chem. Commun*. **2011**, *47*, 7912. d) Church, T. L.; Andersson, P.G. *Coord. Chem. Rev.* **2008**, *252*, 513. e) Verendel, J. J.; Pàmies, O.; Diéguez, M.; Andersson, P. G. *Chem. Rev.* **2014**, *114*, 2130. f) Pàmies, O.; Andersson, P. G.; Diéguez, M. Chem. Eur. J. 2010, 16, 14232.

[121] See for example: a) Chan, A. S. C.; Pluth, J. J.; Halpern, J. *J. Am. Chem. Soc.* **1980**, *102*, 5952. b) *Asymmetric Hydrogenation Reactions Using Chiral Diphosphine Complexes of Rhodium.* Brown, J.M.; Chaloner, P. A. *Homogeneous Catalysis with Metal Phosphine Complexes*. Louis H. Pignolet, Plenum Publishing Corporation, **1983**, 137.

[122] Church, T. L.; Rasmussen, T.; Andersson, P. G. *Organometallics* **2010**, *29*, 6769.

[123] Hopmann, K.H.; Bayer, A. *Organometallics* **2011**, *30*, 2483.

[124] Mazuela, J.; Norrby, P-O.; Andersson, P.G.; Pàmies, O.; Diéguez, M.; *J. Am. Chem. Soc*., **2011**, *133*, 13634.

[125] Gruber, S.; Pfaltz, A. *Angew. Chem. Int. Ed.* **2014**, *53*, 1896.

[126] a) Margalef, J.; Caldentey, X.; Karlsson, E. K.; Coll, M.; Mazuela, J.; Pàmies, O.; Diéguez, M.; Pericàs, M. A. *Chem. Eur. J.* **2014**, *20*, 12201. b) Borràs, C.; Biosca, M.; Pàmies, O.; Diéguez, M. *Organometallics* **2015**, *34*, 5321.

[127] a) Crabtree, R. H.; Felkin, H.; Morris, G. E. *J. Organomet. Chem*. **1977**, *141*, 205. b) Crabtree, R. H.; Gautier, A.; Giordano, G.; Khan, T. *J. Organomet. Chem.* **1977**, *141*, 113. c) Crabtree, R. H. *Acc. Chem. Res.* **1979**, *12*, 331.

[128] Lightfoot, A.; Schnider, P.; Pfaltz, A*. Angew. Chem. Int. Ed.* **1998**, *37*, 2897.

[129] Goulioukina, N.S.; Dolgina, T.; Bondarenko, G.N.; Beletskaya, I. P.; Ilyin, M. M.; Davankov, V. A.; Pfaltz, A. *Tetrahedron: Asymmetry* **2003**, *14*, 1397.

[130] a) Lu, S.-M.; Bolm, C. *Angew. Chem. Int. Ed.* **2008**, *47*, 8920. b) Lu, S.-M.; Bolm, C. *Chem. Eur. J.* **2008**, *14*, 7513.

[131] a) Coll, M.; Pàmies, O.; Diéguez, M. *Chem. Commun.* **2011**, *47*, 215. b) Coll, M.; Pàmies, O.; Diéguez, M. *Ad. Synth. Catal.* **2013**, *355*, 143. c) Biosca, M.; Coll, M.; Lagarde, F.; Bremond, E.; Routaboul, L.; Manoury, E.; Pàmies, O.; Poli, R.; Diéguez, M. *Tetrahedron*, **2015**. DOI 10.1016/j.tet.2015.01.047.

[132] a) Rageot, D.; Woodwansee, D. H.; Pugin, B.; Pfaltz, A. *Angew. Chem. Int. Ed.* **2011**, *50*, 9598. b) Rageot, D.; Pfaltz, A. *Helv. Chim. Acta.* **2012**, *95*, 2176.

[133] a) Perry, M. C.; Cui, X.; Powell, M. T.; Hou, D.-R.; Reibenspies, J. H.; Burgess, K. *J. Am. Chem. Soc.* **2003**, *125*, 113. b) Nanchen, S.; Pfaltz, A. *Chem. Eur. J.* **2006**, *12*, 4550. c) Källström, K.; Andersson, P. G. *Tetrahedron Lett.* **2006**, *47*, 7477. d) Nachen, S.; Pfaltz, A. *Helv. Chim. Acta* **2006**, *89*, 1559. e) Zhu, Y.; Burgess, K. *Acc. Chem. Res.* **2012**, *45*, 1623.

[134] Bernardinelli, G.H.; Kündig, E.P.; Meier, P.; Pfaltz, A.; Radkowski, K.; Zimmermann, N.; Neuburger-Zehnder, M. *Helv. Chim. Acta.* **2001**, *84*, 3233.

[135] Hou, D.-R.; Reibenspies, J.; Calacot, T.J.; Burgess, K. *Chem. Eur. J.* **2001**, *24*, 5391.

[136] Liu, D.; Tang, W.; Zhang, X. *Org. Lett.* **2004**, 6, 513.

[137] Cozzi, P.G.; Menges, F.; Kaiser, S. *Synlett*, **2003**, 833.

[138] Schrems, M. G.; Neumann, E.; Pfaltz, A. *Angew. Chem. Int. Ed*. **2007**, *46*, 8274.

[139] a) Lu, W.-J.; Chen, Y.-W.; Hou, X.-L. *Angew. Chem. Int. Ed*. **2008**, *47*, 10133. b) Lu, W.-J.; Chen, Y.-W.; Hou, X.-L. *Adv. Synth. Catal.* **2010**, *352*, 103.

[140] a) Schrems, M.G.; Pfaltz, A*. Chem. Commun.* **2009,** 6210. b) Bernasconi, M.; Ramella, V.; Tosatti, P.; Pfaltz, A. *Chem. Eur. J.* **2014**, *20*, 2440.

[141] a) Li, S.; Zhu, S.-F.; Xie, J.-H.; Song, S.; Zhang, C.-M.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2010**, *132*, 1172. b) Song, S.; Zhu,S. F.; Yu, Y. B.; Zhou, Q.-L. Angew. Chem. Int. Ed. 2013, 52, 1556.

[142] Zhang, Y.; Han, Z.; Li, F.; Ding, K.; Zhang, A. *Chem. Commun*. **2010**, *46*, 156.

[143] Shang, J.; Han, Z.; Li, Y.; Wang, Z.; Ding, K. *Chem. Commun.,* **2012**, *48*, 5172.

[144] Wang, X.; Han, Z.; Wang, Z.; Ding, K. *Angew. Chem. In. Ed.* **2012**, *51*, 936.

[145] Cozzi, P.G.; Zimmermann, N.; Hilgraf, R.; Schaffner, S.; Pfaltz, A. *Adv. Synth. Catal*. **2001**, *343*, 450.

[146] Xu, G.; Gilberston, S.R. *Tetrahedron Lett.* **2003**, *44*, 953

[147] a) Trifonova, A.; Diesen, J.S.; Andersson, P.G. *Chem.Eur.J.* **2006**, *12*, 2318. b) Cheruku, P.; Diensen, J.; Andersson, P.G*. J. Am. Chem. Soc*. **2008**, *130*, 5595. c) Cheruku, P.; Gohil, S.; Andersson, P.G. *Org. Lett.* **2007**, *9*, 1659. d) Källström, K.; Munslow, I. J.; Hedber, C.; Andersson, P. G*. Adv Synth. Catal.* **2006**, *348*, 2575. e) Engman, M.; Diesen, J.S.; Paptchikhine, A.; Andersson, P.G. J. Am. Chem. Soc. **2007**, *129*, 4536. f)

Paptchikhine, A.; Cheruku, P.; Engman, M.; Andersson, P. G. Chem Commun. **2009**, 5996. g) Verendel, J.J.; Li, J.-Q.; Quan, X.; Peters, B.; Zhou, T.; Gautun, O. R.; Govender, T.; Andersson, P. G. Chem. Eur. J. **2012**, 15, 6507.

[148] Chakka, S.K.; Peter, B.K.; Andersson, P. G.; Maguire, G. E. M.; Kruger, H. G.; Govender, T. *Tetrahedron: Asymmetry* **2010**, *21*, 2295.

[149] a) Blankenstein, J.; Pfaltz A. *Angew. Chem. Int. Ed.* **2001,** *40*, 4445. b) Menges, F.; Pfaltz, A. *Adv. Synth*. *Catal.* **2002**, *344*, 40. c) McIntyre, S.; Hörmann, E.; Menges, F.; Smidt, S.P.; Pfaltz, A. *Adv. Synth. Catal.* **2005**, *347*, 282. d) Baeza, A.; Pfaltz, A.Chem. Eur. J. 2009, 15, 2266. e) Müller, M. A.; Pfaltz, A. *Angew. Chem. Int. Ed.* **2014**, *53*, 8668.

[150] a) Smidt, S.P.; Menges, F.; Pfaltz, A. *Org. Lett*, **2004**, *6*, 2023. b) Ganic, A.; Pfaltz, A. *Chem. Eur. J.* **2012**, *18*, 6724.

[151] Maurer F.; Huch, V.; Ullrich, A.; Kazmaier, U. *J. Org. Chem.* **2012**, *77*, 5139.

[152] See for instance: a) Claver, C.; Fernandex, E.; Gillon, A.; Heslop, K; Hyett, D.J.; Martorell, A.; Orpen, A.G.; Pringle, P.G. *Chem Commun*. **2000**, 961. b) Mata. Y.; Pàmies, O.; Diéguez, M*. Chem Eur. J.* **2007**, *13*, 3296. c) Peña, D.; Minnaard, A.; de Vries, J.G.; Feringa, L.J. *J. Am. Chem. Soc.* **2002**, *124*, 14552. d) Alexakis, A.; Polet, D.; Rosset, S.; March, S. *J. Org. Chem.* **2004**, *69*, 5660. e) van Leeuwen, P. W. N. M.; Kamer, P. C. J.; Claver, C.; Pàmies, O.; Diéguez, M. *Chem. Rev.* **2011**, *11*, 2077-2118.

[153] a) Hilgraf, R.; Pfaltz, A*. Synlett* **1999**, 1814. b) Hilgraf, R.; Pfaltz, A. *Adv. Synth. Catal*. **2005**, *347*, 61. c) Schönleber, M.; Hilgraf, R.; Pfaltz, A. *Adv. Synth. Catal.* **2008,** *350*, 2033.

[154] Diéguez, M.; Mazuela, J.; Pàmies, O.; Verendel, J. J.; Andersson, P. G. J. Am. Chem. Soc. **2008**, *130*, 7208.

[155] a) Diéguez, M.; Mazuela, J.; Pàmies, O.; Verendel, J. J.; Andersson, P. G. *Chem. Commun.* **2008**, 3888. b) Mazuela, J.; Verendel, J. J.; Coll, M.; Scha¨ffner, B.; Bo¨rner, A.; Andersson, P. G.; Pàmies, O.; Diéguez, M. *J. Am. Chem. Soc*. **2009**, *131*, 12344.

[156] Biosca, M.; Paptchikhine, A.; Pàmies, O.; Andersson, P. G.; Diéguez, M. *Chem. Eur. J.* **2015**, *21*, 3455.

[157] Bunlaksananusorn, T.; Polborn, K.; Knochel, P. *Angew. Chem. Int. Ed.* **2003**, *42*, 3941.

[158] a) Drury, W. J.; Zimmermann, N.; Keenan, M.; Hayashi, M.; Kaiser, S.; Goddard, R.; Pfaltz, A. *Angew. Chem. Int. Ed.* **2004**, *43*, 70. b) Zalubovskis, R.; Hörmann, E.; Pfaltz, A.; Moberg, C. *ARKIVOC* **2008**, *14*, 58.

[159] a) Kaiser, S.; Smidt, S. P.; Pfaltz, A. *Angew. Chem., Int. Ed*. **2006**, *45*, 5194. b) Woodmansee, D. H.; Muller, M.-A.; Neuburger, M.; Pfaltz, A. *Chem. Sci*. **2010**, *1*, 72. c) Wang, A.; Fraga, R. P. A.; Ho¨rmann, E.; Pfaltz, A. *Chem.-Asian J.* **2011**, *6*, 599. d) Liu, Q.-B.; Yu, C.-B.; Zhou, Y.-G. *Tetrahedron Lett.* **2006**, *47*, 4733. e) Baeza, A.; Pfaltz, A. *Chem. Eur. J.* **2010**, *16*, 2036. f) Ganic, A.; Pfaltz, A. *Chem. Eur. J.* **2012**, *18*, 6724. g) Woodmansee, D. H.; Müller, M. A.; Tröndlin, L.; Hörmann, E.; Pfaltz, A. *Chem. Eur. J.* **2012**, *18*, 13780. h) Pauli, L.; Tannert, R.; Scheil, R.; Pfaltz, A. *Chem. Eur. J.* **2015**, *21*, 1482.

[160] Li, X.; Kong, L.; Gao, Y.; Wang, X. *Tetrahedron Lett.* **2007,** 5603.

[161] a) Mazuela, J.; Pàmies, O.; Diéguez, M. *Adv. Synth. Catal*. **2013**, *355*, 2569., For other succesfully applied phosphite-pyridine, reported by Díeguez and Ruffo, see: b) Margalef, J.; Lega, M.; Ruffo, F.; Pàmies, O.; Diéguez, M. *Tetrahedron Asymmetry* **2012**, **23**, 945

[162] Qu, B.; Samankumara, L. P.; Savoie, J.; Fandrick, D. R.; Haddad, N.; Wei, X.; Ma, S.; Lee, H.; Rodriguez, S.; Busacca, C. A.; Yee, N. K.; Song, J. J.; Senanayake, C. H. *J. Org. Chem.* **2014**, *79*, 993.

[163] Menges, F.; Neuburger, C.; Pfaltz, A. *Org. Lett.* **2002**, *26*, 4713.

[164] Franke, A.; Pfaltz, A. *Chem. Eur. J.* **2011**, *17*, 4131.

[165] Kaukoranta, P.; Engman, M.; Hedberg, C.; Berquist, J.; Andersson, P. G. *Adv. Synth. Catal.* **2008**, *350*, 1168.

[166] Källström, K.; Hedberg, C.; Brandt, P.; Bayer, A.; Andersson, P. G. *J. Am. Chem. Soc.* **2004**, *126*, 14308.

[167] a) Hedberg, C.; Källström, K.; Brandt, P.; Hansen, L. K.; Andersson, P. G. *J. Am. Chem. Soc.* **2006**, *128*, 2995. b) Engman, M.; Cheruku, P.; Tolstoy, P.; Bergquist, J.; Völker, S. F.; Andersson, P. G. *Adv. Synth. Catal.* **2009**, *351*, 375. c) Tolstoy, P.; Engman, M.; Paptchikhine, A.; Bergquist, J.; Church, T. L.; Leung, A. W.-M.; Andersson, P. G. *J. Am. Chem. Soc.* **2009**, *131*, 8855.

[168] Cheruku, P.; Paptchikhine, A.; Church, T. L.; Andersson, P. G. *J. Am. Chem. Soc.* **2009**, *131*, 8285.

[169] a) Li, J.-Q.; Paptchikhine, A.; Govender, T.; Andersson, P.G. *Tetrahedron: Asymmmetry* **2010**, *21*, 1328. b) Zhou, T.; Peters, B.; Maldonado, M. F.; Govender, T.; Andersson, P. G. *J. Am. Chem. Soc.* **2012**, *134*, 13592. C) Peters, B. K.; Zhou, T.; Rujirawanich, J.; Cadu, A.; Singh, T.; Rabten, W.; Kerdphon, S.; Andersson, P. G. *J. Am. Chem. Soc.* **2014**, *136*, 16557.

[170] Schenkel, L. B.; Ellman, J. A. *J. Org. Chem.* **2004**, *69*, 1800.

[171] Mazuela, J.; Paptchikhine, A.; Pàmies, O.; Andersson, P.G.; Diéguez, M. *Chem. Eur. J.* **2010**, *16*, 4567.

[172] Mazuela, J.; Pàmies, O.; Diéguez, M. *ChemCatChem* **2013**, *5*, 2410.

[173] Zhu, S. F.; Yu, Y.-B.; Li, S.; Wang, L.-X.; Zhou, Q.-L. *Angew. Chem. Int. Ed.* **2012**, *51*, 8872.

[174] For examples of bioactive compounds with the 2-aminotetraline structure, see: a) Osende, J. I.; Shimbo, D.; Fuster, V.; Dubar, M.; Badimon, J. J. *J. Thromb. Haemostasis* **2004**, *4*, 492. b) Chen, J. J.; Swope, D. M.; Dashtipour, K.; Lyons, K. E. *Pharmacotherapy* **2009**, *29*, 1452. c) Stanley, W. C.; Li, B.; Bonhaus, D. W.; Johnson, L. G.; Lee, K.; Porter, S.; Walker, K.; Martinez, G.; Eglen, R. M.; Whiting, R. L.; Hegde, S. S. *Br. J. Pharmacol.* **1997**, *121*, 1803.

[175] Renaud, J. L.; Dupau, P.; Hay, A.-E.; Guingouain, M.; Dixneuf, P. H.; Bruneau, C. *Adv. Synth. Catal.* **2003**, *345*, 230.

[176] Pautigny, C.; Debouit, C.; Vayron, P.; Ayad, T.; Ratovelomanana-Vidal, V. *Tetrahedron: Asymmetry* **2010**, *21*, 1382.

[177] Arribas, I.; Rubio, M.; Kleman, P.; Pizzano, A. *J. Org. Chem.* **2013**, *78*, 3997.

[178] Jiang, X.-B.; Lefort, L.; Goudriaan, P. E.; de Vries, A. H. M.; van Leeuwen, P. W. N. M.; de Vries, J. G.; Reek, J. N. H. *Angew. Chem. Int. Ed.* **2006**, *45*, 1223.

[179] Liu, G.; Liu, X.; Cai, Z.; Jiao, G.; Xu, G.; Tang, W. *Angew. Chem. Int. Ed.* **2013**, *52*,4253.

[180] Salomó, E.; Orgué, S.; Riera, A.; Verdaguer, X. *Angew. Chem. Int. Ed.* **2016**. DOI: 10.1002/anie.201602219

[181] For selected reviews, see: A) Brown, H. C.; Krishnamurthy, S. *Tetrahedron* **1979**, *35*, 567. B) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. c) Crudden, C. M.; Edwards, D. *Eur. J, Org. Chem.* **2003**, 4695. d) Carrol, A.-M.; O'Sullivan, T. P.; Guiry, P. J. *Adv. Synth. Catal.* **2005**, *347*, 609. e) Crudden, C. M.; Glasspoole, B. W.; Lata, C. J. *Chem. Commun.* **2009**, 6704.

[182] Thomas, S. P.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2009**, *48*, 1896.

[183] Pelter, A.; Smith, K.; Brown, H. C. *Borane Reagents.* Academic Press, New York, **1988**. B) Bubnov, Y. in *Science of Synthesis*, Thieme, Stuttgart, **2004**, *6*, 945.

[184] Burgess, K.; Ohlmeyer, M. J. *Chem. Rev.* **1991**, *91*, 1179.

[185] a) Sato, M.; Miyaura, N.; Suzuki, A. *Tetrahedron Lett.* **1990**, *31*, 231. b) Burgess, K.; Ohlmeyer, M. J. *J. Org. Chem.* **1988**, *53*, 5178. c) Burgess, K.; van der Donk, W. A.; Ohlmeyer, M. J. *Tetrahedron: Asymmetry* **1991**, *2*, 613. d) Hayashi, T, Matsumoto, Y, Ito, Y. *Tetrahedron: Asymmetry* **1991**, *2*, 601.

[186] Gonzalez, A. Z.; Román, J. G.; Gonzalez, E.; Martinez, J.; Medina, J. R.; Matos, K.; Soderquist, J. A. *J. Am. Chem. Soc.* **2008**,*130*, 9218.

[187] Corberán, R.; Mszar, N. W.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2011**, *50*, 7079.

[188] Mazet, C.; Gérard, D. *Chem. Commun.* **2011,** *47*, 298.

[189] a) Westcott, S. A.; Marder, T. B.; Baker, R. T. *Organometallics* **1993**, *12*, 975. b) Crudden, C. M.; Hleba, Y. B.; Chen, A. C. *J. Am. Chem. Soc.* **2004**, *126*, 9200. c) Yamamoto, Y.; Fujikawa, R.; Umemoto, T.; Miyaura, N. *Tetrahedron* **2004**, *60*, 10695. d) Noh, D.; Chea, H.; Ju, J.; Yun, J. *Angew. Chem. Int. Ed.* **2009,** *48*, 6062. e) Crudden, C. M.; Lata, C. J. *J. Am. Chem. Soc.* **2010**, *132*, 131.

[190] a) Soai, K.; Shibata, T. *Alkylation of carbonyl groups. In: Comprehensive asymmetric catalysis.* Eds. Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. **2000**, Vol II, Springer, Berlin. b) Pu, L.; Yu, H.-B. *Chem. Rev.* **2001**, *101*, 757. c) Luderer, M. R.; Bailey, W. F.; Fair, J. D.; Sommer, M. B. *Tetrahedron: Asymmetry* **2009**, *20*, 981. d) Trost, B. M.; Weiss, A. H. *Adv. Synth. Catal.* **2009**, *351*, 963. e) Binder, V. M.; Singaram, B. *Org. Prep. Proced. Int.* **2011**, *43*, 139. f) Kolb, A.; Von Zezschwitz, P. *Organoaluminum Couplings to Carbonyls, Imines and Halides.* In *Top. Organomet. Chem.* **2013**, *41*, 245. Eds. Woodward, S.; Dagone, S. Springer-Verlag Berlin Heidelberg.

[191] a) Kitamura, M.; Okada, S.; Suga, S.; Noyori, R. *J. Am. Chem. Soc.* **1989**, *111*, 4028. b) Boezio, A. A.; Pytkowicz, J.; Cöté, A.; Charette, A. B. *J. Am. Chem. Soc.* **2003**, *125*, 14260.

[192] Oishi, M. *Triorganoaluminum compounds.* Ed. Yamamoto, H. *Science of Synthesis*, **2004**, vol 7. Thieme, Stuttgart.

[193] a) Andrus, M. B.; Meredith, E. L.; Hicken, E. J.; Simmons, B. L.; Glancey, R. R.; Ma, W. *J. Org. Chem.* **2003**, *68*, 8162. b) Liu, B.; Zhou, W.-S. *Org. Lett.* **2004**, *6*, 71. c) Chanu, A.; Safir, I.; Basak, P.; Chiaroni, A.; Arseniyadis, S. *Org. Lett.* **2007**, *9*, 1351.

[194] Cotton, F. A.; Wilkinson, G. *Advanced Inorganic Chemistry*, 5th ed. Wiley, New York, **1988**, 224.

[195] a) Andrews, P.; Latham, C. M.; Magre, M.; Willcox, D.; Woodward, S. *Chem. Commun.* **2013**, *49*, 1488. b) Willcoz, D.; Woodward, S.; Alexakis, A. *Chem. Commun.* **2014**, *50*, 1655. c) Willcox, D.; Gondal, H.; Civit-Garcia, M.; Woodward, S. *Tetrahedron Lett.* **2014**, *55*, 1720.

[196] a) Chan, A. S. C.; Zhang, F.-Y.; Yip, C.-W.; *J. Am. Chem. Soc.* **1997**, *119*, 4080. b) Pagenkopf, B. L.; Carreira, E. M. *Tetrahedron Lett.* **1998**, *39*, 9593. c) Lu, J.-F.; You, J.-S.; Gau, H.-M.; *Tetrahedron: Asymmetry* **2000**, *11*, 2531. d) You, J.-S.; Hseih, S.-H.; Gau, H.-M.; *Chem. Commun.* **2001**, 1546. e) Fernández-Mateos, E.; Maciá, B.; Yus, M. *Tetrahedron; Asymmetry* **2012**, *23*, 789.

[197] a) Biswas, K.; Prieto, O.; Goldsmith, P. J.; Woodward, S. *Angew. Chem. Int. Ed.* **2005**, *44*, 2232. b) Biswas, K.; Chapron, A.; Copper, T.; Fraser, P. K.; Novak, A.; Prieto, O.; Woodward, S. *Pure Appl. Chem.* **2006**, *78*, 511.

[198] a) Mata, Y.; Diéguez, M.; Pàmies, O.; Woodward, S. *J. Org. Chem.* **2006**, *71*, 8159. b) Mata, Y.; Diéguez, M.; Pàmies, O.; Woodward, S. *Inorg. Chim. Acta.* **2008**, *361*, 1381.

[199] Alegre, S.; Diéguez, M.; Pàmies, O. *Tetrahedron: Asymmetry* **2011**, *22*, 834.

[200] a) Raluy, E.; Diéguez, M.; Pàmies, O. *Tetrahedron Lett.* **2009**, *50*, 4495. b) Raluy, E.; Diéguez, M.; Pàmies, O. *Tetrahedron: Asymmetry* **2009**, *20,* 1575.

[201] a) Dubois, N.; Glynn, D.; McInally, T.; Rhodes, B.; Woodward, S.; Irvine, D. J.; Dodds, C. *Tetrahedron* **2013**, *69*, 9890. b) Lee, D. S.; Amara, Z.; Poliakoff, M.; Harman, T.; Reid, G.; Rhodes, B.; Brough, S.; McInally, T.; Woodward, S. *Organic Process Research & Development* **2015**, *19*, 831.

[202] a) Walther, D. *J. Organomet. Chem.* **1980**, *190*, 393. b) Kaiser, J.; Sieler, J.; Walther, D.; Dinjus, D.; Golic, L. *Acta Crystallogr. Sec. B* **1982**, *38*, 1584.c) Ogoshi, S.; Oka, M.; Kurusawa, H. *J. Am. Chem. Soc.* **2004**, *126*, 11802.

[203] Ichiyanagi, T.; Kuniyama, S.; Shimizu, M.; Fujisawa, T. *Chem. Lett.* **1998**, 1033.

Chapter 2

Objectives

UNIVERSITAT ROVIRA I VIRGILI
DESIGN OF TAILOR-MADE CHIRAL LIGAND LIBRARIES FOR C-X BOND FORMING REACTIONS. STUDY OF THE KEY INTERMEDIATES BY NMR AND DFT
Marc Magre Rosich

2. Objectives

The objective of this thesis is to develop new chiral π-acceptor ligands and their application to several important metal-catalyzed asymmetric reactions. The more specific aims are:

1. To synthesize PHOX-type phosphite-oxazoline ligands **L1**-**L7a**-**g** (Figure 2.1) and their application in Pd-allylic substitution, Ir-hydrogenation of olefins, Ir-hydroboration of 1,1-disusbtituted olefins and Ni-1,2-addition of triorganoaluminum reagents to aldehydes.

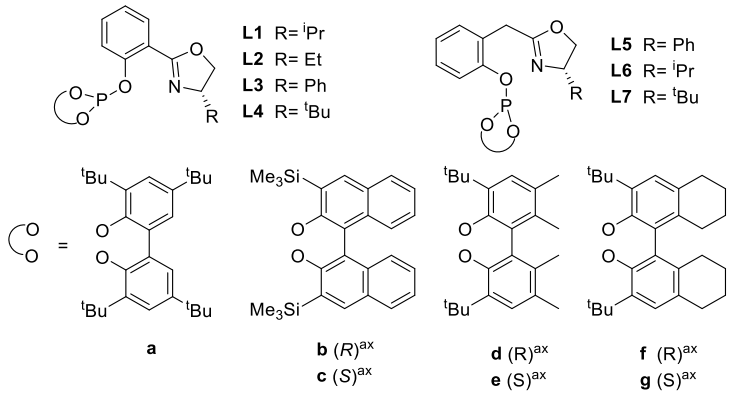


Figure 2.1. PHOX-type phosphite-oxazoline ligands **L1**-**L7a**-**g**.

2. To synthesize phosphite/phosphinite-oxazoline ligands **L8**-**14a**-**h** (Figure 2.2) and their application in the Pd-allylic substitution, Ir-hydrogenation of olefins and Ni-1,2-addition of triorganoaluminum reagents to aldehydes.

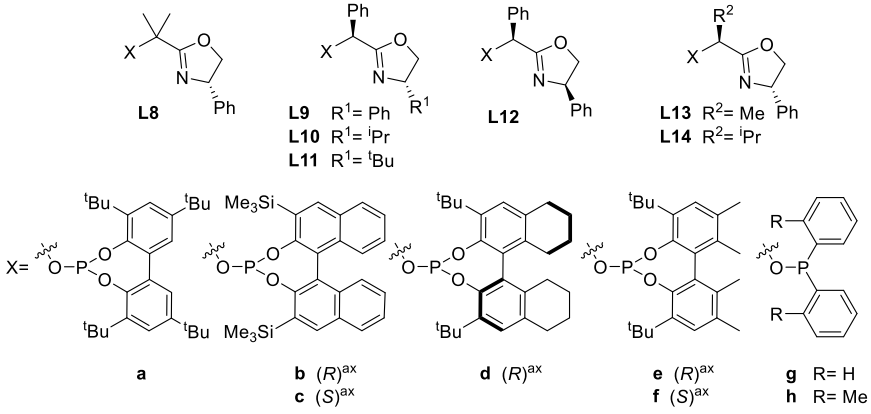


Figure 2.2. Phosphite-oxazoline ligands **L8**-**L14a**-**h**.

3. To synthesize amino-phosphite ligands **L15**-**L20a**-**g** (Figure 2.3) and their application in the Pd-allylic substitution.

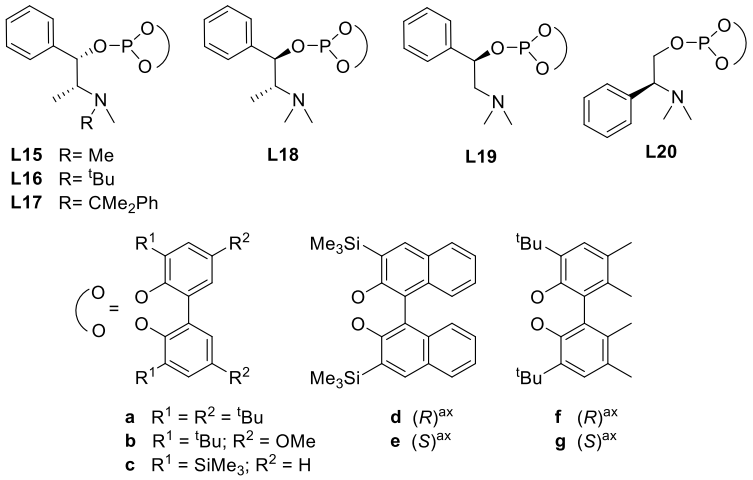


Figure 2.3. Amino-phosphite ligands **L15**-**L20a**-**g.**

4. Application of furanoside-based phosphite-phosphoramidite and diphosphoramidite ligands **L21**-**L25a**-**f** (Figure 2.4) to Cu-catalyzed asymmetric allylic alkylation reactions.

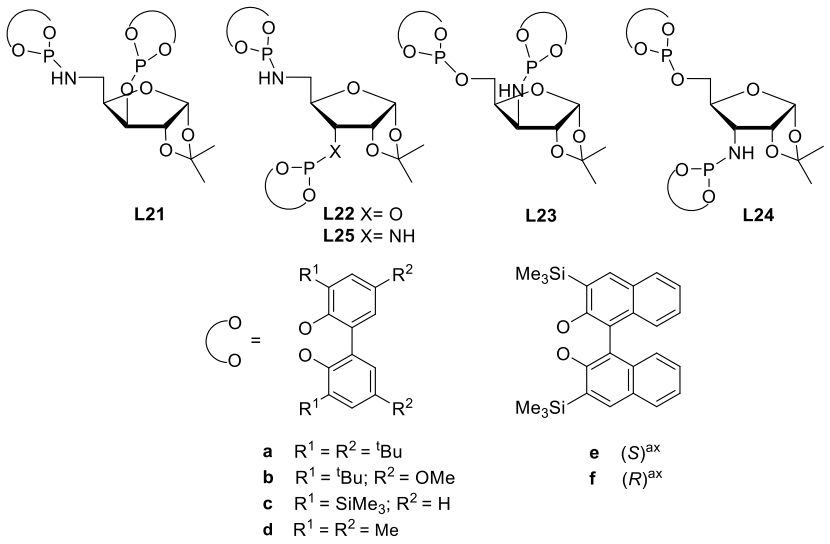


Figure 2.4. Furanoside phosphite-phosphoramidite and diphosphoramidite ligands **L21**-**L25a**-**f** applied to Cu-catalyzed asymmetric allylic substitution reactions.

5. Application of phosphite-nitrogen ligands **L1**-**L4a** and **L26**-**L37a**-**e** (Figure 2.5) to Pd-catalyzed asymmetric decarboxylative protonation of α-aryl-β-amido allyl esters to synthesize α-aryl oxindoles.

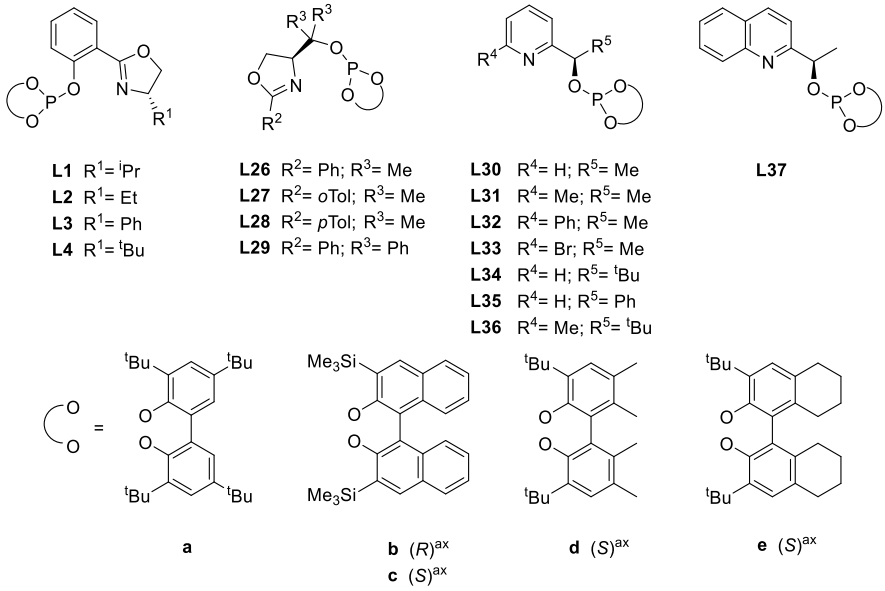
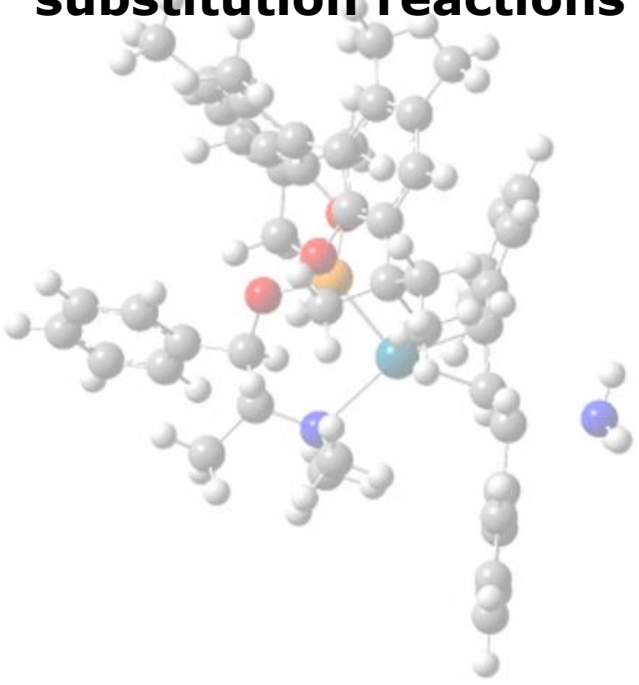


Figure 2.5. Phosphite-nitrogen ligands **L1**-**L4a** and **L26**-**L37a**-**e** screened in the Pd-decarboxylative protonation of α–aryl–β–amido allyl esters.

OBJECTIVES

Chapter 3

Asymmetric allylic substitution reactions



UNIVERSITAT ROVIRA I VIRGILI
DESIGN OF TAILOR-MADE CHIRAL LIGAND LIBRARIES FOR C-X BOND FORMING REACTIONS. STUDY OF THE KEY INTERMEDIATES BY NMR AND DFT
Marc Magre Rosich

3. Asymmetric allylic substitution reactions

3.1. Background

As previously mentioned in the introduction (Chapter 1), most of the successfully applied ligands in Pd-catalyzed allylic substitution reactions have been synthesized following two main strategies: the first strategy is based on secondary interactions between the ligand and the nucleophile directing the nucleophilic attack to one allylic carbon, whereas the second strategy, which this chapter is based on, consists in the electronic differentiation between the two allyl carbon terminus. This differentiation is due to the ligand effect, more precisely the *trans* effect provided by the use of heterodonor ligands (mainly P,N ligands).

More recently, our group has found that the use of biaryl phosphite-containing heterodonor ligands is highly advantageous by overcoming the most common limitations of this process, such as low reaction rates and high substrate specificity. By introducing a π-acceptor biaryl phosphite moiety, the reaction rates increase and due to its flexible cavity provided by the biaryl phosphite, a wide range of substrates can be adapted to the chiral pocket.

Regarding phosphite-containing heterodonor ligands, a breakthrough was reported by Diéguez *et al.* in 2005, who reported the first application of PHOX-based phosphite-oxazoline ligands in Pd-catalyzed asymmetric allylic alkylation of several hindered and unhindered substrates, achieving enantioselectivities up to <99%. After that discovery, plenty of phosphite-containing heterodonor ligands (oxazolines, thiazolines, oxazoles, thiazoles, pyridines, thioether…) have been successfully applied to Pd-catalyzed allylic alkylation, achieving excellent results in terms of substrate versatility. However, the enantioselectivities obtained for unhindered and cyclic substrates are not completely satisfactory. On the other hand, the potential of phosphite-containing ligands is quite limited to malonate-type nucleophiles, whereas for other type of C-, O- and N-nucleophiles require much attention. This encourages further research into phosphite-nitrogen ligands.

For this purpose, in this chapter we present the synthesis and application of different phosphite-nitrogen ligand libraries for asymmetric Pd-catalyzed allylic substitution reactions. More specifically, in Section 3.2 we expand the use of the previously successfully applied PHOX-based phosphite-oxazoline **L1a** with the synthesis of ligands **L1f** and **L1g**. We therefore present a deep study based on the NMR studies of the Pd-olefins complexes and DFT calculations to fully understand the privileged behavior of these ligands, in terms of substrate versatility. Moreover, we expand both substrate and nucleophile scope to prove the exceptional high versatility that these PHOX-based phosphite-oxazoline ligands present.

In Section 3.3, we present the synthesis and application of PHOX-derivative phosphite-oxazolines **L5**-**7a**-**c**, in order to study the influence on the catalytic performance by the introduction of a methylene linker between the phosphite moiety and the oxazoline group. A wide range of substrates and nucleophiles have been studied, all complemented with DFT calculations to further understand the catalytic behavior.

In Section 3.4 we present the synthesis and application of a new family of phosphite-oxazoline ligands containing an alkyl chain **L8**-**L14a**-**c** with the purpose of expanding both substrate and nucleophile versatility. We will study the effect on the catalytic performance by the presence of a second stereogenic center on the ligand backbone.

In section 3.5 we report the synthesis and application of simple, easy to synthesize and robust phosphite-amine **L15**-**L20a**-**g**. Alternating DFT calculations and experimental data, we have been able to optimize the ligand parameters to achieve the highest levels of enantioselectivity for a broad range of substrates and nucleophiles. Moreover, using NMR techniques, we have been able to identify the Pd-π-allyl intermediates, the key species for enantioselectivity.

Whereas Pd-catalyzed asymmetric allylic substitution reactions proceed via the attack of a stabilized nucleophile (such as malonates and benzylamine derivatives) to a Pd-π–allyl system, the use of non-stabilized nucleophiles (such as organometallic reagents) have been mainly reported using Cu-based catalysts. In terms of nucleophile versatility, Grignard reagents and diorganozinc compounds have been extensively used. In this respect, for the successful application of Grignard reagents, mainly the use of phosphines has been reported. Regarding the use of diorganozinc reagents, amine-based ligands have been successfully applied.

In this respect, in Section 3.6 we present the application of furanoside-based phosphite-phosphoramidite and diphosphoramidite ligands **L21**-**L25a**-**f** to Cu-catalyzed asymmetric allylic alkylation in a wide range of cinammyl-type substrates and different organometallic species as non-stabilized nucleophiles, to achieve high level of regio- and enantioselectivity.

3.2. Conformational preferences of a *tropos* biphenyl phosphino-oxazoline - a ligand with wide substrate scope

Magre, M.[+]; Bellini, R.[+]; Biosca, M.; Norrby, P.-O.; Pàmies, O.; Diéguez, M.; Moberg, C. *ACS Catal*. **2016**, *6*, 1701. [+]*These authors contributed equally to this study.*

Abstract: *Excellent enantioselectivities are observed in palladium-catalyzed allylic substitutions of a wide range of substrate types and nucleophiles using a bidentate ligand composed of oxazoline and chirally flexible biaryl phosphite elements. This unusually wide substrate scope is shown by experimental and theoretical studies of its* η^3 *-allyl and* η^2 *-olefin complexes not to be a result of configurational interconversion of the biaryl unit, since the ligand in all reactions adopts an* S_a*,S configuration on coordination to palladium, but rather the ability of the ligand to adapt the size of the substrate-binding pocket to the reacting substrate. This ability also serves as an explanation to its excellent performance in other types of catalytic processes*

3.2.1. Introduction

Enantioselective metal-catalyzed synthetic processes are ubiquitous for the construction of nonracemic chiral organic compounds.[1] The stereodirecting power of a catalyst usually relies on the choice of chiral ligand bound to the metal. Ligands with broad substrate scope are desirable in order to limit time-consuming ligand design and preparation. The identification of privileged ligands[2] useful for a wide range of substrates and for different types of reactions is therefore an important issue.

Conformationally flexible ligands are viable candidates for the design of catalysts with wide substrate scope. Mikami and co-workers[3] have demonstrated that stereochemically dynamic, tropos[3d,4] ligands are capable of adapting their sense of chirality to a proximal chiral motif bound to the same metal center, and consequently to be able to replace rigid analogues with either absolute configuration. In a similar manner, adaptable ligand systems composed of a stereochemically flexible part covalently bound to a group with a rigid stereogenic element have been successfully employed in asymmetric catalysis.[5] In order to further exploit self-adaptable ligands in asymmetric catalysis, studies of their conformational preferences under different reaction conditions are desirable.

Moberg *et al.* have previously studied the conformational behavior of phosphepine and azepine ligands, such as **1** and **2** (Figure 3.2.1 (a)).[6]

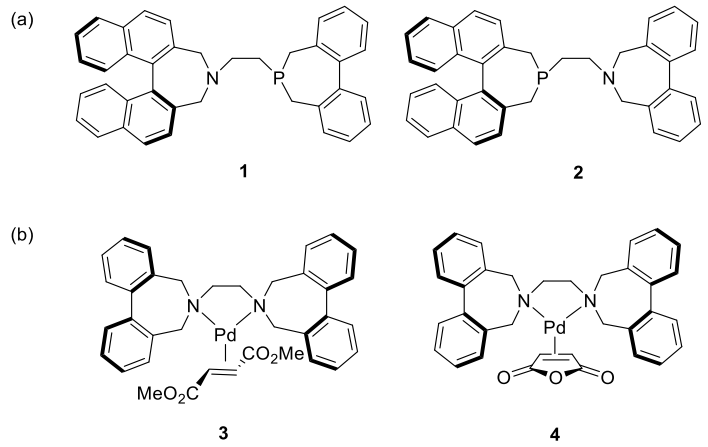


Figure 3.2.1. (a) Conformationally flexible phosphepine and azepine ligands **1** and **2**. (b) Palladium olefin complexes **3** and **4**.

By using palladium-catalyzed asymmetric allylic alkylation as an illustrative model process to probe the conformational issues, they found that the conformation of these flexible ligands may be influenced not only by structural units present in the catalyst, but also by the substrate undergoing reaction. In this particular catalytic process, different ligands are usually required for different types of substrates in order to obtain products with high enantiopurity.[7] By using bisazepine ligands with two flexible biaryl moieties, they were able to demonstrate that in palladium olefin complexes **3** and **4**, aimed to mimic the product olefin complexes from reaction of bulky linear ("broad") and small cyclic ("narrow") substrates, respectively, *R**,*R** (C_2) configuration was preferred in the complex containing the trans olefin, whereas *R**,*S** (C_s) was preferred in the complex with the cis olefin (Figure 3.2.1 (b)).[8] In contrast, *R**,*S** configuration of the ligand was observed in η^3-allyl palladium complexes derived from (*E*)-1,3-diphenyl-2-propenyl acetate as well as from 3-cyclohexenyl acetate (not shown).

Although tropoisomerization in azepine derivatives occurs while the ligand is coordinated to the metal center,[9] conformational change in ligands **1** and **2** was slow compared to nucleophilic attack, and the flexible ligands therefore behaved essentially as a mixture of the analogous rigid ligands, and thus proved to be less general than desired.

Ligands that tolerate a wide range of substrates are indeed rare. In this context, Diéguez *et al.* were able to show that substrate versatility in Pd-catalyzed allylic substitutions can benefit from the introduction of a conformationally flexible biaryl phosphite element.[10] Thus, phosphite-oxazoline (*S*)-**L1a** (Figure 3.2.2) constitutes one of the few examples of ligands that have provided high ee's in the Pd-catalyzed allylic alkylation of both the hindered model compound *rac*-(*E*)-1,3-diphenyl-2-propenyl acetate (**S1**) and unhindered cyclic substrate *rac*-3-cyclohexenyl acetate (**S2**).[11] This ligand has also been

successfully applied in enantioselective palladium-catalyzed Heck reactions,[12] and iridium-catalyzed hydroboration of 1,1-disubstituted olefins.[13] Since the barrier to inversion in phosphite ligands is known to be lower than that in phosphepine and azepine ligands,[14] we assumed that the broad substrate tolerance of (*S*)-**L1a** may originate in its ability to adapt the conformation to the substrate undergoing reaction. In order to test if this was the case, we decided to study the conformational preferences of ligand (*S*)-**L1a** in palladium complexes with relevance for asymmetric allylic alkylation. To this aim, we needed access to rigid analogues of (*S*)-**L1a**. For this reason, (R_a,*S*)-**L1f** and (S_a,*S*)-**L1g** were prepared (Figure 3.2.2), their behavior in the catalytic reactions investigated, and the structures of the corresponding olefin complexes studied by NMR spectroscopy and DFT calculations.

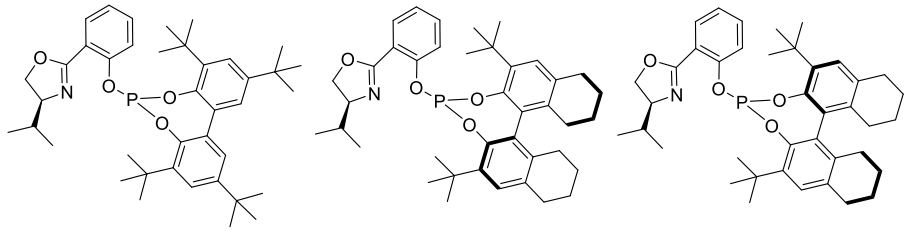


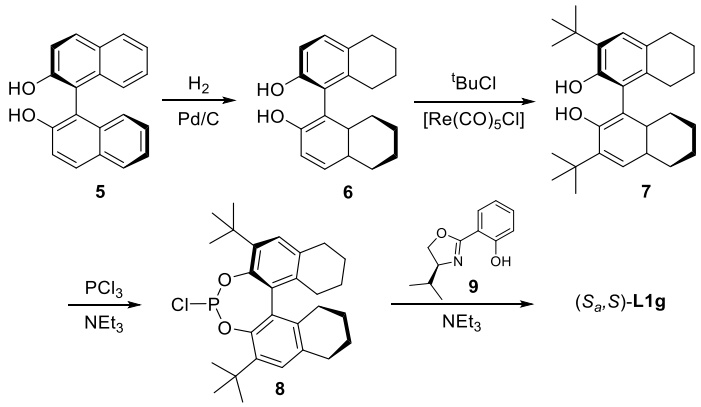
Figure 3.2.2. Phosphite-oxazoline ligands (*S*)-**L1a**, (R_a,*S*)-**L1f** and (S_a,*S*)-**L1g**.

We have also extended the previous work on dimethyl malonate and benzylamine to other C-nucleophiles and to O-nucleophiles, among which are the rarely studied α-substituted malonates, β-diketones, alkyl alcohols, silanols, and fluorobis(phenylsulfonyl)methane, and to alkylations of other substrates, thereby further underlining the versatility of ligand **L1a**.

3.2.2. Results

3.2.2.1. Preparation of Ligands

Ligand (S_a,*S*)-**L1g** was prepared starting from (*S*)-binol (**5**), as shown in Scheme 3.2.1. Catalytic hydrogenation following a published procedure gave (*S*)-**6**,[15] which was reacted with *tert*-butyl chloride in the presence of chloropentacarbonylrhenium(I)[16] to yield (*S*)-**7**. Reaction with phosphorus trichloride gave compound (*S*)-**8**. Condensation of chlorophosphite (*S*)-**8** with (*S*)-2-(4-isopropyl-4,5-dihydrooxazol-2-yl)phenol [17] **9** afforded in good yield the final product (S_a,*S*)-**L1g**. Ligand (R_a,*S*)-**L1f** was prepared analogously starting from (*R*)-binol. The flexible ligand (*S*)-**L1a** was prepared as previously described.[11]

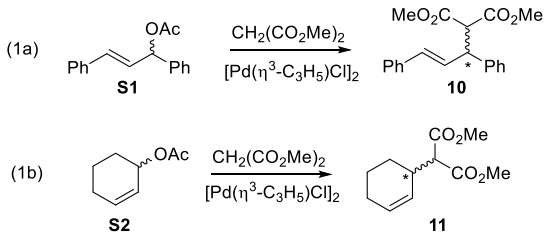


Scheme 3.2.1. Preparation of ligand (S_a,*S*)-**L1g**.

The rigid ligands gave rise to single signals in the ^{31}P NMR spectra, (S_a,*S*)-**L1g** at 127.9 ppm and (R_a,*S*)-**L1f** at 129.3 ppm. A single ^{31}P resonance was also observed from compound (*S*)-**L1a**, at 136.6 ppm. Interestingly, upon gradual cooling this signal first broadened and at around −20 °C split into two signals originating from the S_a and R_a conformers, as a result of tropoisomerization being slow on the NMR time scale. The original spectrum, containing a single ^{31}P resonance, was restored by warming the sample to 25 °C. In the ^{1}H NMR spectrum several signals were split upon cooling (See Supporting Information, 3.2.7.1).

3.2.2.2. Catalytic Reactions

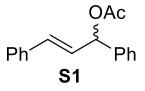
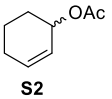
Palladium-catalyzed allylic alkylations of *rac*-(*E*)-1,3-diphenyl-2-propenyl acetate (**S1**) and *rac*-3-cyclohexenyl acetate (**S2**), with dimethyl malonate as nucleophile and [Pd(η^3-C_3H_3)Cl]$_2$ as palladium source were studied employing the three ligands **L1a**,**f**-**g** (Scheme 3.2.2 and Table 3.2.1). In reactions with **S1** as substrate, the use of the catalyst containing flexible ligand (*S*)-**L1a** resulted in full conversion to the product (**10**) with *S* absolute configuration with >99% ee within 10 minutes (Table 3.1.1, entry 1). Whereas use of (S_a,*S*)-**L1g** also gave essentially enantiopure product with *S* absolute configuration (entry 2), a catalyst containing (R_a,*S*)-**L1f** gave the opposite product enantiomer with merely 20% ee (entry 3). By employing a mixture of (S_a,*S*)-**L1g** and (R_a,*S*)-**L1f**, the (*S*)-enantiomer was obtained with 90% ee (entry 4). This demonstrates that the catalyst containing the former ligand forms a considerably more reactive catalyst. These experiments also demonstrate that the flexible ligand thus behaved essentially in the same way as ligand (S_a,*S*)-**L1g**.



Scheme 3.2.2. (1a) Allylic alkylations of *rac*-(*E*)-1,3-diphenyl-2-propenyl acetate (**S1**) and (1b) *rac*-3-cyclohexenyl acetate (**S2**).

Also with **S2** as substrate the flexible ligand (*S*)-**L1a** gave the same product enantiomer, (*S*)-**11**, as (S_a,*S*)-**L1g** (Table 3.2.1, entries 1 and 2), but with somewhat lower selectivity (94% as compared to 99% ee). Reaction in the presence of ligand (R_a,*S*)-**L1f** resulted in the formation of the opposite enantiomer with lower enantioselectivity also in reactions with this substrate, although the difference was considerably smaller than for **S1** (entry 3). The higher reactivity of (S_a,*S*)-**L1g** was again shown from the results of an experiment where a mixture of the two rigid ligands was used (entry 4). The absolute configurations of the products obtained demonstrate that the binaphthyl part of the ligand is mainly responsible for chirality transfer, and that the conformation of (*S*)-**L1a** in the selectivity-determining complex resembles that of (S_a,*S*)-**L1g**.

Table 3.2.1. Palladium-catalyzed allylic alkylation of **S1** and **S2** with ligands (*S*)-**L1a**, (S_a,*S*)-**L1g** and (R_a,*S*)-**L1f**.[a]

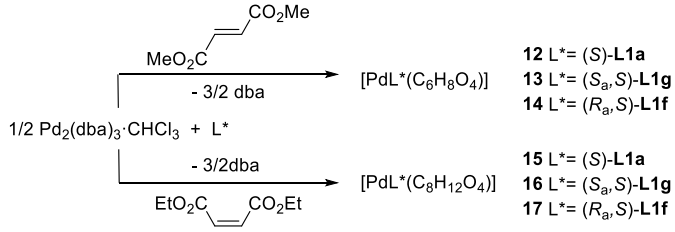
		 S1		 S2	
Entry	Ligand	% Conv[b]	% ee[c]	% Conv[d]	% ee[e]
1	(*S*)-**L1a**	100	>99 (*S*)	100	94 (*S*)
2	(S_a,*S*)-**L1g**	100	>99 (*S*)	100	99 (*S*)
3	(R_a,*S*)-**L1f**	100	20 (*R*)	100	92 (*R*)
4	(S_a,*S*)-**L1g** + (R_a,*S*)-**L1f**	100	90 (*S*)	100	68 (*S*)

[a] 0.5 mol % $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$, 1.1 mol % ligand, CH_2Cl_2 as solvent, BSA/KOAc as base, r.t. [b] Measured by ^1H NMR after 10 min. [c] Determined by HPLC. [d] Determined by GC after 30 min. [e] Determined by GC.

3.2.2.3. Preparation and NMR Studies of Palladium Olefin Complexes

Nucleophilic attack on the allyl group in palladium-catalyzed allylic alkylations has been argued to occur via a late, *i.e.* product-like, transition state, and the stereochemistry accordingly governed by formation of the most stable olefin complex.[18] With the aim of gaining a deeper insight into the conformation of flexible ligand (*S*)- **L1a** in the

selectivity-determining step, palladium(0) olefin complexes with the three ligands were prepared in order to mimic the product olefin complexes from allylic alkylations.



Scheme 3.2.3. Preparation of Pd(0)-olefin complexes **12**–**17**.

Dimethyl fumarate and diethyl maleate were selected as olefins in order to form complexes with sufficient stability to allow isolation and studies by NMR spectroscopy. The complexes were obtained by stirring equimolar amounts of ligand and olefin with one equivalent of $Pd_2(dba)_3.CHCl_3$ in deuterated dichloromethane (Scheme 3.2.3). Complex formation with dimethyl fumarate was achieved within 30 minutes at ambient temperature, whereas 16 hours were required to obtain the desired complexes from diethyl maleate. As a result of the symmetry of the olefins employed, a maximum of two olefin complexes can form with each ligand, those from dimethyl fumarate depicted as **A** and **B** and those from diethyl maleate as **C** and **D**, in Figure 3.2.3.

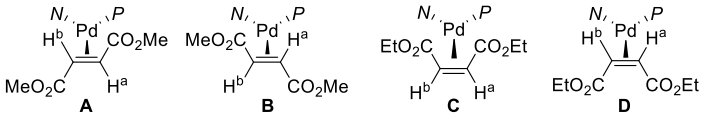


Figure 3.2.3. Possible isomers of palladium(0) olefin complexes.

Attempts were first made to determine the configuration of flexible ligand (*S*)-**L1a** in complexes with the two types of olefins by comparison of the spectra of **12** and **15** with those of the complexes with rigid ligands, *i.e.* **13**–**14** and **16**–**17**, respectively (Scheme 3.2.3).

The ^{31}P as well as ^{1}H NMR spectra of the complexes containing rigid ligands (**13**–**14** and **16**–**17**) suggested that essentially single isomers were obtained in each case. For instance, the proton coupled ^{31}P NMR spectrum of complex **13**, containing (S_a,*S*)-**L1g** and dimethyl fumarate, showed a doublet of doublet at δ 152.6 (J_{PH} = 15.9 and 4.7 Hz), along with a small signal at 151.7 (ratio ca 50:1), while the fumarate complex with (R_a,*S*)-**L1f** (**14**) showed a doublet of doublet at δ 154.0 (J_{PH} = 15.1 and 5.5 Hz) and a minor signal at 145.6 ppm (ratio ca 12:1), as well as a signal at 151.1, probably originating from a complex with dba. Diethyl maleate complex **16** showed a ^{31}P NMR signal at 153.2 ppm, which slowly replaced an initially observed signal at 149.3 ppm and

that of **17** a signal at 155.1 (minor signal at 147.7 ppm and a signal at 152.5 ppm originating from a complex with dba). In the ^{31}P NMR spectra of complexes **12** and **15**, with the flexible ligand (*S*)-**L1a**, signals at 153.6 and 155.8 ppm, respectively, were observed together with minor signals (155.7 in **12** and at 156.6 ppm in **15**) originating from minor isomers (ratio ca 11:1 in both cases). No separation of signals in the ^{31}P or ^{1}H NMR spectra occurred upon cooling to −70 °C, thus demonstrating that the spectra observed at ambient temperature are not a result of rapid equilibration of isomers (See Supporting Information 3.2.7.2 and 3.2.7.3). Characteristic ^{1}H and ^{31}P signals are shown in Table 3.2.2.

Although the NMR spectra of the three complexes **12**–**14** have many features in common (Table 3.2.2), that of **12**, with flexible ligand (*S*)-**L1a**, resembles more that of the complex with rigid ligand S_a,*S*-**L1g** than that with R_a,*S*-**L1f**, as judged by the chemical shifts and coupling constants of the oxazoline ring protons and the olefinic protons as well as by the chemical shift difference of the *tert*-butyl protons *ortho* to the phosphite function ($\Delta\delta$ ppm ca 0.2 ppm in **12** and **13** and 0.01 ppm in **14**), which is influenced by the proximity of the coordinated olefin and thereby by the conformation of the ligand. These spectral features suggest that the ligand in complex **12** adopts S_a,*S* configuration. Complete assignment of the ^{1}H NMR spectrum of **16** was hampered due to overlapping signals, but due to the similarity of the spectra **15** and **16**, in particular the chemical shifts of the oxazoline ring protons and the *tert*-butyl protons *ortho* to the phosphite moiety, it was assumed that **15** and **16** have the same absolute configuration. Although the NMR study thus suggests that the flexible ligand adopts (S_a,*S*) configuration in complexes with both types of olefins, the spectra do not allow definite conclusions about the configuration of the flexible ligand in the two complexes. For this reason, DFT calculations were performed (see below, section 3.2.2.4.).

Table 3.2.2. Characteristic NMR data for olefin protons H^a and H^b for complexes **12**–**17**.

Cmpd	δ H^a (ppm)	δ H^b (ppm)	δ P (ppm)	$J_{H^aH^b}$ (Hz)	J_{H^aP} (Hz)	J_{H^bP} (Hz)	δ Me$_{ligand}$ (ppm)	δ Me$_{olefin}$ (ppm)	δ ^{t}Bu (ppm)
12	3.72	3.57	153.6	10.2	4.6	15	0.94, 1.01	3.42, 2.93	1.10, 1.3
13	3.72	3.55	152.6	10	4.7	16	0.88, 1.01	3.07, 3.41	1.07, 1.32
14	3.86	3.51	154.0	10	5.5	15	0.69, 0.95	2.97, 3.37	1.26, 1.29
15	3.76	3.42	155.8	10	5.1	12	0.93, 1.04	0.65, 1.04	1.10, 1.3
16[a]			153.2				0.90, 1.04	0.83, 1.03	1.08, 1.31
17	3.88	3.49	155.1	10	5.5	15	0.72, 1.00	0.78, 1.38	1.28, 1.29

[a] Assignments hampered due to overlapping signals

Knowing that the catalyst with (S_a,*S*)-**L1g** leads to the (*S*)-product enantiomer and that with (R_a,*S*)-**L1f** to the opposite enantiomer, each olefin was expected to coordinate with different faces to palladium in complexes with the two ligands. Nucleophilic attack trans to phosphorus rather than trans to nitrogen is expected as a result of the stronger trans influence of phosphorus.[19] Due to the analogy of the product olefin complexes and our model complexes, those containing the (S_a,*S*)-**L1g** ligand were thus expected to be **A** and **C**, and those with the diastereomeric (R_a,*S*)-**L1f** ligand, **B** and **D** (Figure 3.2.3). However, NOESY experiments of the three palladium fumarate complexes **12**–**14** showed NOE interactions between the olefinic proton located trans to the phosphite moiety (H^b) and the proton of the isopropyl oxazoline substituent (Figure 3.2.4). This suggests that, in contrast to expectations, all fumarate complexes coordinate as in **A**, regardless of the configuration of the biaryl phosphite moiety.

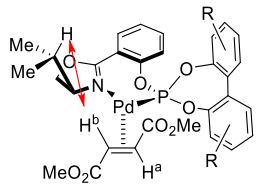


Figure 3.2.4. Relevant NOE contacts of Pd-complexes **12**–**14**.

3.2.2.4. Theoretical Studies

In order to determine the configuration of the flexible ligand in reactions with the two substrates as well as whether the olefins coordinate via the same face in complexes with the two rigid ligands although products with different absolute configuration were obtained, DFT calculations were performed. The relative stabilities of the product olefin complexes were initially calculated, using the olefin complexes obtained from nucleophilic addition of dimethyl malonate to allyl complexes derived from the two substrates (Figure 3.2.5 and Figure 3.2.6).

In agreement with the results of the NMR study, it was found that complexes containing product olefins with *S* absolute configuration were more stable than those with *R* configuration for both ligands and for both olefins (Figures 3.2.5 and 3.2.6); large energy differences were indeed found for the two complexes (S_a,*S*)-*S* (**A**) and (S_a,*S*)-*R* (**B**) with linear olefin **10** (Figure 3.2.5a) as well as for (R_a,*S*)-*S* (**C**) and (R_a,*S*)-*R* (**D**), containing cyclic olefin **11** (Figure 3.2.6a).

A smaller energy difference between the two olefin complexes (R_a,*S*)-*S* (**A**) and (R_a,*S*)-*R* (**B**) was observed, although the configuration of the product **10** predicted by the calculations is opposite to that observed experimentally (Figure 3.2.5b).

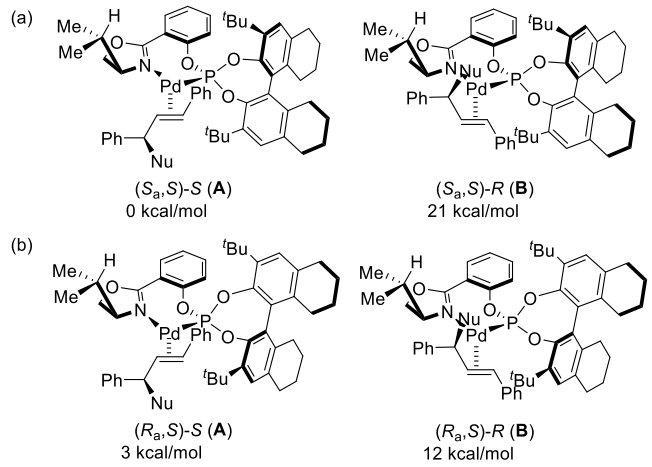


Figure 3.2.5. Calculated relative energies for palladium complexes **A** and **B** containing olefin **10** using ligands (a) (S_a,*S*)-**L1g** and (b) (R_a,*S*)-**L1f**. For use of **A** and **B**, compare Figure 3.2.3.

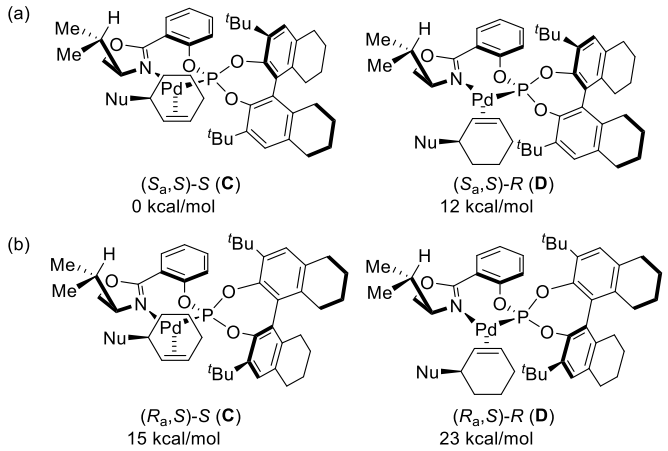


Figure 3.2.6. Calculated relative energies for palladium complexes **C** and **D** containing olefin **11** using ligands (a) (S_a,*S*)-**L1g** and (b) (R_a,*S*)-**L1f**. For use of **C** and **D**, compare Figure 3.2.3.

The opposite isomer is also predicted for reaction with 3-cyclohexenyl acetate using (R_a,*S*)-**L1f** (Figure 3.2.6b). The explanation for the formation of products with opposite absolute configuration from catalytic reactions using complexes containing (S_a,*S*)-**L1g** and (R_a,*S*)-**L1f** should therefore be sought in the relative stabilities of the transition states leading to the different products. Transition state (TS) calculations were therefore performed. In order to simplify the calculations, NH_3 was used as the nucleophile.

Neglecting *anti*,*anti* and *anti*,*syn* complexes, which constitute minor isomers, two *syn*,*syn* Pd-η^3-allyl, *exo* and *endo*, complexes derived from *rac*-(*E*)-1,3-diphenyl-2-

propenyl acetate are possible from each ligand, as illustrated for (S_a,*S*)-**L1g**, (R_a,*S*)-**L1f**, and (*S*)-**L1a** in Figure 3.2.7 Assuming that nucleophilic attack on the allyl complex to form the product olefin complex proceeds by a least-motion reaction path,[20] allyl complexes (S_a,*S*)-*exo* and (R_a,*S*)-*endo* are those which lead to the observed products, with *S* and *R* configuration, respectively.

The calculated energies of the transition states leading to the observed product and the enantiomers are shown in Table 3.2.3. A larger energy difference was found between the two TSs leading to opposite enantiomers in reactions with ligand (S_a,*S*)-**L1g** as compared to those with (R_a,*S*)-**L1f**, which is in accordance with the experimental results (>99% (*S*) vs 20% (*R*); Table 3.2.1, entries 2 vs 3). In addition, the TSs for (R_a,*S*)-**L1f** are higher in energy than the most stable TS for (S_a,*S*)-**L1g**, which fully accounts for the lower reactivity observed for the Pd/(R_a,*S*)-**L1f** catalytic system. The high ee's observed in reactions using (*S*)-**L1a** as ligand are also reflected in the energy difference calculated for the *endo* and *exo* structures with this ligand.

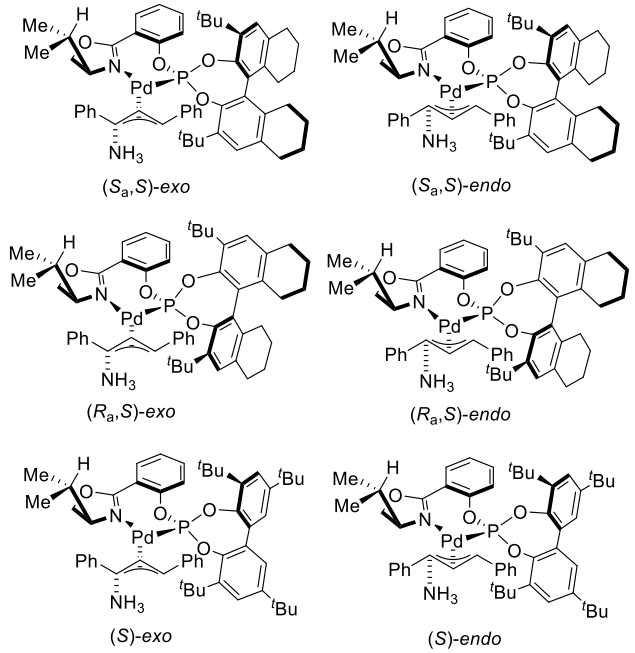


Figure 3.2.7. Pd-η^3-allyl *exo* and *endo* TSs from 1,3-diphenyl-2-propenyl acetate (**S1**).

Table 3.2.3. Calculated relative energies (in kcal/mol) for the TSs from *exo* and *endo* Pd-η^3-allyl intermediates, using **S1** and **S2** and NH_3 as nucleophile.

	S1		**S2**	
Ligand	*exo*	*endo*	*exo*	*endo*
(S_a,*S*)-**L1g**	0	4	2	0
(R_a,*S*)-**L1f**	2.6[a]	2.5[a]	2.2[b]	2.8[b]
(*S*)-**L1a**	0	4.3	1	0

[a] Energies relative to that of *exo*-(S_a,*S*)-**L1g**. [b] Energies relative to that of *endo*-(S_a,*S*)-**L1g**.

Analogous calculations were performed for complexes from 3-cyclohexenyl acetate (Figure 3.2.8). The calculated TS energy differences between the *exo* and *endo* complexes (Table 3.2.3) are in agreement with the high enantiomeric excesses observed using (S_a,*S*)-**L1g** as ligand, and also with the observation of opposite enantiomers of alkylated product **11** using the two diastereoisomeric ligands (S_a,*S*)-**L1g** and (R_a,*S*)-**L1f** (99% (*S*) using (S_a,*S*)-**L1g** vs 92% (*R*) for (R_a,*S*)-**L1f**; Table 3.2.1, entries 2 vs 3). Again, the energy of the TS for the reaction catalyzed by (R_a,*S*)-**L1f** is higher than that of the reaction catalyzed by (S_a,*S*)-**L1g**, which is in agreement with the higher reactivity observed for Pd/(S_a,*S*)-**L1g** compared to Pd/(R_a,*S*)-**L1f** catalyst.

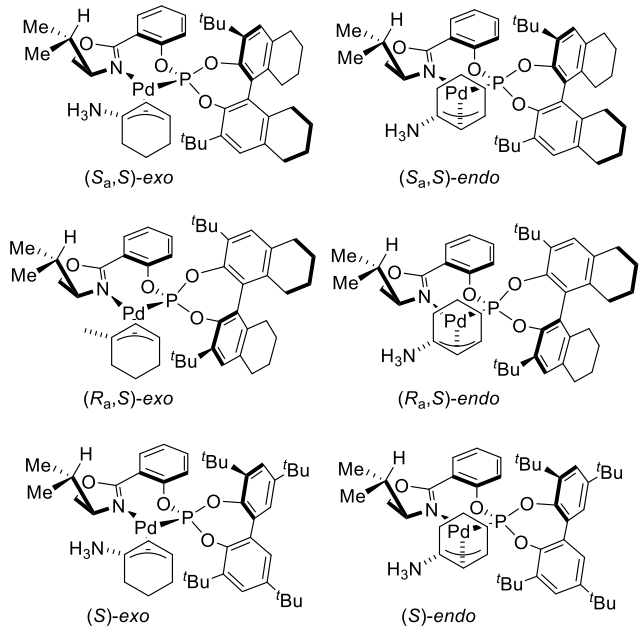


Figure 3.2.8. Pd-η^3-allyl *exo* and *endo* TSs from 3-cyclohexenyl acetate (**S2**).

The conclusion of the calculations is thus that in the reaction of *rac*-(*E*)-1,3-diphenyl-2-propenyl acetate with (S_a,*S*)-**L1g** the TS leading to the product with *S* configuration,

which is the product observed experimentally, is lowest in energy, and the olefin complex of this product is that which is most stable. In contrast, for (R_a,*S*)-**L1f**, the TS leading to the product with *R* configuration, which is the product observed experimentally, is lowest in energy, whereas the olefin complex of the product with *S* configuration is lowest in energy.

In the reaction of *rac*-3-cyclohexenyl acetate with (S_a,*S*,)-**L1g**, the TS leading to the product with *S* configuration, which is the product observed experimentally, is lowest in energy, and the olefin complex of this product is that which is most stable. In contrast, for (R_a,*S*)-**L1f***,* the TS leading to the product with *R* configuration, which is the product observed experimentally, is lowest in energy, whereas the olefin complex of the product with *S* configuration is lowest in energy. Thus, in reactions with both types of substrates where (R_a,*S*)-**L1f** is used as ligand, the lowest energy transition state complexes lead to product olefin complexes which are higher in energy than those from olefins with opposite absolute configuration. The calculations thus provide an explanation why the model olefins coordinate to palladium via the same face in complexes with the two rigid ligands, although they lead to products with opposite absolute configuration in the catalytic reactions.

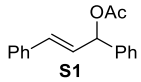
3.2.2.5. Other substrates and nucleophiles. Scope and limitations

To further study the behavior of ligand (*S*)-**L1a** and its rigid analogues (S_a,*S*)-**L1g** and (R_a,*S*)-**L1f**, and to investigate whether the similar behavior of the two best ligands (*S*)-**L1a** and (S_a,*S*)-**L1g** is general, we extended the previous work to O-nucleophiles and C-nucleophiles other than dimethyl malonate as well as to the alkylation of other substrates (Tables 3.2.4–3.2.9).

Table 3.2.4 shows the results of the use of Pd/(*S*)-**L1a** in the allylic substitution of symmetrically disubstituted linear substrate **S1**, using a wide range of C- and O-nucleophiles. We were pleased to note that Pd/(*S*)-**L1a** is very tolerant to variation of the steric properties of the ester moiety and the substituents of the malonate nucleophiles (entries 2–8). A broad range of malonates provided products **18**–**24** in high yields and with excellent enantioselectivities, comparable to those obtained with dimetyl malonate (ee's up to >99%). Of particular interest are the high enantioselectivities achieved with allyl-, butenyl-, pentenyl- and propargyl-substituted malonates, whose products are key intermediates in the synthesis of more complex chiral products.[21] The addition of acetylacetone (compound **25**) also proceeded with similar high enantioselectivities (ee's up to 98%, entry 9). Interestingly, we could also reach ee's up to 99% and high yield in the allylic fluorobis(phenylsulfonyl)methylation of **S1** using Pd/(*S*)-**L1a** (compound **26**, entry 10). The efficient allylic substitution with this type of nucleophile opens up a path for obtaining highly appealing chiral monofluoromethylated compounds, which are attracting significant attention in the field of medicinal

chemistry.[22] Despite this, only one catalytic system has previously been successfully applied, although it resulted in lower enantioselectivity (ee's up to 96%) than the present system and also required lower temperature (0 ºC) than our Pd/(*S*)-**L1a** catalyst.[23]

Table 3.2.4. Pd-catalyzed allylic substitution of disubstituted linear substrates using ligand (*S*)-**L1a**.[a]

Entry	Substrate	H-Nu	Product	% Conv[b] (%Yield)	% ee[c]
1	 **S1**	H-CH(CO_2Me)$_2$	**10**	100 (94)	>99 (*S*)
2	**S1**	H-CH(CO_2Et)$_2$	**18**	100 (93)	>99 (*S*)
3	**S1**	H-CH(CO_2Bn)$_2$	**19**	100 (95)	>99 (*S*)
4	**S1**	H-CMe(CO_2Me)$_2$	**20**	96 (91)	99 (*R*)
5	**S1**	H-Callyl(CO_2Me)$_2$	**21**	100 (92)	>99 (*R*)
6	**S1**	H-Cbutenyl(CO_2Et)$_2$	**22**	100 (89)	>99 (*R*)
7	**S1**	H-Cpentenyl(CO_2Et)$_2$	**23**	100 (93)	93 (*R*)
8	**S1**	H-Cpropargyl(CO_2Me)$_2$	**24**	100 (91)	>99 (*R*)
9	**S1**	H-CH(COMe)$_2$	**25**	100 (89)	98 (*S*)
10[d]	**S1**	H-CF(SO_2Ph)$_2$	**26**	100 (76)	99 (*R*)
11[d]	**S1**	H-OCH_2Ph	**27**	76 (69)	33 (*R*)
12[d]	**S1**	H-OCH_2(*p*-Me-C_6H_4)	**28**	82 (76)	25 (-)
13[d]	**S1**	H-OCH_2(*p*-CF_3-C_6H_4)	**29**	100 (93)	97 (-)
14[d]	**S1**	H-OCH_2(*m*-Me-C_6H_4)	**30**	75 (69)	37 (-)
15[d]	**S1**	H-Oallyl	**31**	89 (81)	32 (-)
16[d]	**S1**	H-Opropargyl	**32**	75 (70)	40 (*R*)
17[d]	**S1**	H-OSi(Me)$_2$Ph	**33**	94 (79)	98 (*R*)[e]
18[d]	**S1**	H-$OSiPh_3$	**34**	100 (91)	99 (*R*)[e]

[a] 0.5 mol % [Pd(η^3-C_3H_5)Cl]$_2$, 1.1 mol % ligand, CH_2Cl_2 as solvent, BSA/KOAc as base, r.t. [b] % Conversion measured after 10 min. Isolated yield shown in parenthesis. [c] Enantiomeric excesses determined by chiral HPLC or GC. [d] Conversions and yields measured after 18 h. [e] Measured after desilylation to the corresponding alcohol.

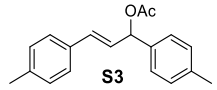
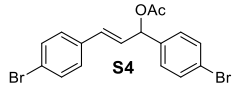
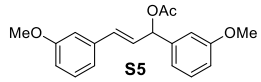
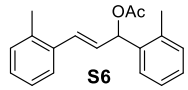
We then considered the allylic substitution of **S1** using several O-nucleophiles (entries 11–18). The asymmetric Pd-catalyzed allylic etherification has recently attracted the attention of many researchers because the resulting chiral ethers and related derivatives are important intermediates in the synthesis of biologically active compounds.[24] Despite its importance, few successful examples exist and most of them use phenols as O-nucleophiles,[25] being aliphatic ethers[26] and silanols[26d] much less studied. The application of Pd/(*S*)-**L1a** to several aliphatic alcohols provided the desired products in excellent yields. For benzylic alcohols, the enantioselectivity was affected by the electronic nature of the nucleophile. The best enantioselectivity (97% ee, entry 13) was achieved with an electron-withdrawing group in the *para* position of the aryl group. Even more interesting

are the almost perfect enantioselectivities (ee's up to 99%) and high yields achieved in the etherification of **S1** with silanols (entries 17–18).

The results surpass those of the only Pd/CycloN$_2$P$_2$-Phos catalytic type system that has provided high enantioselectivities (up to 94%)[26d] so far. Therefore, Pd/(*S*)-**L1a** can be used for preparing chiral silyl ethers that can be easily transformed into high-value compounds such as chiral aromatic allylic alcohols.

The scope of Pd/(*S*)-**L1a** was further investigated by using other symmetrical linear substrates with steric and electronic requirements (**S3**–**S6**) different from those of **S1** (Table 3.2.5).

Table 3.2.5. Pd-catalyzed allylic substitution of disubstituted linear substrates using ligand (*S*)-**L1a**.[a]

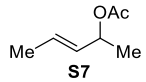
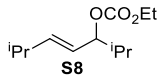
Entry	Substrate	H-Nu	Prod.	% Conv[b] (%I.Y.)	% ee[c]
1	 **S3**	H-CH(CO$_2$Me)$_2$	**35**	100 (93)	99 (*S*)
2	**S3**	H-Callyl(CO$_2$Me)$_2$	**36**	100 (91)	99 (*R*)
3	**S3**	H-Cbutenyl(CO$_2$Et)$_2$	**37**	100 (92)	94 (*R*)[d]
4	 **S4**	H-CH(CO$_2$Me)$_2$	**38**	100 (89)	99 (*S*)
5	 **S5**	H-CH(CO$_2$Me)$_2$	**39**	100 (91)	99 (*S*)
6	 **S6**	H-CH(CO$_2$Me)$_2$	**40**	100 (90)	99 (*S*)

[a] 0.5 mol % [Pd(η^3-C$_3$H$_5$)Cl]$_2$, 1.1 mol % ligand, CH$_2$Cl$_2$ as solvent, BSA/KOAc as base, r.t. [b] % Conversion measured after 10 min. Isolated yield shown in parenthesis. [c] Enantiomeric excesses determined by chiral HPLC or GC. [d] Measured after transformation to the corresponding RCM-adduct.

The Pd/(*S*)-**L1a** catalytic system can also be used for the alkylation of substrates **S3**–**S6**, with different substituents in the aryl groups, with various carbon nucleophiles with excellent enantioselectivities and yields, comparable to those of **S1** (Table 3.2.5, entries 1–6). We also found that the biaryl-phosphite group in Pd/(*S*)-**L1a** can adapt its chiral pocket and successfully catalyze the alkylation of **S7** (Table 3.2.6, entries 1–7). This substrate is less sterically demanding and therefore enantioselectivities tend to be lower than with model substrate **S1**. The present results are among the best in the literature for this substrate,[7] even using highly appealing nucleophiles such as α-substituted with methyl, allyl and butenyl groups, for which only very few catalytic systems have provided high enantioselectivities.[21] Interestingly, Pd/(*S*)-**L1a** can also successfully be used for

the alkylation of **S8** (ee's up to >95%, entry 8). This substrate is more sterically demanding and it usually reacts with inferior catalytic performance than **S1** and **S3**–**S4**.

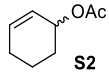
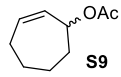
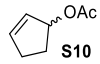
Table 3.2.6. Pd-catalyzed allylic substitution of disubstituted linear substrates **S7**-**S8** using ligand (*S*)-**L1a**.[a]

Entry	Substrate	H-Nu	Product	% Conv[b] (%Yield)	% ee[c]
1[d]	 **S7**	H-CH(CO_2Me)$_2$	**41**	100 (89)	93 (*S*)
2[d]	**S7**	H-CH(CO_2Bn)$_2$	**42**	100 (91)	82 (*S*)
3[d]	**S7**	H-CH(COMe)$_2$	**43**	100 (90)	85 (*S*)
4[d]	**S7**	H-CMe(CO_2Me)$_2$	**44**	100 (86)	80 (*S*)
5[d]	**S7**	H-Callyl(CO_2Me)$_2$	**45**	100 (89)	90 (*S*)
6[d]	**S7**	H-Cbutenyl(CO_2Et)$_2$	**46**	100 (90)	87 (*S*)
7[d]	**S7**	H-Cpropargyl(CO_2Me)$_2$	**47**	100 (87)	72 (*S*)
8[e]	 **S8**	H-CH(CO_2Me)$_2$	**48**	100 (92)	>95 (*S*)[f]

[a] 0.5 mol % [Pd(η^3-C_3H_5)Cl]$_2$, 1.1 mol % ligand, CH_2Cl_2 as solvent, BSA/KOAc as base, r.t. [b] % Conversion measured after 10 min. Isolated yield shown in parenthesis. [c] Enantiomeric excesses determined by chiral HPLC or GC. [d] Reactions carried out at 0 ºC for 18 h. [e] % Conversion measured after 18 h [f] Ee measured by ^{1}H NMR using [Eu(hfc)$_3$].

We then focused our attention on the allylic substitution of cyclic substrate **S2** with more challenging nucleophiles than dimethyl malonate and on the alkylation of other cyclic substrates with different ring sizes (**S9** and **S10**). Table 3.2.7 shows that a wide range of C-nucleophiles, including the less studied α-substituted malonates and acetylacetone, can efficiently react with **S2** to provide the corresponding compounds (**49**–**54**) with high yields and enantioselectivities (ee's up to >99%), comparable to those obtained with dimethyl malonate (**11**). The exception was propargyl-substituted malonate, which led to somewhat lower enantioselectivity (compound **53**, ee's up to 92%), but still good for this challenging C-nucleophile. Remarkably, Pd/(S_a,*S*)-**L1g** also efficiently catalyzes the alkylation of cyclic substrates **S9** and **S10** (Table 3.2.7, entries 8–11, compounds **55**–**58**). Excellent-to-high enantioselectivities (ee's between 96% and >99%) were obtained in both cases, even with **S10**, which usually provides products with much lower enantioselectivities than cyclic **S2**.[7]

Table 3.2.7. Pd-catalyzed allylic substitution of cyclic substrates using ligand (S_a,S)-**L1g**.[a]

Entry	Substrate	H-Nu	Product	% Conv[b] (% yield)	% ee[c]
1	 **S2**	H-CH(CO_2Me)$_2$	**11**	100 (92)	99 (*S*)
2	**S2**	H-CH(CO_2Et)$_2$	**49**	100 (93)	>99 (*S*)
3	**S2**	H-CH(CO_2Bn)$_2$	**50**	100 (90)	97 (*S*)
4	**S2**	H-CMe(CO_2Me)$_2$	**51**	100 (89)	99 (+)
5	**S2**	H-Callyl(CO_2Me)$_2$	**52**	100 (91)	>99 (-)
6	**S2**	H-Cpropargyl(CO_2Me)$_2$	**53**	100 (88)	92 (*S*)
7	**S2**	H-CH(COMe)$_2$	**54**	100 (93)	99 (-)
8	 **S9**	H-CH(CO_2Me)$_2$	**55**	100 (92)	>99 (*S*)
9	**S9**	H-Cpropargyl(CO_2Me)$_2$	**56**	69 (65)	>99 (*S*)
10	 **S10**	H-CH(CO_2Me)$_2$	**57**	100 (86)	>95 (-)[d]
11	**S10**	H-Cpropargyl(CO_2Me)$_2$	**58**	100 (87)	96 (*S*)

[a] 0.5 mol % [Pd(η^3-C_3H_5)Cl]$_2$, 1.1 mol % ligand, CH_2Cl_2 as solvent, BSA/KOAc as base, r.t. [b] % Conversion measured after 30 min. Isolated yield shown in parenthesis. [c] Enantiomeric excesses determined by chiral HPLC or GC. [d] Ee measured by ^{1}H NMR using [Eu(hfc)$_3$].

We next studied if the rigid analogues of (*S*)-**L1a** (ligands (S_a,*S*)-**L1g** and (R_a,*S*)-**L1f**) follow the same trend in the allylic substitution of unsymmetrical monosubstituted substrates **S11** and **S12** (Eqs 2, Table 3.2.8) as in reactions with disubstituted substrates. The challenge in these substrates is that both the enantioselectivity and regioselectivity need to be controlled, and most palladium catalysts favor the formation of the usually undesired achiral linear product.[7,27,28] In our previous work we found that alkylation of **S11** and **S12** catalyzed by Pd/(*S*)-**L1a** proceeded with regio- and enantioselectivities comparable to those of the best ones reported.[11] As observed with the previously studied linear disubstituted substrates, Pd/(S_a*S*)-**L1g** gave excellent results and provided the desired branched isomers (compounds **59** and **61**), with enantioselectivities that were as high as those obtained with Pd/(*S*)-**L1a**, as major products (Table 3.2.6).

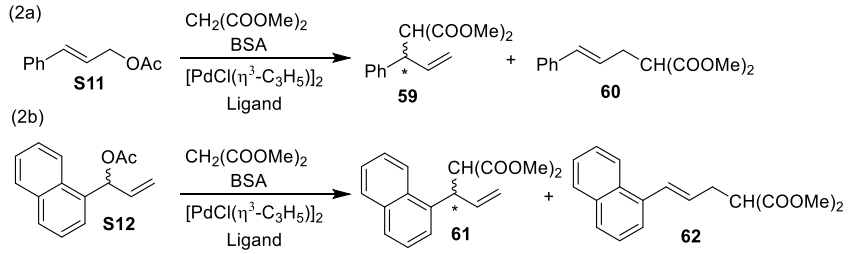
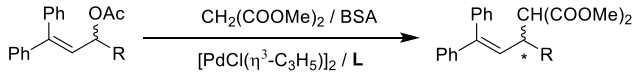


Table 3.2.8. Pd-catalyzed allylic substitution of monosubstituted substrates **S11** and **S12**.[a]

Entry	Substrate	Ligand	% Conv[b] (%yield)	% branched[c]	% ee[d]
1	**S11**	(*S*)-**L1a**	100 (91)	68	86 (*S*)
2	**S11**	(S_a,*S*)-**L1g**	100 (90)	65	85 (*S*)
3	**S11**	(R_a,*S*)-**L1f**	100 (90)	15	42 (*R*)
4	**S11**	(S_a,*S*)-**L1g**+(R_a,*S*)-**L1f**	100 (91)	50	79 (*S*)
5	**S12**	(*S*)-**L1a**	100 (92)	>99	92 (*S*)
6	**S12**	(S_a,*S*)-**L1g**	100 (89)	95	90 (*S*)
7	**S12**	(R_a,*S*)-**L1f**	100 (90)	40	41 (*R*)
8	**S12**	(S_a,*S*)-**L1g**+(R_a,*S*)-**L1f**	100 (91)	70	61 (*S*)

[a] 1 mol % $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$, 2.2 mol % ligand, benzene as solvent, BSA/KOAc as base, 0 °C. [b] % Conversion measured after 2 h. Isolated yield shown in parenthesis. [c] Regioselectivity measured by ^{1}H NMR. [d] Enantiomeric excesses determined by chiral HPLC.

Finally, the good performance of Pd/(*S*)-**L1a** and Pd/(S_a,*S*)-**L1g** also extended to the allylic substitution of unsymmetrical 1,3,3,-trisubstituted allylic substrates (**S13**–**S14**, Table 3.2.9). These reactions have a large interest because the substitution products can easily be transformed into chiral acid derivatives and lactones.[29] Theses substrates have been less studied and less successfully alkylated than disubstituted substrates because they are more sterically demanding than model substrate **S1**.[30] The results shown in Table 3.2.9 show the same trend as for the allylic substitution of **S1**. The Pd-catalysts containing ligands (*S*)-**L1a** and (S_a,*S*)-**L1g** provided the best enantioselectivities (ee's up to >99% for both substrates). Again the flexibility conferred by the biaryl phosphite moiety was enough to adequately control the size of the chiral pocket in order to achieve enantioselectivities comparable to the best one reported.[30] In line with the literature results, and as observed for **S8**, the activities were lower than in the alkylation reaction of **S1**.



S13 R= Ph
S14 R= Me

63 R= Ph
64 R= Me

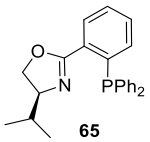
Table 3.2.9. Pd-catalyzed allylic substitution of trisubstituted substrates **S13** and **S14**.[a]

Entry	Substrate	Ligand	% Conv[b] (%yield)	% ee[c]
1	**S13**	(*S*)-**L1a**	87 (84)	>99 (*R*)
2	**S13**	(S_a,*S*)-**L1g**	84 (79)	99 (*R*)
3	**S13**	(R_a,*S*)-**L1f**	65 (62)	41 (*S*)
4	**S14**	(*S*)-**L1a**	98 (95)	>99 (*R*)
5	**S14**	(S_a,*S*)-**L1g**	95 (90)	99 (*R*)
6	**S14**	(R_a,*S*)-**L1f**	71 (65)	24 (*S*)

[a] 2 mol % $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$, 4.4 mol % ligand, CH_2Cl_2 as solvent, BSA/KOAc as base, rt. [b] % Conversion measured after 24 h. Isolated yield shown in parenthesis. [c] Enantiomeric excesses determined by chiral HPLC.

3.2.3. Discussion

High enantiocontrol is achieved in a variety of processes employing metal complexes with phosphinooxazoline, PHOX, ligands (**65**) as catalysts,[31] and for this reason phosphinooxazolines are classified as privileged ligands.[2] In a variety of catalytic processes phosphite ligand (*S*)-**L1** has properties similar to those of phosphine ligands **65**.[32] However, whereas (4*S*)-2-(2'-diphenylphosphino)phenyl-4-isopropyl-4,5-dihydrooxazole (**65**, R = ^{i}Pr; Figure 3.2.9) gives excellent results in asymmetric allylic alkylations with *rac*-(*E*)-1,3-diphenyl-2-propenyl as substrate (98% ee), modest to good results are obtained with *rac*-(*E*)-1,3-dialkyl-2-propenyl substrates, and racemic product with the *rac*-3-cyclohexenyl derivatives. In contrast, **L1a** provides excellent results with all these types of substrates. The chiral PHOX ligands interact with the substrate mainly at its wings. As a consequence, allylic systems with bulky substituents show high *exo*:*endo* ratios and high enantioselectivities, whereas narrow systems give low selectivity.[32] In contrast, ligands (*S*)-**L1a** and (S_a,*S*)-**L1g** are more flexible and can accommodate a wider range of substrates, thereby yielding excellent enantioselectivities for both "broad" and "narrow" substrates. In fact, by replacing the phosphine moiety by a biaryl phosphite in the PHOX ligand, we were able to identify unprecedented catalytic systems (Pd/(*S*)-**L1a** and Pd/(S_a,*S*)-**L1g**) that with high enantiocontrol generate C-C, C-N, and C-O bonds for a number of hindered and unhindered mono-, di- and tri-substituted substrates using a wide range of C, N and O-nucleophiles.



65

Figure 3.2.9. Phosphinooxazoline ligand **65**.

The enantioselectivity of the catalytic reactions is reflected by the energy difference between the *exo* and *endo* like transition states, provided that nucleophilic attack occurs only trans to phosphorus. In the reaction of *rac*-(*E*)-1,3-diphenyl-2-propenyl acetate (**S1**) in the presence of (S_a,*S*)-**L1g** (with NH_3 as nucleophile) this difference was calculated to 4 kcal/mol, in good agreement with the selectivity observed experimentally (>99% ee). The selectivity observed experimentally in reaction with the cyclic substrate **S2** was slightly lower (99% ee), well corresponding to the computed energy difference between the two transition states, 2 kcal/mol. For reactions of the two substrates in the presence of PHOX ligand **65** (R = ^{i}Pr; Figure 3.2.9) the corresponding values were calculated to 2.2 and 0 kcal/mol, respectively, thus reflecting the somewhat lower selectivity obtained from **S1** as compared to that obtained using (S_a,*S*)-**L1g** , and the formation of racemic product from **S2**.[20]

Contrary to expectations, the absolute configuration of the products could not be entirely predicted from the structure of the most stable olefin complex, implying that at least for reactions employing (R_a,*S*)-**L1f** as ligand, the transition states resemble the palladium allyl complexes rather than the olefin complexes. For (*S*)-**L1a** and (S_a,*S*)-**L1g** *exo* complexes are more stable than *endo* complexes, in analogy to complexes with PHOX ligands, whereas for (R_a,*S*)-**L1f** the *endo* complex has slightly higher stability than the *exo* complex.

While the previously studied semiflexible ligands **1** and **2** (Figure 3.2.1) adopt different configurations in product olefin complexes obtained in reactions with the two types of substrates, (*S*)-**L1a** prefers a (S_a,*S*) configuration with both "broad" and "narrow" substrates. The ability of this ligand to adapt the size of the substrate-binding pocket to the reacting substrate is therefore a result of the high flexibility of the biaryl phosphite group.

3.2.4. Conclusions

Contrary to previously studied flexible ligands, (*S*)-**L1a** adopts (S_a,*S*) configuration in complexes mimicking product olefin complexes obtained in palladium catalyzed allylic alkylations of both "broad" and "narrow" allylic substrates. Although the olefins coordinate with the same face to palladium in diastereomeric rigid ligands with (S_a,*S*)

and (R_a,*S*) configuration, products with opposite absolute configuration are obtained. The explanation is found in the different energies of the transition state complexes.
The origin of the exceptionally broad substrate scope of the ligand as well as its ability to control the stereochemistry in a variety of catalytic processes is connected to its defined stereochemical structure combined with the high flexibility of the *tropos* unit. The unique ability of the ligand to modify its chiral pocket would justify its addition to the family of privileged ligands.

3.2.5. Experimental Part

3.2.5.1. General Procedures

Unless stated otherwise, reactions were carried out under an atmosphere of nitrogen using standard Schlenk techniques. NMR spectra (^{1}H, ^{13}C, and ^{31}P) were measured on Bruker DRX 400 MHz and Bruker DRX 500 MHz instruments; $CDCl_3$ was used as a solvent, if not further specified.

3.2.5.2. Materials

With exception of the compounds given below, all reagents were purchased from commercial suppliers and used without further purification. The following compounds were synthesized according to published procedures: (*S*)-5,6,7,8,5,6,7,8-octahydro-(1,1'-binaphtalene)-2,2'-diol (*S*)-**6**,[15] (*R*)-5,6,7,8,5,6,7,8-octahydro-(1,1'-binaphtalene)-2,2'-diol (*R*)-**6**,[15] and (*S*)-2-(4-isopropyl-4,5-dihydrooxazol-2-yl)phenol.[17] Racemic substrates **S1**–**S14**,[33] diethyl 2-(3-butenyl)malonate[34] and diethyl 2-(4-penten-1-yl)malonate[35] were prepared as previously reported.

3.2.5.3. Computational details

The geometries of all intermediates were optimized using the Gaussian 09 program,[36] employing the B3LYP[37] density functional and the LANL2DZ[38] basis set for iridium and the 6-31G* basis set for all other elements.[39] Solvation correction was applied in the course of the optimizations using the PCM model with the default parameters for dichloromethane.[40] 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**[41] basis set was used for all elements except palladium, and by applying dispersion correction using DFT-D3[42] model. All energies reported are Gibbs free energies at 298.15 K and calculated as $G_{reported} = G_{6\text{-}31G^*} + (E_{6\text{-}311+G^{**}} - E_{6\text{-}31G^*}) + EDFT\text{-}D3$.

3.2.5.4. Procedures for the synthesis of L1a, L1f-g.

Synthesis compound (*S*)-7.[16] In a Schlenk were placed (*S*)-**6** (1.0 g, 3.4 mmol), *tert*-butyl chloride (9.2 mL, 85 mmol), and chloropentacarbonylrhenium(I) (10 mol %). The reaction mixture was heated at reflux for 18 h under stream of nitrogen. The mixture was cooled to room temperature and concentrated. The residue was purified by flash chromatography (silica gel, hexane/CH_2Cl_2 3:1) to afford (*S*)-**7** (1.34 g, yield 97%) as a white foam. ^{1}H NMR (500 MHz, $CDCl_3$): δ =1.33 (s, 18H), 1.59 (m, 4H), 1.65 (m, 4H), 2.11 (m, 2H), 2.02 (m, 2H), 2.66 (m, 4H), 4.78 (s, 2H), 6.99 (s, 2H); ^{13}C NMR (126 MHz): δ= 23.2 (CH_2), 26.8 (CH_2), 29.5 (CH_2), 29.6 (CH_3), 34.5 (CH), 119.5 (C), 128.3 (C), 129.1 (C), 133.8 (C), 134.5 (C), 150.1 (C).

Synthesis of compound (*S*)-8.[43] In a flame-dried Schlenk, distilled PCl_3 (0.21 mL, 2.46 mmol) and Et_3N (0.70 mL, 4.92 mmol) were dissolved in dry toluene (22 mL). The solution was cooled to -78 °C and a solution of (*S*)-**7** (500 mg, 1.23 mmol) and DMAP (10 mol %) in toluene (3 mL) was added dropwise over 10 min. The mixture was left to warm to room temperature overnight. After this time the formation of product was checked by ^{31}P NMR. The solvent and the residual PCl_3 were removed under vacuum. The resulting solid was used for the next step without any further purification.

Synthesis compound (S_a,*S*)-L1g. To a solution of compound (*S*)-**8** in dry toluene (7 mL) in a flame-dried Schlenk, a solution of (*S*)-2-(4-isopropyl-4,5-dihydrooxazol-2-yl)phenol **9** (252.4 mg, 1.23 mmol), Et_3N (0.51 mL, 3.69 mmol), and DMAP (10 mol %) in toluene (3 mL) was added dropwise at -78 °C. The mixture was left to warm to room temperature and stirred overnight at this temperature. The precipitate formed was filtered over a pad of celite and the solvent was evaporated under vacuum. The residue was purified by flash chromatography (silica gel, hexane/Et_2O 10:1 to 3:1) and then crystallized from hexane/Et_2O 5:1 to afford (S_a,*S*)-**L1g** (75 mg, 10% over two steps) as white crystals. ^{31}P NMR (202 MHz): δ= 129.0. ^{1}H NMR (500 MHz, CD_2Cl_2): δ= 0.86 (dd, *J* = 10.0, 6.8 Hz, 3H), 0.97 (dd, *J* = 10.0, 6.7 Hz, 3H), 1.21 (d, *J* = 10.1 Hz, 9H), 1.40 (d, *J* = 10.1 Hz, 9H), 1.46 (m, 1H), 1.57 (m, 4H), 1.71 (m, 4H), 1.94 – 1.77 (m, 2H), 2.25 (m, 2H), 2.67 (m, 2H), 2.84 – 2.74 (m, 2H), 3.95 (dd, *J* = 18.1, 8.3 Hz, 1H), 4.02 (dd, *J* = 17.1, 7.7 Hz, 1H), 4.29 (dd, *J* = 17.8, 9.6 Hz, 1H), 5.58 (m, 1H), 6.92 (s, 1H), 6.93 (s, 1H), 6.98 (m, 1H), 7.12 (d, *J* = 10.1 Hz, 1H), 7.64 (m, 1H). ^{13}C NMR (126 MHz): δ=18.8 (CH_3), 19.3 (CH_3), 23.3 (CH_2), 23.4 (CH_2), 23.5 (CH_2), 23.6 (CH_2), 27.4 (CH_2), 27.7 (CH_2), 29.9 (CH_2), 30.7 (CH_2), 31.2 (CH_3), 33.6 (CH_2), 34.7 (CH), 34.9 (CH), 70.2 (CH_2), 73.5 (CH_2), 123.7 (C), 124.1 (CH), 127.6 (CH), 127.8 (CH), 130.2 (CH), 131.5 (C), 133.6 (CH), 135.5 (CH), 135.7 (CH), 138.3 (CH), 138.8 (C), 145.4 (C), 151.0 (C), 151.7 (C), 160.9 (CH). MS HR-ESI [found 662.3377, $C_{40}H_{50}NO_4P$ $(M\text{-}Na)^+$ requires 662.3375].

Synthesis compound (*R*)-7.[16] In a Schlenk were placed (*R*)-**6** (1.0 g, 3.4 mmol), *tert*-butyl chloride (9.2 mL, 85 mmol), and chloropentacarbonylrhenium(I) (10 mol %). The reaction mixture was heated at reflux for 18 h under a stream of nitrogen. The mixture was cooled to room temperature and concentrated. The residue was purified by flash chromatography (silica gel, hexane/CH_2Cl_2 3:1) to afford (*R*)-**7** (1.0 g, yield 72 %) as a white foam. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.33 (s, 18H), 1.59 (m, 4H), 1.65 (m, 4H), 2.02 (m, 2H), 2.11 (m, 2H), 2.66 (m, 4H), 4.78 (s, 2H), 6.99 (s, 2H).; ^{13}C NMR (126 MHz): δ = 23.2 (CH_2), 26.8 (CH_2), 29.5 (CH_2), 29.6 (CH_3), 34.5 (CH), 119.5 (C), 128.3 (C), 129.1 (C), 133.8 (C), 134.5 (C), 150.1 (C).

Synthesis compound (*R*)-8.[43] In a flame-dried Schlenk, distilled PCl_3 (0.21 mL, 2.46 mmol) and Et_3N (0.70 mL, 4.92 mmol) were dissolved in dry toluene (22 mL). The solution was cooled to −78 °C and a solution of (*R*)-**7** (500 mg, 1.23 mmol) and DMAP (10 mol %) in toluene (3 mL) was added dropwise over 10 min. The mixture was left warming to room temperature overnight. After this time the formation of product was checked by ^{31}P NMR. The solvent and the residual PCl_3 were removed under vacuum. The resulting solid was used for the next step without any further purification.

Synthesis compound (R_a,*S*)-L1f. To a solution of compound (*R*)-**8** in dry toluene (7 mL) in a flame-dried Schlenk, a solution of the (*S*)-2-(4-isopropyl-4,5-dihydrooxazol-2-yl)phenol **9** (252.4 mg, 1.23 mmol), Et_3N (0.51 mL, 3.69 mmol), and DMAP (10 mol %) in toluene (3 mL) was added dropwise at -78 °C. The mixture was left to warm to room temperature and stirred overnight at this temperature. The precipitate formed was filtered over a pad of celite and the solvent was evaporated under vacuum. The residue was purified by flash chromatography (silica gel, hexane/Et_2O 10:1) to afford (R_a,*S*)-**L1f** (69 mg, 9% over two steps) as a white foam. ^{31}P NMR (162 MHz): δ= 129.33. ^{1}H NMR (400 MHz, CD_2Cl_2): δ= 0.82 (d, *J* = 8.0 Hz, 3H), 0.96 (d, *J* = 8.0 Hz, 3H), 1.21 (m, 10H), 1.34 (m, 1H), 1.38 (m, 9H), 1.47 (s, 2H), 1.66 (m, 8H), 1.92 (m, 2H), 2.30 (m, 2H), 2.70 (m, 2H), 2.77 (m, 2H), 3.94 (m, 2H), 4.28 (m, 1H), 6.12 (m, 1H), 6.98 (m, 2H), 7.09 (m, 1H), 7.71 (m, 1H). ^{13}C NMR (101 MHz): δ= 18.7 (CH_3), 19.6 (CH_3), 23.35 (CH_2), 23.38 (CH_2), 23.47 (CH_2), 23.5 (CH_2), 23.6 (CH_2), 27.9 (CH_2), 30.2 (CH_2), 31.3 (CH_2), 31.5 (CH_3), 33.6 (CH_2), 35.0 (CH), 35.1 (CH), 70.7 (CH_2), 73.6 (CH_2), 121.7 (C), 124.2 (CH), 127.8 (CH), 128.1 (CH), 130.0 (CH), 131.8 (C), 133.2 (CH), 133.9 (CH), 135.47 (CH), 135.45 (CH), 138.6 (CH), 139.0 (C), 144.9 (C), 145.3 (C), 150.8 (C), 161.7 (CH). MS HR-ESI [found 662.3379, $C_{40}H_{50}NO_4P$ $(M\text{-}Na)^+$ requires 662.3375].

3.2.5.5. General procedure for the preparation of the Pd(0)-olefin complexes for NMR studies.

A solution of ligand (0.015 mmol)**,** olefin (dimethyl fumarate or diethyl maleate) (0.015 mmol), and $[Pd_2(dba)_3{\cdot}CHCl_3]$ (0.0075 mmol) in CD_2Cl_2 (15 mM) was stirred for 30 min

when dimethyl fumarate was used, and for 16 h when diethyl maleate was used. After this time the mixture was transferred into a 5 mm NMR tube and the spectra were recorded. For NMR data, see Table 3.2.2 and Supporting Information.

3.2.5.6. Typical procedure for the allylic alkylation of linear (S1, S3–S8 and S11–S12) and cyclic (S2, S9 and S10) substrates.

A degassed solution of $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (1.8 mg, 0.005 mmol) and the desired phosphite-oxazoline ligand **L1** (0.011 mmol) in dichloromethane (0.5 mL) was stirred for 30 min. After this time, a solution of substrate (0.5 mmol) in dichloromethane (1.5 mL), nucleophile (1.5 mmol), *N,O*-bis(trimethylsilyl)-acetamide (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 $MgSO_4$. For compounds **10**[31b], **18**–**26**[48], **35**–**40**[50-51], **42**[52], **45**–**47**[22a,54], **49**–**52**[22a], **56**[22b], **59**[57], **61**[20] and **63**–**64**[31b], the solvent was removed, conversions were measured by ^{1}H NMR and enantiomeric excesses were determined by HPLC. For compounds **11**[31b], **41**[31b], **43**–**44**[22a,53], **53**–**55**[22a,22b] and **58**[22b], conversion and enantiomeric excesses were determined by GC. For compounds **48**[31b] and **57**[31b], conversion was measured by ^{1}H NMR and ees were determined by ^{1}H NMR using $[Eu(hfc)_3]$.

3.2.5.7. Typical procedure for the allylic etherification and silylation of substrate S1.

A degassed solution of $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (1.8 mg, 0.005 mmol) and the desired phosphite-oxazoline ligand **L1** (0.011 mmol) in dichloromethane (0.5 mL) was stirred for 30 min. Subsequently, a solution of **S1** (31.5 mg, 0.125 mmol) in dichloromethane (1.5 mL) was added. After 10 min, Cs_2CO_3 (122 mg, 0.375 mmol) and the corresponding alkyl alcohol or silanol (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 $MgSO_4$. Conversion was measured by ^{1}H NMR. HPLC was used to determine enantiomeric excesses of substrates **27**–**34**[27c,d].

3.2.6. References

1 *Catalytic Asymmetric Synthesis*; Ojima, J., Ed.; Wiley: Hoboken, New Jersey, 2010.

2 a) Yoon, T. P.; Jacobsen, E. N. *Science* **2003**, 299, 1691–1693. b) *Privileged Chiral Ligands and Catalysts*; Zhou, Q.-L., Ed.; Wiley-VCH, Weinheim, 2011.

[3] a) Mikami, K.; Korenaga, T.; Terada, M.; Ohkuma, T.; Pham, T.; Noyori, R.; *Angew. Chem., Int. Ed*. **1999**, 38, 495. b) Mikami, K.; Aikawa, K. Korenaga, T.; *Org. Lett*. **2001**, *3*, 243–245. c) Mikami, K.; Aikawa, K.; Yusa, Y.; Hatano, M. *Org. Lett*. **2002**, 4, 91. d) Aikawa, K.; Mikami, K. *Chem. Commun*. **2012**, 48, 11050.

[4] Mikami, K.; Aikawa, K.; Yusa, Y.; Jodry, J. J.; Yamanaka, M. *Synlett* **2002**, 1561.

[5] a) Buisman, G. J. H.; van der Veen, L. A.; Klootwijk, A.; de Lange, W. G. J.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Vogt, D. *Organometallics* **1997**, 16, 2929. b) Reetz, M. T.; Neugebauer, T. *Angew. Chem., Int. Ed.* **1999**, 38, 179. c) Alexakis, A.; Rosset, S.; Allamand, J.; March, S.; Guillen, F.; Benhaim, C. *Synlett* **2001**, 1375. d) Diéguez, M.; Ruiz, A.; Claver, C. *Tetrahedron: Asymmetry* **2001**, 12, 2895. e) Monti, C.; Gennari, C.; Piarulli, U.; de Vries, J. G.; de Vries, A. H. M.; Lefort, L. *Chem.–Eur. J*. **2005**, 11, 6701.

[6] a) Stranne, R.; Vasse, J.-L.; Moberg, C. *Org. Lett.,* **2001**, 3*,* 2525. b) Vasse, J.-L.; Stranne, R.; Zalubovskis, R.; Gayet C.; Moberg, C. *J. Org. Chem*. **2003**, 68, 3258.

[7] For reviews, see: a) *Palladium Reagents and Catalysts, Innovations in Organic Synthesis*; Tsuji, J., Ed.; Wiley: New York, 1996. b) Trost, B. M.; van Vranken, D. L. *Chem. Rev.* **1996**, 96, 395. c) Johannsen, M.; Jørgensen, K. A. *Chem. Rev.* **1998**, 98, 1689. d) Pfaltz, A.; Lautens, M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, 1999, Vol. 2; p 833. e) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, 103, 2921. f) Lu, Z.; Ma, S. *Angew. Chem., Int. Ed.* **2008**, 47, 258. g) Trost, B. M.; Zhang, T.; Sieber, J. D. *Chem. Sci.* **2010**, 1, 427. h) Trost, B. M. *Org. Process Res. Dev.* **2012**, 16, 185.

[8] Zalubovskis, R.; Bouet, A.; Fjellander, E.; Constant, S.; Linder, D.; Fischer, A.; Lacour, J.; Privalov, T. Moberg, C. *J. Am. Chem. Soc*. **2008**, 130, 1845.

[9] Fjellander, E.; Szabó, Z.; Moberg, C. *J. Org. Chem*. **2009**, 74, 9120.

[10] a) Pàmies, O.; Diéguez, M. *Acc. Chem. Res.* **2010**, 43, 212. b) van Leeuwen, P. W. N. M.; Kamer, P. C. J.; Claver, C.; Pàmies, O.; Diéguez, M. *Chem. Rev.* **2011**, 111, 2077.

[11] Pàmies, O.; Diéguez, M.; Claver, C. *J. Am. Chem. Soc.* **2005**, 127, 3646.

[12] Mazuela, J.; Pàmies, O.; Diéguez, M. *Chem. Eur. J.* **2010**, 16, 3434.

[13] Magre, M.; Biosca, M.; Pàmies, O.; Diéguez, M. *ChemCatChem* **2015**, 7, 114.

[14] Zalubovskis, R.; Fjellander, E.; Szabó, Z.; Moberg, C. *Eur. J. Org. Chem*. **2007**, 108.

[15] Korostylev, A.; Tararov, V. I.; Fischer, C.; Monsees, A.; Börner, A. *J. Org. Chem.* **2004**, *69*, 3220.

[16] Nishiyama, Y.; Kakushou, F.; Sonoda, N. *Bull. Chem. Soc. Jpn*, **2000**, 73, 2779.

[17] Gómez-Simón, M.; Jansat, S.; Muller, G.; Panyella, D.; Font-Bardía, M; Solans, X. *J. Chem. Soc., Dalton Trans.* **1997**, 3755.

[18] Brown, J. M.; Hulmes, D. I.; Guiry, P. J. *Tetrahedron* **1994**, 50, 4493.

[19] Constantine, R. N.; Kim, N.; Bunt, R. C. *Org. Lett.* **2003**, 5, 2279.

[20] a) Steinhagen, H.; Reggelin, M.; Helmchen, G. *Angew. Chem. Int., Ed. Engl*. **1997**, 36, 2108. b) Junker, J.; Reif, B.; Steinhagen, H.; Junker, B.; Felli, I. C.; Reggelin, M.; Griesinger, C. *Chem.–Eur. J.* **2000**, 6, 3281.

[21] a) Mazuela, J.; Pàmies, O.; Diéguez, M. *Chem.–Eur. J.* **2013**, 19, 2416. b) Coll, M.; Pàmies, O.; Diéguez, M. *Org. Lett.* **2014**, 16, 1892. c) Mazuela, J.; Pàmies, O.; Diéguez, M. *ChemCatChem* **2013**, 5, 1504.

[22] a) Smart, B. E. In *Organofluorine Chemistry: Principles and Commercial Applications*; Banks, R. E., Smart, B. E.; Tatlow, J. C. Eds.; Plenum, New York, 1994; p 57. b) Smart, B. E. *J. Fluorine Chem.* **2001**, 109, 3.

[23] Fukuzumi, T.; Shibata, N.; Sugiura, M.; Yasui, H.; Nakamura, S.; Toru, T. *Angew. Chem., Int. Ed.* **2006**, 45, 4973.

[24] a) *Dictionary of Natural Products*; Buckingham, J., Ed.; Cambridge University Press.: Cambridge, 1994. b) Lumbroso, A.; Cooke, M. L.; Breit, B. *Angew. Chem. Int., Ed.* **2013**, 52, 1890.

[25] For successful examples of Pd-catalysts, see: a) Trost, B. M.; Shen, H. C.; Dong, L.; Surivet, J.-P. *J. Am. Chem. Soc.* **2003**, 125, 9276. b) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1998**, 120, 815. c) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1999**, 121, 4545. d) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **2000**, 122, 11262. e) Uozumi, Y.; Kimura, M. *Tetrahedron: Asymmetry* **2006**, 17, 161. f) Tietze, L. F.; Lohmann, J. K.; Stadler, C. *Synlett* **2004**, 1113. For successful applications of Ir-catalysts with phenols, see: g) Shu, C.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2004**, 43, 4794. h) Fischer, C.; Defieber, C.; Suzuki, T.; Carreira, E. M. *J. Am. Chem. Soc.* **2004**, 126, 1628. i) López, F.; Ohmura, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, 125, 3426. j) Lyothier, I.; Defieber, C.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2006**, 45, 6204. k) Welter, C.; Dahnz, A.; Brunner, B.; Streiff, S.; Dübon, P.; Helmchen, G. *Org. Lett.* **2005**, 7, 1239. l) Kimura, M.; Uozumi, Y. *J. Org. Chem.* **2007**, 72, 707.

[26] a) Iourtchenko, A.; Sinou, D. *J. Mol. Catal. A* **1997**, 122, 91. b) Haight, A. R.; Stoner, E. J.; Peterson, M. J.; Grover, V. K. *J. Org. Chem.* **2003**, 68, 8092. c) Lam, F. L.; Au-Yeung, T. T.-L.; Kwong, F. Y.; Zhou, Z.; Wong, K. Y.; Chan, A. S. C. *Angew. Chem., Int. Ed.* **2008**, 47, 1280. d) Ye, F.; Zheng, Z.-J.; Li, L.; Yang, K.-F.; Xia, C.-G.; Xu, L.-W. *Chem.–Eur. J.* **2013**, 19, 15452. e) Caldentey, X.; Pericàs, M. A. *J. Org. Chem.* **2010**, 75, 2628. f) Liu, Z.; Du, H. *Org. Lett.* **2010**, 12, 3054. g) Kato, M.; Nakamura, T.; Ogata, K.; Fukuzawa, S.-i. *Eur. J. Org. Chem.* **2009**, 5232. h) Feng, B.; Cheng, H.-G.; Chen, J.-R.; Deng, Q.-H.; Lu, L.-Q.; Xiao, W.-J. *Chem. Commun.* **2014**, 50, 9550. For a report based on Ir-catalysts, see: i) Ueno, S.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2008**, 47, 1928.

[27] For successful applications of Pd-catalysts, see: a) Prétôt, R.; Pfaltz, A. *Angew. Chem., Int. Ed.* **1998**, 37, 323. b) You, S.-L.; Zhu, X.-Z.; Luo, Y.-M.; Hou, X.-L.; Dai, L.-X. *J. Am. Chem. Soc.* **2001**, 123, 7471. c) Hilgraf, R.; Pfaltz, A. *Synlett* **1999**, 1814. d) Hilgraf, R.; Pfaltz, A. *Adv. Synth. Catal*. **2005**, 347, 61. e) Diéguez, M.; Pàmies, O. *Chem. Eur. J.* **2008**, 14, 3653. f) Mata, Y.; Pàmies, O.; Diéguez, M. *Adv. Synth. Catal.* **2009**, 351, 3217.

[28] In contrast to the Pd-catalytic systems, Ir and Mo catalysts provide very high selectivity for the attack to the non-terminal carbon to give the chiral product. See, for instance: a) Bartels, B.; Helmchen, G. *Chem. Commun.* **1999**, 741. b) Trost, B. M.; Hildbrand, S.; Dogra, K. *J. Am. Chem. Soc.* **1999**, 121, 10416. c) Hartwig, J. F.; Pouy, M. J. in *Top. Organomet. Chem*. **2011**, 34, 169. d) Moberg, C. *Org. React* **2014**, 84, 1.

[29] See, for instance: a) Sudo, A.; Saigo, K. *J. Org. Chem.* **1997**, 62, 5508. b) Dawson, G. J.; Williams, J. M. J.; Coote, S. J. *Tetrahedron: Asymmetry* **1995**, 6, 2535. c) Martin, C. J.; Rawson, D. J.; Williams, J. M. J. *Tetrahedron: Asymmetry* **1998**, *9*, 3723.

[30] For successful applications, see also: a) Dawson, G. J.; Williams, J. M. J.; Coote, S. J. *Tetrahedron Lett.* **1995**, 36, 461. b) Evans, D. A.; Campos, K. R.; Tedrow, J. S.; Michael, F. E.; Gagné, M. R. *J. Am. Chem. Soc.* **2000**, 122, 7905. c) Popa, D.; Puigjaner, C.; Gómez, M.; Benet-Buchholz, J.; Vidal-Ferran, A.; Pericàs, M. A. *Adv. Synth. Catal.* **2007**, 349, 2265.

[31] a) Helmchen, G.; Kudis, S.; Sennhenn, P.; Steinhagen, H. *Pure Appl. Chem*. **1997**, 69, 513. b) Pfaltz, A. *Acta Chem. Scand. B* **1996**, 50, 189–194. c) Williams, J. M. J. *Synlett* **1996**, 705.

[32] Helmchen, G.; Pfaltz, A. *Acc. Chem. Res*. **2000**, 33, 336.

[33] a) Auburn, P. R.; Mackenzie, P. B.; Bosnich, B. *J. Am. Chem. Soc.* **1985**, 107, 2033. b) Jia, C.; Müller, P.; Mimoun, H. *J. Mol. Cat. A: Chem.* **1995**, 101, 127. c) Lehmann, J.; Lloyd-Jones, G. C. *Tetrahedron* **1995**, 51, 8863. d) Hayashi, T.; Yamamoto, A.; Ito, Y.; Nishioka, E.; Miura, H.; Yanagi, K. *J. Am. Chem. Soc.* **1989**, 111, 6301. e) Kinoshita, N.; Kawabata, T.; Tsubaki, K.; Bando, M.; Fuji, K. *Tetrahedron* **2006**, 62, 1756. f) Du, L.; Cao, P.; Liao, J. *Acta Chim. Sinica* **2013**, 71, 1239. g) Jayakumar, S.; Kumarswamyreddy, N.; Prakash, M.; Kesavan V. *Org. Lett.* **2015**, 17, 1066.

[34] Sautier, B.; Lyons, S. E.; Webb, M. R.; Procter, D. J. *Org. Lett*. **2012**, 14, 146.

[35] Kotha, S.; Shirbhate, M. E. *Synlett* **2012**, 23, 2183.

[36] Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A.; Peralta, J. E., Jr.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, O.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. Revision A.02 ed; Gaussian: Wallingford, CT, 2009.

[37] a) Lee, C.; Yang,W.; Parr, R. G. *Phys. Rev*. B **1988**, 37, 785. b) Becke, A. D. *J. Chem. Phys*. **1993**, 98, 5648.

[38] Hay, P. J.; Wadt, W. R. *J. Chem. Phys.* **1985**, 82, 299.

[39] a) Hehre, W. J.; Ditchfield, R.; Pople, J. A. *J. Chem. Phys.* **1972**, 56, 2257. b) Hariharan, P. C.; Pople, J. A. *Theor*. *Chim. Acta* **1973**, 28, 213. c) Francl, M. M.; Pietro,W. J.; Hehre,W. J.; Binkley, J. S.; Gordon, M. S.; Defrees, D. J.; Pople, J. A. *J. Chem. Phys*. **1982**, 77, 3654.

[40] a) Miertus, S.; Tomasi, *J. Chem. Phys.* **1982**, *65*, 239. b) Mennucci, B.; Tomasi, J. *J. Chem. Phys.* **1997**, 106, 5151. c) Cossi, M.; Barone, V.; Menucci, B.; Tomasi, J. *Chem. Phys. Lett*. **1998**, 286, 253.

[41] a) Krishnan, R.; Binkley, J. S.; Seeger, R.; Pople, J. A. *J. Chem. Phys.* **1980**, 72, 650. b) McLean, A. D.; Chandler, G. S. *J. Chem. Phys*. **1980**, 72, 5639.

[42] a) Grimme, S.; Antony, J.; Ehrlich, S.; Krieg, H. *J. Chem. Phys.* **2010**, 132, 15410. b) Grimme, S.; Ehrlich, S.; Goerigk, L. *J. Comput. Chem.* **2011**, 32, 1456.

[43] Arnold, L. A.; Imbos, R.; Mandoli, A; de Vries, A. H. M; Naasz, R; Feringa, B. L. *Tetrahedron* **2000**, 56, 2865.

[45] Ramillien, M.; Vanthuyne, N.; Jean, M.; Gherase, D.; Giorgi, M.; Naubron, J.V.; Piras, P.; Roussel, C. *J. Chromatogr. A* **2012**, *1269*, 82.

[46] Tanaka, Y.; Mino, T.; Akita, K.; Sakamoto, M.; Fujita, T. *J. Org. Chem.* **2004**, *69*, 6679.

[47] Dugal-Tessier, J.; Dake, G. R.; Gates, D. P. *Org. Lett.* **2010**, *12*, 4667.

[48] Frölander, A.; Lutsenko, S.; Privalov, T.; Moberg, C. *J. Org. Chem.* **2005**, *70*, 9882.

[49] Li, B.-S.; Yang, B.-M.; Wang, S.-H.; Zang, Y.-O.; Cao, X.-P.; Tu, Y.-O. *Chem. Sci.* **2012**, *3*, 1975.

[50] Mei, L.-Y.; Yuan, Z.-L.; Shi, M. *Organometallics* **2011**, *30*, 6466.

[51] Magre, M.; Biosca, M.; Norrby, P.-O.; Pàmies, O.; Diéguez, M. *ChemCatChem*, **2015**, *7*, 4091.

[52] Trost, B.; Radinov, R. *J. Am. Chem. Soc.* **1997**, *119*, 5962.

[53] Trost, B.; Breit, B.; Peukert, S.; Zambrano, J.; Ziller, J. W. *Angew. Chem. Int. Ed.* **1995**, *34*, 2386.

[54] Trost, B.; Lautens, M. *J. Am. Chem. Soc.* **1985**, *107*, 1781.

[55] Jin, L.; Nemoto, T.; Nakamura, H.; Hamada, Y. *Tetrahedron: Asymmetry* **2008**, *19*, 1106.

[56] Leitner, A.; Larsen, J.; Steffens, C.; Hartwig, J. F. *J. Org. Chem.* **2004**, *69*, 7552.

[57] Loyd-Jones, G. C.; Pfaltz, A. *Angew. Chem. Int. Ed.* **1995**,*34*, 462.

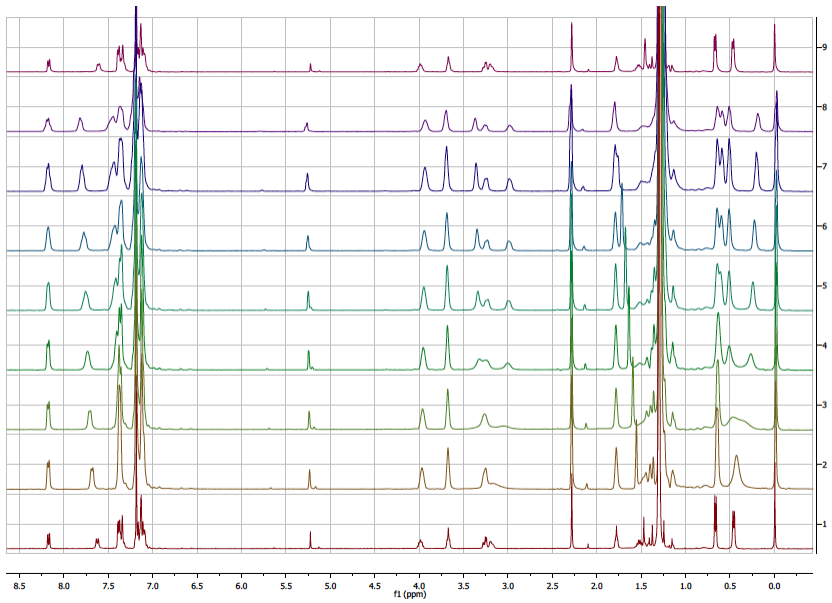
3.2.7. Supporting Information

3.2.7.1. Low temperature NMR spectra of ligands (*S*)-L1a

The low temperature NMR experiment was conducted varying the temperature from 25 °C to -70 °C and then back to 25 °C.

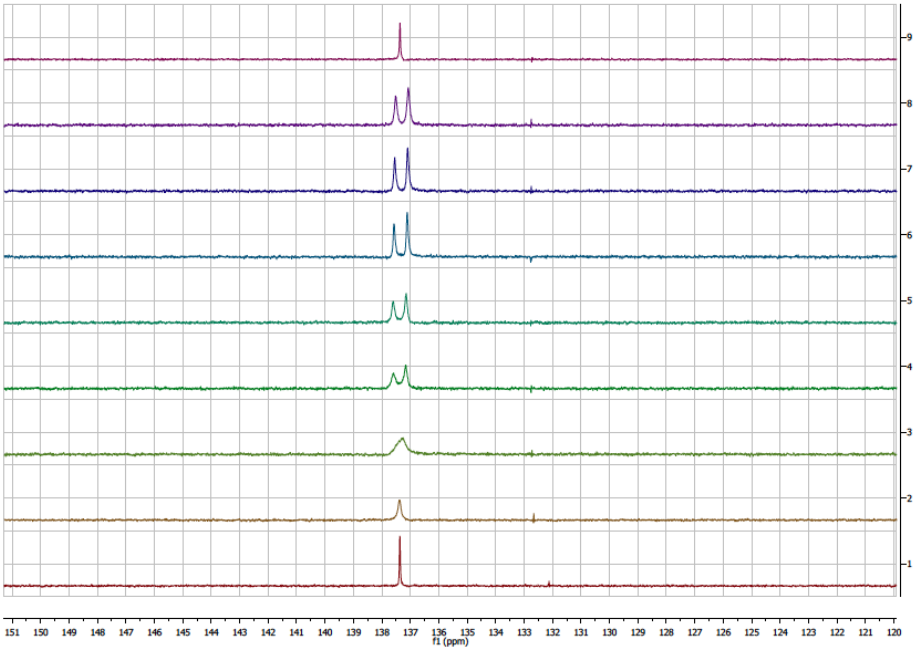
^{1}H NMR of ligand (*S*)-L1a:

Spectra: 1 = 25 °C, 2 = 0 °C, 3 = - 10 °C, 4 = - 20 °C, 5 = - 30 °C, 6 = - 40 °C, 7 = - 50 °C, 8 = - 70 °C, 9 = 25 °C.



$^{31}P\{^{1}H\}$ NMR of ligand (*S*)-L1a:

Spectra: 1 = 25 °C, 2 = 0 °C, 3 = - 10 °C, 4 = - 20 °C, 5 = - 30 °C, 6 = - 40 °C, 7 = - 50 °C, 8 = - 70 °C, 9 = 25 °C.

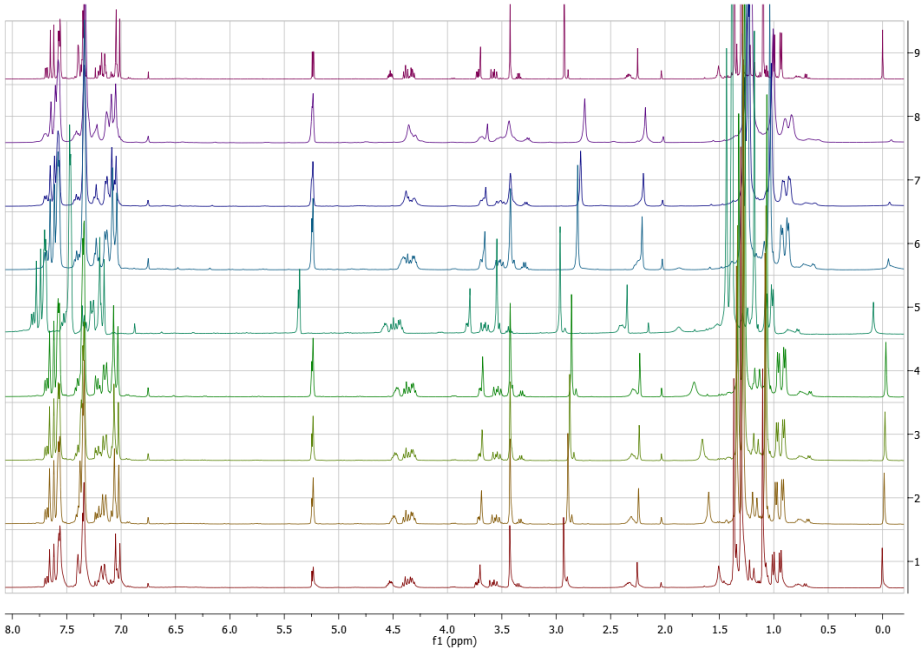


3.2.7.2. Low temperature NMR spectra of [Pd((*S*)-L1a)($C_6H_8O_4$)] complex (12)

Low temperature NMR of [Pd((*S*)-**L1a**)($C_6H_8O_4$)] complex **12**. The low temperature NMR experiment was conducted varying the temperature from 25 °C to -70 °C and then back to 25 °C.

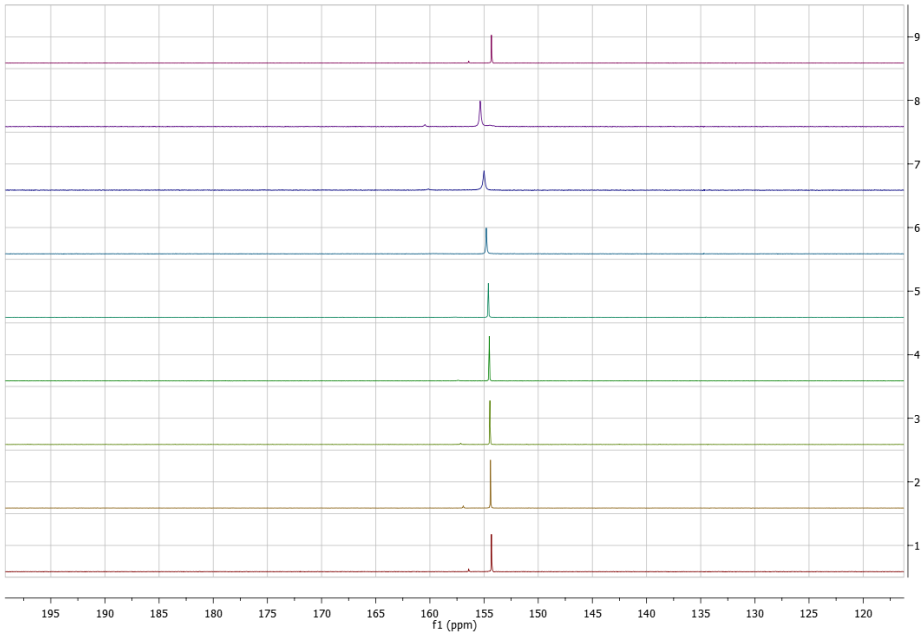
^{1}H NMR spectra of [Pd((*S*)-L1a)($C_6H_8O_4$)] complex (12):

Spectra: 1 = 25 °C, 2 = 0 °C, 3 = - 10 °C, 4 = - 20 °C, 5 = - 30 °C, 6 = - 40 °C, 7 = - 50 °C, 8 = - 70 °C, 9 = 25 °C.



^{31}P{^{1}H} NMR spectra of [Pd((*S*)-L1a)($C_6H_8O_4$)] complex (12):

Spectra: 1 = 25 °C, 2 = 0 °C, 3 = - 10 °C, 4 = - 20 °C, 5 = - 30 °C, 6 = - 40 °C, 7 = - 50 °C, 8 = - 70 °C, 9 = 25 °C.

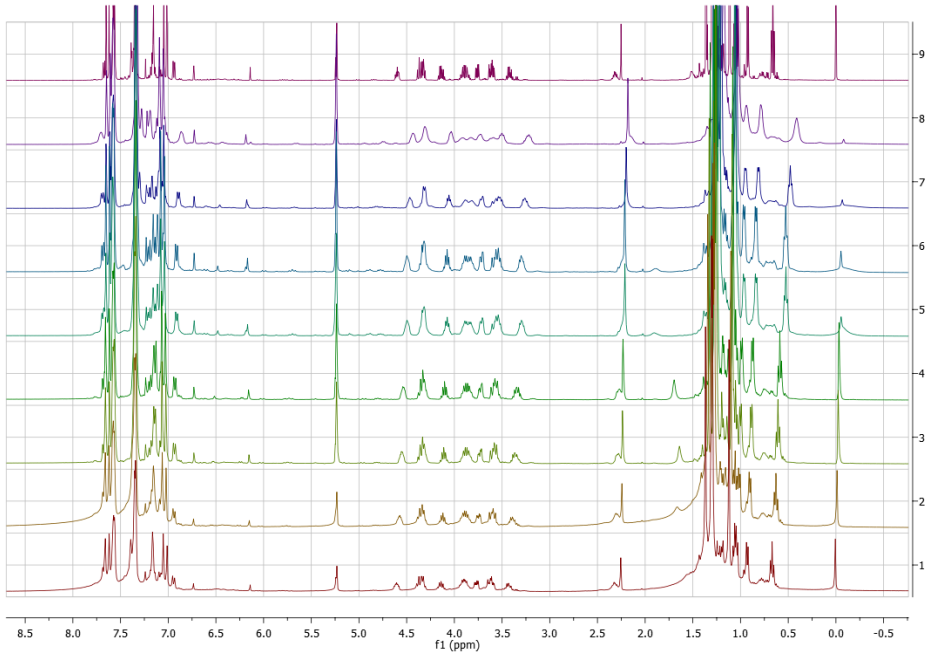


3.2.7.3. Low temperature NMR spectra of [Pd((*S*)-L1a)($C_8H_{12}O_4$)] complex (15)

Low temperature NMR of [Pd(*S*)-(**L1a**)($C_8H_{14}O_4$)] complex **15**. The low temperature NMR experiment was conducted varying the temperature from 25 °C to -70 °C and then back to 25 °C.

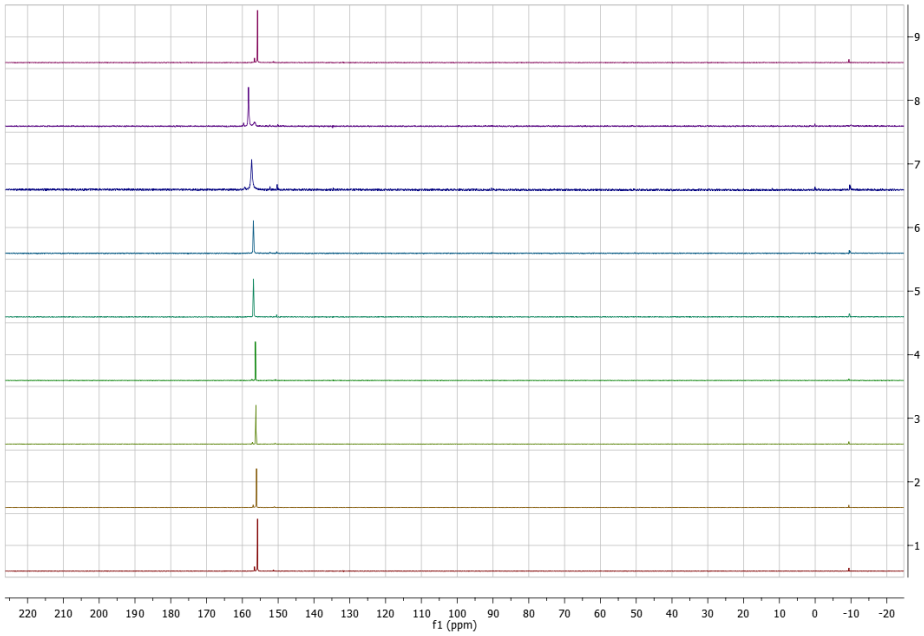
^{1}H NMR spectra of [Pd((*S*)-L1a)($C_8H_{12}O_4$)] complex (15):

Spectra: 1 = 25 °C, 2 = 0 °C, 3 = - 10 °C, 4 = - 20 °C, 5 = - 30 °C, 6 = - 40 °C, 7 = - 50 °C, 8 = - 70 °C, 9 = 25 °C.



^{31}P-{^{1}H} NMR spectra of [Pd((*S*)-L1a)($C_8H_{12}O_4$)] complex (15):

Spectra: 1 = 25 °C, 2 = 0 °C, 3 = - 10 °C, 4 = - 20 °C, 5 = - 30 °C, 6 = - 40 °C, 7 = - 50 °C, 8 = - 70 °C, 9 = 25 °C.



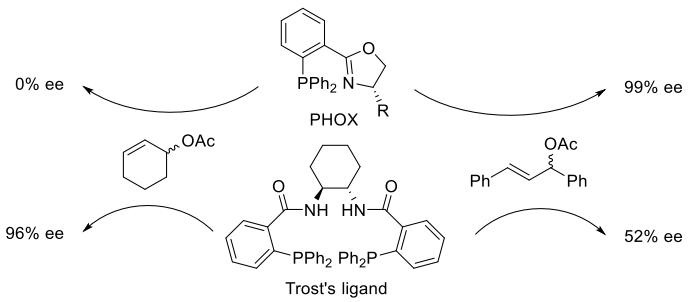
3.3. Asymmetric Pd-catalyzed allylic substitution using phosphite-oxazoline PHOX-based ligands containing a methylene linker.

Magre, M.; Biosca, M.; Coll, M.; Pàmies, O.; Diéguez, M. *Manuscript in preparation.*

Abstract: *We report a reduced but structurally valuable phosphite-oxazoline ligand library* ***L5***-***L7a***-***c*** *for the Pd-catalyzed allylic substitution of several substrate types. These ligands not only allow to study the effect on catalytic performance of introducing a methylene spacer between the oxazoline group in previous phosphite-based PHOX ligands* ***L1***-***L4****, but also the effect of varying the oxazoline substituent and the biaryl phosphite group. By suitable tuning the ligand parameters we have been able to achieve high activities (TOF > 4000 mol substrate×(mol Pd×h)$^{-1}$) and good-to-excellent enantioselectivities for a range of hindered and unhindered substrates. DFT calculations agree with an early transition state (TS)*.

3.3.1. Introduction

The palladium-mediated allylic substitution reaction has become an efficient synthetic tool for the formation of carbon-carbon and carbon-heteroatom bonds.[1] Over the last decades a great number of ligands have been successfully applied for this transformation. Most of the ligands 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[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.



Scheme 3.3.1. Typical enantioselectivities achieved using phosphine-oxazoline PHOX and diphosphine Trost ligand.

Thus, most of the best catalytic systems only afford high enantioselectivities for either hindered (*i.e.* phosphine-oxazoline PHOX ligand) or unhindered (*i.e.* diphosphine Trost ligand) substrates (Scheme 3.3.1).

In this context our group has recently shown that the introduction of biaryl-phosphite moieties into the ligand design is highly advantageous.[5] As already mentioned in Section 3.2, the benefits have been attributed, on the one hand, to the larger π-acceptor ability of the phosphite groups, which increases reaction rates and, on the other hand, to the flexibility of the phosphite moieties, which allows the catalyst chiral pocket to adapt to both hindered and unhindered substrates. Thus, we have shown that the common substrate limitation of the phosphine-oxazoline PHOX-ligands could be overcome by replacing the phosphine moiety by a biaryl phosphite group.[5b,g] In particular, the excellent enantioselectivities achieved for both hindered and unhindered substrates justify the inclusion of the phosphite-based PHOX ligands to the small list of privileged ligands,[6] able to tolerate a broad range of substrates and nucleophiles. However, there are important nucleophiles that still don't provide excellent levels of enantioselectivity (*i.e.* aliphatic alcohols).[5g] The search for more efficient catalytic systems constitutes therefore a key issue for the production of all sorts of enantiopure carbon-carbon and carbon-heteroatom bonds.

To further investigate the possibilities of phosphite-based PHOX-based ligands, in this chapter we decided to study the effect of introducing a methylene linker in our previous phosphite-based PHOX-based ligands **L1**-**L4** (Section 3.2). For this purpose, we report a reduced but structurally valuable ligand library for the Pd-catalyzed allylic substitution reactions (**L5**-**L7a**-**c**; Figure 3.3.1). With these ligands we also studied the effect on catalytic performance of systematically varying the oxazoline substituent (**L5**-**L7**) and the biaryl phosphite group (**a**-**c**). By suitable tuning the ligand parameters we have been able to achieve high enantioselectivities for a range of substrates and nucleophiles. We have also performed a DFT study to gain further insight into the selectivity-determining step.

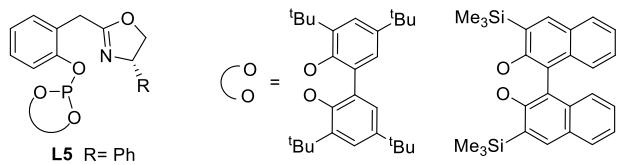
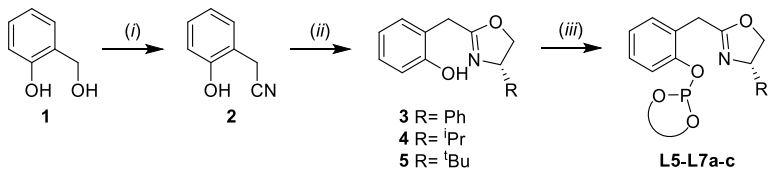


Figure 3.3.1. PHOX-based phosphite-oxazoline ligands **L5**-**L7a**-**c**.

3.3.2. Results

3.3.2.1. Preparation of Ligands

The synthesis of new phosphite-oxazoline **L5**-**L7a**-**c** is straightforward in only three steps from readily available 2-hydroxybenzyl alcohol **1** (Scheme 3.3.2). The first step of the synthesis is the formation of the corresponding hydroxyl-cyanide **2** by treatment with sodium cyanide (step *i*).[7] The coupling of hydroxyl-cyanide **2** with the corresponding amino alcohol afforded the hydroxyl-oxazolines **3**-**5** (step *ii*).[8] The desired diversity in the oxazoline substituent was achieved in this step. Then, condensation of the desired *insitu* formed phosphorochloridites ($ClP(OR)_2$ $(OR)_2$= **a**-**c**) with the corresponding hydroxyl-oxazoline yielded phosphite-oxazoline ligands **L5**-**L7a**-**c**, with different biaryl phosphite groups (step *iii*). All ligands were isolated in high yields as white solids. They were stable in air and very stable to hydrolysis, so further manipulation and storage was performed in air. HRMS-ESI spectra were in agreement with the assigned structures. The ^1H, ^{31}P and ^{13}C NMR spectra were as expected for these C_1 ligands (see Section 3.3.5).



Scheme 3.3.2. Synthetic route for the synthesis of phosphite-oxazoline ligands **L5**-**L7a**-**c**. (*i*) NaCN, DMF, 130 ºC, 16 h (48% yield);[7] (*ii*) amino alcohol, $ZnCl_2$, C_6H_5Cl, reflux, 16 h (yields 68-78%);[8] (*iii*) $ClP(OR)_2$ ($(OR)_2$= **a**-**c**), Py, toluene at rt for 18 h (yields 60-78%).

3.3.2.2. Allylic substitution of disubstituted substrates S1-S2 using dimethyl malonate as nucleophile

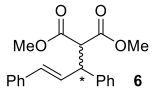
Bearing in mind that the stereochemical outcome of this reaction is highly dependent on the steric demands of the substrate, in this section, the Pd-catalyzed allylic substitution of *rac*-(*E*)-1,3-diphenyl-3-acetoxyprop-1-ene **S1** and *rac*-3-acetoxycyclohexene **S2**, with different steric properties, with dimethyl malonate as nucleophile were studied employing ligands **L5**-**L7a**-**c**. The catalysts were generated in situ from π-allyl-palladium chloride dimer $[PdCl(\eta^3\text{-}C_3H_5)]_2$, the corresponding ligand and nucleophile. The results, which are shown in Table 3.3.1, indicate that enantioselectivities are affected by the biaryl phosphite group and the steric properties of the oxazoline substituent.

For both substrates, the results using ligands **L5a**-**c** indicated that the ligand backbone is not able to fully control the tropoisomerization of the biphenyl phosphite moiety. This contrast with the almost perfect tropoisomerization control exerted by the ligand backbone in phosphite-based PHOX-ligands **L1**-**L4** presented in Section 3.2.[5g] Thus, the presence of an enantiopure (*S*)^{ax}-biaryl phosphite group (**c**) is necessary to maximize enantioselectivities (entry 3 vs 1 and 2).

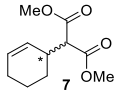
The effect of the oxazoline substituent on enantioselectivities depends on the substrate type. Thus, for instance, while for substrate **S1** the use of ligands **L7**, containing a bulky *tert*-butyl oxazoline substituent, has a negative effect on enantioselectivity (entry 9 vs 3 and 6), the use of ligands **L7** afforded the highest ee's for substrate **S2** (entry 9 vs 3 and 6).

In summary, by carefully selecting the ligand components we have been able to achieve high activities (TOF's up to >4000 mol substrate×(mol Pd×h)$^{-1}$) and enantioselectivities in the Pd-catalyzed allylic substitution of both substrates types. Thus, the use of Pd-**L6c** and Pd-**L7c** catalytic systems provided the highest enantioselectivities for linear substrate **S1** (ee's up to 96%; entry 6) and for cyclic substrate **S2** (ee's up to 87%; entry 9), respectively.

Table 3.3.1. Asymmetric Pd-catalyzed allylic alkylation of substrates **S1** and **S2** using phosphite-oxazoline ligands **L5**-**L6a**-**c**[a]



6



7

Entry	Ligand	% Conv[b]	% ee[c]	% Conv[d]	% ee[e]
1	**L5a**	100	92 (*S*)	100	60 (*R*)
2	**L5b**	100	86 (*S*)	100	51 (*R*)
3	**L5c**	100	95 (*S*)	100	66 (*S*)
4	**L6a**	100	89 (*S*)	100	50 (*R*)
5	**L6b**	100	82 (*S*)	100	30 (*R*)
6	**L6c**	100[f]	96 (*S*)[f]	100	48 (*S*)
7	**L7a**	100	73 (*S*)	100	30 (*R*)
8	**L7b**	100	72 (*S*)	100	80 (*R*)
9	**L7c**	100	92 (*S*)	100	86 (*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 (cat). [b] Conversion percentage determined by ^{1}H-NMR after 30 min. [c] Enantiomeric excesses determined by HPLC. Absolute configuration drawn in parentheses. [d] Conversion percentage determined by GC after 2 h. [e] Enantiomeric excesses determined by GC. Absolute configuration drawn in parentheses. [f] Reactions carried for 10 min using 0.1 mol% of catalyst precursor. TOF= 4048 mol **S1**×(mol Pd×h)$^{-1}$ measured after 5 min (68% conversion).

3.3.2.3. Allylic substitution of disubstituted substrates using several nucleophiles. Scope and limitations

We next considered studying the scope of Pd-**L6c** and Pd-**L7c** catalytic systems by using a range of C, N and O-nucleophiles with several linear and cyclic substrates, with different steric and electronic requirements (Figure 3.3.2).

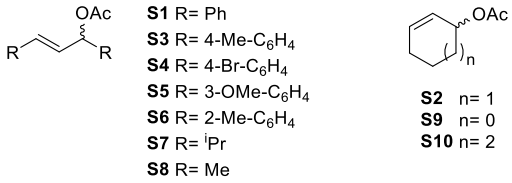


Figure 3.3.2. Substrates **S1**-**S10** used in this study

We initially considered the allylic substitution of **S1** with Pd-**L6c** catalyst using a range C-, N- and O-nucleophiles, among which are the more challenging functionalized malonates, β-diketones and alkyl alcohols (Figure 3.3.3). Several malonates, including those substituted with allyl-, butenyl, pentenyl- and propargyl-groups; reacted cleanly to **S1** to afford products **8**-**14** in high yields and enantioselectivities (ee's ranging from 96% to 99%). The reaction also worked well when malononitrile (compound **15**) and acetylacetone (compound **16**) were used as nucleophiles (ee's up to 96%). Similarly to previous reports, the use of isopropyl cyanoacetate (compound **17**) as nucleophile resulted in the formation of two diastereoisomers with low diastereoselectivity,[9] albeit both diastereoisomers were obtained in almost enantiopure form (ee's up to 99%). The use of benzylamine as model N-nucleophile also provided the substitution product **18** in high enantioselectivity (97% ee). Interestingly, the excellent enantiocontrol also extends to the use of several aliphatic alcohols and silanols (compounds **19**-**22**, ee's up to 97%). As already mentioned in Section 3.2, although the Pd-allylic etherification is currently studied by relevant research groups, few successful examples have been reported and most of them are phenols,[10] while aliphatic alcohols and silanols have been less studied.[11] The results, which are among the best that have been reported, showed that enantioselectivities are relatively insensitive to the electronic properties of the nucleophile. This represents an improvement regarding to the previously reported phosphite-based PHOX-ligands **L1**-**L4** in Chapter Section 3.2.

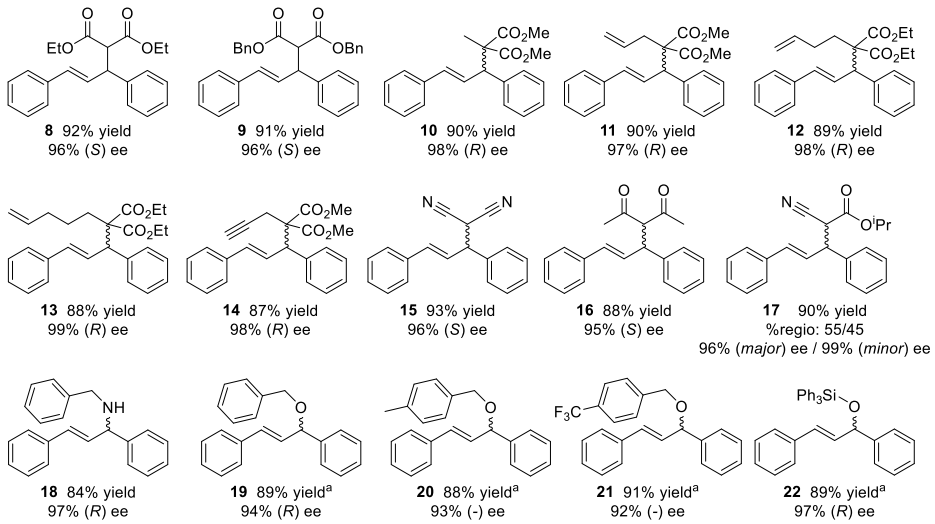


Figure 3.3.3. Allylic substitution of **S1** with C-, N- and O-nucleophiles using Pd-**L6c** catalytic system. Reactions were run at 23 °C with $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (0.5 mol %), CH_2Cl_2 as solvent, ligand (1.1 mol %), BSA (3 equiv), and KOAc. Full conversions were achieved after 2 h. [a] Reactions carried out using 2 mol % $[PdCl(\eta^3\text{-}C_3H_5)]_2$, 4 mol % ligand, and Cs_2CO_3 (3 equiv). Full conversions were achieved after 18 h.

The scope of Pd-**L6c** catalytic system was further investigated by using other symmetrical linear substrates **S3**-**S8** with steric and electronic requirements different from those of **S1**. The results, which are collected in Figure 3.3.4, indicated that Pd-**L6c** can also be used for the alkylation of substrates **S3**–**S6**, with different substituents in the aryl groups, with various carbon nucleophiles with high yields and enantioselectivities, comparable to those of **S1** (compounds **23**-**29**, ee's from 96% to 99%). Interestingly, Pd-**L6c** can also successfully be used for the alkylation of **S7** (compound **30**, >95% ee). This substrate is more sterically demanding than **S1** and it usually reacts with inferior catalytic performance.

We also found that Pd-**L6c** is able to alkylate **S8** with good enantiocontrol (compounds **31**-**32**, ee's up to 71%). This substrate is less sterically demanding and therefore enantioselectivities tend to be much lower than with model substrate **S1**. The present results are very appealing for this elusive unhindered substrate.

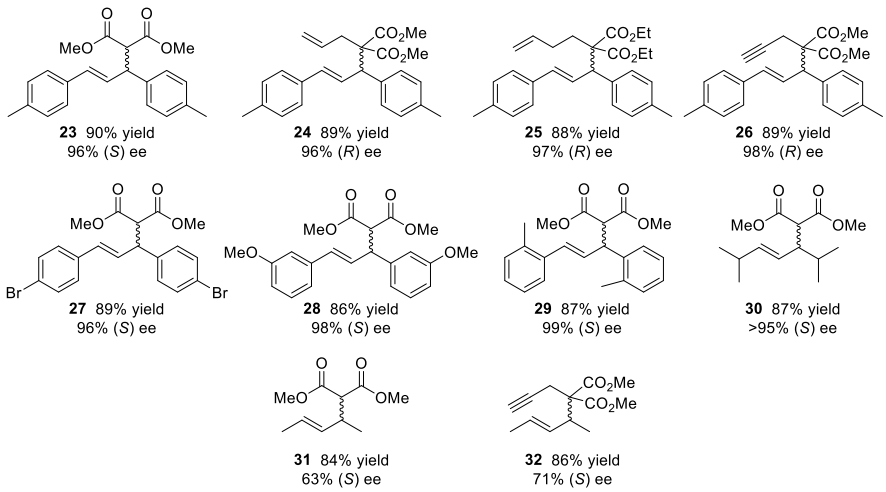


Figure 3.3.4. Allylic substitution of **S3-S8** with C-nucleophiles using Pd-**L6c** catalytic system. Reactions were run at 23 °C with $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (0.5 mol %), CH_2Cl_2 as solvent, ligand (1.1 mol %), BSA (3 equiv), and KOAc. Full conversions were achieved after 4 h.

We then studied the allylic substitution of cyclic substrate **S2** with more challenging nucleophiles than dimethyl malonate and on the alkylation of other cyclic substrates with different ring sizes (**S9** and **S10**) using Pd-**L7c** catalytic system. The results, which are summarized in Figure 3.3.5, indicated that a wide range of C-nucleophiles, including the less studied α-substituted malonates and acetylacetone, can efficiently react with **S2** to provide the corresponding compounds (**33**-**38**) with high yields and enantioselectivities (ee's up to 92%), comparable to those obtained with alkylated product **7** with dimethyl malonate.

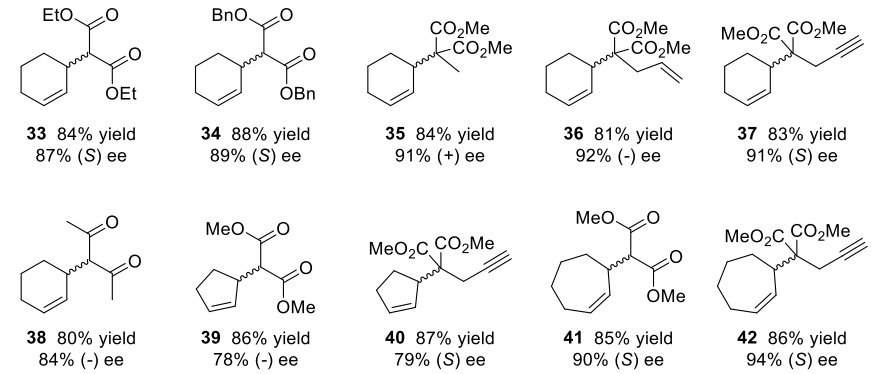


Figure 3.3.5. Allylic substitution of **S2**, **S9**-**S10** with C-nucleophiles using Pd-**L7c** catalytic system. Reactions were run at 23 °C with $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (0.5 mol %), CH_2Cl_2 as solvent, ligand (1.1 mol %), BSA (3 equiv), and KOAc. Full conversions were achieved after 2 h.

Pd-**L7c** also efficiently catalyzed the alkylation of cyclic substrates **S9** and **S10** (compounds **39**-**42**). High enantioselectivities (ee's up to 94%) were obtained in both cases, even with **S9**, which usually provides products with much lower enantioselectivities than cyclic **S2**.[1]

3.3.2.4. Theoretical studies. Origin of enantioselectivity

Mechanistic studies have shown that the irreversible nucleophilic attack on the allyl group in palladium-catalyzed allylic substitutions controls enantioselectivity. Nevertheless, transition state (TS) for this step can be either early or late depending on the nature of the nucleophile, ligands, and reaction conditions. In an early transition state, the interactions leading to stereochemical differentiation are governed by both the population of the Pd-η^3-allyl intermediates and the relative electrophilicity of the allylic carbon atoms, with an allyl terminus *trans* to a phosphorus atom generally being more reactive than one *trans* to a nitrogen.[12] On the other hand, a late transition state is more reminiscent of the Pd-alkene product complex, and therefore the formation of the most stable Pd-olefin complex controls enantioselectivity.[13]

In order to have further insight into the nature of the transition state and therefore gain further information into the selectivity-determining step, we performed a DFT study of the transition states and key reaction intermediates for the Pd-catalyzed allylic substitution of **S1** using ligands **L6b** and **L6c**. Calculation were carried out using the B3LYP-D3 functional, the 6-31G*/LANL2DZ basis set, and the PCM solvent model with parameters for CH_2Cl_2, as implemented in Gaussian 09. The energies were further refined by performing single-point calculations at the 6-311+G**/SDD level. Previous experience has shown that ammonia can be used as a good model nucleophile, avoiding the problems related to charge separation in conjunction with a continuum solvent model.[14] Note that the use of ammonia as nucleophile instead of dimethyl malonate results in the inversion of the CIP descriptor for **S1**, due to the change in priority of the groups, although the sense of stereoselectivity is maintained.

We initially calculated the relative stabilities of the product olefin complexes, using the olefin complexes obtained from nucleophilic addition of ammonia to allyl complexes derived from substrate **S1** (Figure 3.3.6). The DFT calculations predict the formation of the correct enantiomer of the substituted products for both ligands. However, larger energy differences were found for the two complexes containing **L6b** ligand (ΔG= 19.3 kJ/mol) than for the two olefin complexes containing **L6c** (ΔG= 3 kJ/mol). These results do not agree with the enantioselectivities achieved experimentally (82% for **L6b** and 96% for **L6c**; Table 3.3.1). Thus, they erroneously indicate that ligand **L6b** must provide higher enantioselectivity than ligand **L6c** if the reaction proceeds via a late transition state.

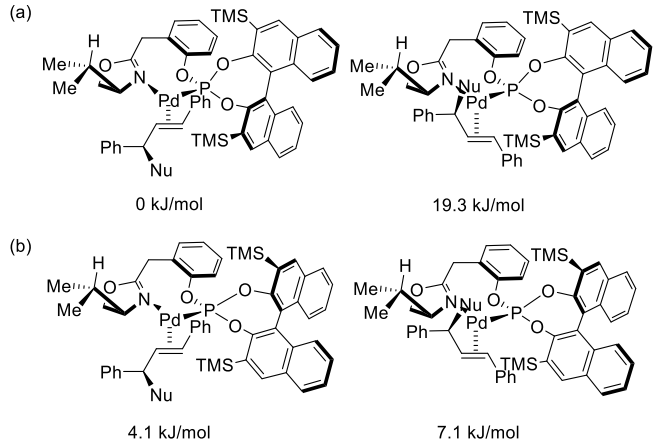


Figure 3.3.6. Calculated relative energies for Pd-olefin complexes using ligands (a) **L6b** and (b) **L6c**.

Then, we calculated energy for the transition states using ligands **L6b** and **L6c** which are shown in Figure 3.3.7. In agreement with the experimental results, larger energy differences were found for the two TSs containing **L6c** ligand (ΔG= 6 kJ/mol) than for the two TSs containing **L6b** (ΔG= 4.2 kJ/mol). These results therefore indicated that the Pd-allylic substitution using ligands **L5**-**L7a**-**c** proceeds via an early transition state. So further studies of the reactivity of the corresponding Pd-allyl intermediates will be crucial to determine the origin of the enantioselectivities. These studies are underway.

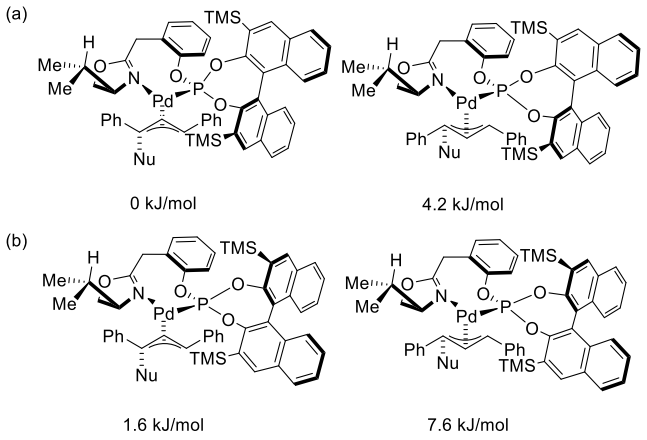


Figure 3.3.7. Calculated relative energies of transition states using ligands (a) **L6b** and (b) **L6c**.

3.3.4. Conclusions

We report a reduced but structurally valuable phosphite-oxazoline ligand library **L5**-**L7a**-**c** for the Pd-catalyzed allylic substitution of several substrate types. These ligands, which are easily accessible in three steps, differ from previous phosphite-based PHOX ligands **L1**-**L4** in the presence of a methylene spacer between the oxazoline group and the phenyl ring. With these ligands we also studied the effect of varying the oxazoline substituent and the biaryl phosphite group. By suitable tuning the ligand parameters we have been able to achieve high activities (TOF > 4000 mol substrate×(mol Pd×h)$^{-1}$) and excellent enantioselectivities for a range of hindered substrates using a wide range of nucleophiles. We have found that he introduction of a methylene spacer has been positive in terms of nucleophile scope. Thus, in contrast to the phosphite-based PHOX ligands **L1**-**L4**, a range of aliphatic alcohols with different electronic properties could be successfully used as nucleophiles. Nevertheless, although good enantioselectivities were also achieved when using unhindered substrates (such as **S2** and **S8**-**S10**), ee's were lower than with previous PHOX-based ligands **L1**-**L4**. As for ligands **L1**-**L4** the DFT calculations agree with an early TS and the enantioselectivities can be therefore explained by both the population of the Pd-η^3-allyl intermediates and the relative electrophilicity of the allylic carbon atoms.

3.3.5. Experimental Part

3.3.5.1. General Procedures.

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}) or H_3PO_4 (^{31}P{^{1}H}) as internal standard. Racemic substrates **S1**-**S10**[15] and compound **2**[7] were prepared as previously reported.

3.3.5.2. Computational details.

The geometries of all intermediates were optimized using the Gaussian 09 program,[16] employing the B3LYP[17] density functional and the LANL2DZ[18] basis set for palladium and the 6-31G* basis set for all other elements.[19] Solvation correction was applied in the course of the optimizations using the PCM model with the default parameters for dichloromethane.[20] 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**[21] basis set was used for all elements except iridium, and

by applying dispersion correction using DFT-D3[22] model. All energies reported are Gibbs free energies at 298.15 K and calculated as $G_{reported} = G_{6\text{-}31G^*} + (E_{6\text{-}311+G^{**}} - E_{6\text{-}31G^*}) + EDFT\text{-}D3$.

3.3.5.3. Typical procedure for the preparation of hydroxyl-oxazolines 3-5.

To a solution of $ZnCl_2$ (27.3 mg, 0.2 mmol) in dry chlorobenzene (1 mL), a solution of **2** (532.6 mg, 4 mmol) in dry chlorobenzene (7 mL) was added. Subsequently, the corresponding amino alcohol (4 mmol) was added to the reaction mixture and it was left stirring at 90 ºC for 16 h. After that time, the solvent was evaporated and the crude was dissolved in the minimum amount of CH_2Cl_2 (2 mL). Then, Et_2O was slowly added and a white solid precipitates. The precipitate solution is left at -18 ºC for 5 h and the corresponding pure hydroxyl-oxazoline was obtained.

(*S*)-2-((4-phenyl-4,5-dihydrooxazol-2-yl)methyl)phenol 3. As a white solid (709 mg, 70% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 3.69 (d, 1H, CH_2, $^2J_{H\text{-}H}$= 16 Hz), 3.81 (d, 1H, CH_2, $^2J_{H\text{-}H}$= 16 Hz), 4.17 (pt, 1H, CH-O, $J_{H\text{-}H}$= 8 Hz), 4.70 (dd, 1H, CH-O, $^2J_{H\text{-}H}$= 12 Hz, $^3J_{H\text{-}H}$= 8 Hz), 5.24 (t, 1H, CH-N, $^3J_{H\text{-}H}$= 8 Hz), 6.87 (m, 1H, CH=), 6.97 (d, 1H, CH=, $^3J_{H\text{-}H}$= 8 Hz), 7.19 (d, 1H, CH=, $^3J_{H\text{-}H}$= 8 Hz), 7.26-7.34 (m, 6H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 31.7 (CH_2), 68.9 (CH-N), 75.7 (CH_2-O), 119.1 (C), 120.6 (CH=), 122.0 (CH=), 126.5 (CH=), 127.9 (CH=), 129.0 (CH=), 129.3 (CH=), 130.8 (CH=), 141.4 (C), 156.4 (CH=), 170.1 (C=N).

(*S*)-2-((4-isopropyl-4,5-dihydrooxazol-2-yl)methyl)phenol 4. As a yellowish solid (596.4 mg, 68% yield). Spectroscopic data are in agreement with the reported values.[8] ^{1}H NMR (400 MHz, $CDCl_3$): δ= 0.86 (d, 3H, CH_3, ^{i}Pr, $^3J_{H\text{-}H}$= 6.8 Hz), 0.94 (d, 3H, CH_3, ^{i}Pr, $^3J_{H\text{-}H}$ = 6.8 Hz), 1.70 (m, 1H, CH, ^{i}Pr), 3.57 (d, 1H, CH_2, $^3J_{H\text{-}H}$ = 16.0 Hz), 3.65 (d, 1H, CH_2, $^2J_{H\text{-}H}$= 16.0 Hz), 3.91 (m, 1H, CH-N), 4.02 (pt, 1H, CH-O, $J_{H\text{-}H}$ = 8.0 Hz), 4.32 (dd, 1H, CH-O, $^2J_{H\text{-}H}$ = 9.6 Hz, $^3J_{H\text{-}H}$ = 8.4 Hz), 6.83 (dt, 1H, CH=, $^3J_{H\text{-}H}$ = 7.2 Hz, $^4J_{H\text{-}H}$ = 1.2 Hz), 6.98 (dd, 1H, CH=, $^3J_{H\text{-}H}$ = 7.2 Hz, $^4J_{H\text{-}H}$ = 1.2 Hz), 7.05 (dd, 1H, CH=, $^3J_{H\text{-}H}$ = 7.2 Hz, $^4J_{H\text{-}H}$ = 1.2 Hz), 7.19 (dt, 1H, CH=, $^3J_{H\text{-}H}$ = 7.2 Hz, $^4J_{H\text{-}H}$ = 1.2 Hz).

(S)-2-((4-(*tert*-butyl)-4,5-dihydrooxazol-2-yl)methyl)phenol 5. As a green solid (727.9 mg, 78% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 0.86 (s, 9H, CH_3, ^{t}Bu), 3.59 (d, 1H, CH_2, $^2J_{H\text{-}H}$= 16 Hz), 3.65 (d, 1H, CH_2, $^2J_{H\text{-}H}$= 16 Hz), 3.88 (m, 1H, CH-N), 4.17 (m, 1H, CH-O), 4.70 (m, 1H, CH-O), 6.83 (t, 1H, CH=, $^3J_{H\text{-}H}$= 8 Hz), 6.98 (dd, 1H, CH=, $^3J_{H\text{-}H}$= 8 Hz, $^4J_{H\text{-}H}$= 4 Hz), 7.05 (dd, 1H, CH=, $^3J_{H\text{-}H}$= 8 Hz, $^4J_{H\text{-}H}$= 4 Hz), 7.19 (t, 1H, CH=, $^3J_{H\text{-}H}$= 8 Hz). ^{13}C NMR (100.6 MH, $CDCl_3$): δ= 25.8 (CH_3, ^{t}Bu), 31.8 (CH_2), 33.7 (C, ^{t}Bu), 68.9 (CH_2-O), 74.9 (CH-N), 119.2 (CH=), 120.3 (CH=), 122.1 (C), 129.2 (CH=), 130.7 (CH=), 156.6 (C), 169.0 (C=N).

3.3.5.4. Typical procedure for the preparation of phosphite-oxazoline ligands L5-L7a-c.

To a solution of *in situ* generated phosphochloridite (1.1 mmol) in dry toluene (6 mL), pyridine (0.16 mL, 2.0 mmol) was added. Then, this solution was placed in a -78 ºC bath. After 2 min at that temperature, a solution of the corresponding alcohol-oxazoline (1.0 mmol) and pyridine (0.16 mL, 2.0 mmol) in toluene (6 mL) was added dropwise at -78 °C. The mixture was left to warm to room temperature and stirred overnight at this temperature. The precipitate formed was filtered under argon and the solvent was evaporated under vacuum. The residue was purified by flash chromatography (under argon, using neutral alumina and dry toluene as eluent system) to afford the corresponding phosphite-oxazoline **L5**-**L7a**-**c** as white solids.

L5a: Yield: 449.7 mg (65%); ^{31}P NMR (161.9 MHz, C_6D_6): $\delta = 139.1$ ppm (s); ^{1}H NMR (400 MHz, C_6D_6): δ = 1.27 (s, 9H, CH_3, ^{t}Bu), 1.28 (s, 9H, CH_3, ^{t}Bu), 1.51 (s, 9H, CH_3, ^{t}Bu), 1.52 (s, 9H, CH_3, ^{t}Bu), 3.6 (pt, 1H, CH-O, J_{H-H}= 8.4 Hz), 3.8 (s, 2H, CH_2), 4.73 (dd, 1H, CH-O, $^2J_{H-H}$= 10.0 Hz, $^3J_{H-H}$= 8.0 Hz), 4.9 (m, 1H, CH-N), 6.8-7.15 (m, 7H, CH=), 7.39 (m, 4H, CH=), 7.59 (m, 2H, CH=). ^{13}C (1006. MHz, C_6D_6): δ= 28.7 (CH_2), 30.9 (CH_3, ^{t}Bu), 31.2 (CH_3, ^{t}Bu), 34.3 (C, ^{t}Bu), 35.3 (C, ^{t}Bu), 69.6 (CH-N), 74.1 (CH_2-O), 120.8-150.2 (aromatic carbons), 166.0 (C=N). MS HR-ESI [found 714.3679, $C_{44}H_{54}NO_4P$ (M-Na)$^+$ requires 714.3683].

L5b: Yield: 512.5 mg (72%); ^{31}P NMR (161.9 MHz, C_6D_6): $\delta = 144.2$ ppm (s); ^{1}H NMR (400 MHz, C_6D_6): d = 0.4 (s, 9H, CH_3, $SiMe_3$), 0.6 (s, 9H, CH_3, $SiMe_3$), 3.1 (pt, 1H, CH-O, J_{H-H}= 8.4 Hz), 3.2 (d, 1H, CH_2, $^2J_{H-H}$ = 16.0 Hz) 3.36 (d, 1H, CH_2, $^2J_{H-H}$ = 16.0 Hz), 3.5 (dd, 1H, CH-O, $^2J_{H-H}$= 10.0 Hz, $^3J_{H-H}$= 8.0 Hz), 4.9 (m, 1H, CH-N), 6.91 (m, 4H, CH=), 7.02-7.23 (m, 7H, CH=), 7.43 (m, 4H, CH=), 7.78 (m, 2H, CH=), 8.16 (s, 1H, CH=), 8.27 (s, 1H, CH=). ^{13}C (100.6 MHz, C_6D_6): δ= -0.5 (d, CH_3, $SiMe_3$, J_{C-P}= 4.6 Hz), 0.1 (CH_3, $SiMe_3$), 28.3 (CH_2), 69.6 (CH-N), 73.9 (CH_2-O), 120.3-152.4 (aromatic carbons), 165.7 (C=N). MS HR-ESI [found 734.2280, $C_{42}H_{42}NO_4PSi_2$ (M-Na)$^+$ requires 734.2282].

L5c: Yield: 555.3 mg (78%); ^{31}P NMR (161.9 MHz, C_6D_6): $\delta = 143.5$ ppm (s); ^{1}H NMR (400 MHz, C_6D_6): d = 0.0 (s, 9H, CH_3, $SiMe_3$), 0.2 (s, 9H, CH_3, $SiMe_3$), 3.1 (pt, 1H, CH-O, J_{H-H}= 8.4 Hz), 3.2 (d, 1H, CH_2, $^2J_{H-H}$ = 16.0 Hz) 3.3 (d, 1H, CH_2, $^2J_{H-H}$ = 16.0 Hz), 3.5 (dd, 1H, CH-O, $^2J_{H-H}$= 10.0 Hz, $^3J_{H-H}$= 8.0 Hz), 4.4 (m, 1H, CH-N), 6.54 (m, 4H, CH=), 6.69-6.82 (m, 8H, CH=), 7.04 (m, 4H, CH=), 7.38 (m, 5H, CH=), 7.75 (s, 1H, CH=), 7.86 (s, 1H, CH=). ^{13}C (100.6 MHz, C_6D_6): δ= -0.5 (d, CH_3, $SiMe_3$, J_{C-P}= 4.6 Hz), 0.0 (CH_3, $SiMe_3$), 28.3 (CH_2), 69.5 (CH-N), 73.9 (CH_2-O), 120.5-149.5 (aromatic carbons), 165.7 (C=N). MS HR-ESI [found 734.2279, $C_{42}H_{42}NO_4PSi_2$ (M-Na)$^+$ requires 734.2282].

L6a: Yield: 394.72 mg (60%); ^{31}P NMR (161.9 MHz, C_6D_6): δ = 139.2 ppm (s); ^{1}H NMR (400 MHz, C_6D_6): δ = 0.71 (d, 3H, CH_3, ^{i}Pr, $^{3}J_{H-H}$ = 6.8 Hz), 0.90 (d, 3H, CH_3, ^{i}Pr, $^{3}J_{H-H}$ = 6.4 Hz), 1.28 (s, 18H, CH_3, ^{t}Bu), 1.5 (s, 18H, CH_3, ^{t}Bu), 1.55 (m, 1H, CH, ^{i}Pr), 3.55 (m, 1H, CH-O), 3.64 (m, 1H, CH-O), 3.77 (m, 3H, CH_2, CH-N), 6.8-6.9 (m, 2H, CH=), 7.0-7.15 (m, 2H, CH=), 7.38 (m, 2H, CH=), 7.59 (m, 2H, CH=). ^{13}C (100.6 MHz, C_6D_6): δ= 19.0 (CH_3, ^{i}Pr), 19.4 (CH_3, ^{i}Pr), 28.7 (CH_2), 31.6 (CH_3, ^{t}Bu), 31.7 (CH_3, ^{t}Bu), 31.9 (CH_3, ^{t}Bu), 33.6 (CH, ^{i}Pr), 35.0 (C, ^{t}Bu), 36.0 (C, ^{t}Bu), 70.5 (CH_2-O), 73.2 (CH-N), 121.5-150.8 (aromatic carbons), 165.1 (C=N). MS HR-ESI [found 680.3834, $C_{41}H_{56}NO_4P$ $(M-Na)^+$ requires 680.3839].

L6b: Yield: 467.8 mg (69%); ^{31}P NMR (161.9 MHz, C_6D_6): δ = 143.7 ppm (s); ^{1}H NMR (400 MHz, C_6D_6): d = 0.3 (s, 9H, CH_3, $SiMe_3$), 0.5 (s, 9H, CH_3, $SiMe_3$), 0.59 (d, 3H, CH_3, ^{i}Pr, $^{3}J_{H-H}$ = 6.4 Hz), 0.78 (d, 3H, CH_3, ^{i}Pr, $^{3}J_{H-H}$ = 6.8 Hz), 1.33 (m, 1H, CH, ^{i}Pr), 3.34 (pt, 1H, CH-O, J_{H-H}= 7.6 Hz), 3.4-3.6 (m, 4H, CH_2, CH-O, CH-N), 6.7-6.83 (m, 3H, CH=), 6.96-7.11 (m, 5H, CH=), 7.29 (m, 2H, CH=), 7.64 (d, 1H, CH=, $^{3}J_{H-H}$ = 8.4 Hz), 7.68 (d, 1H, CH=, $^{3}J_{H-H}$ = 8.4 Hz), 8.03 (s, 1H, CH=), 8.15 (s, 1H, CH=). ^{13}C (100.6 MHz, C_6D_6): δ= 0.2 (d, CH_3, $SiMe_3$, J_{C-P}= 4.8 Hz), 0.7 (CH_3, $SiMe_3$), 18.9 (CH_3, ^{i}Pr), 19.3 (CH_3, ^{i}Pr), 29.3 (CH_2), 33.4 (CH, ^{i}Pr), 70.4 (CH_2-O), 73.0 (CH-N), 121.3-154.5 (aromatic carbons), 164.9 (C=N). MS HR-ESI [found 700.2435, $C_{39}H_{44}NO_4PSi_2$ $(M-Na)^+$ requires 700.2439].

L6c: Yield: 508.4 mg (75%); ^{31}P NMR (161.9 MHz, C_6D_6): δ = 143.3 ppm (s); ^{1}H NMR (400 MHz, C_6D_6): d = 0.33 (s, 9H, CH_3, $SiMe_3$), 0.55 (s, 9H, CH_3, $SiMe_3$), 0.66 (d, 3H, CH^3, ^{i}Pr, $^{3}J_{H-H}$ = 6.4 Hz), 0.85 (d, 3H, CH_3, ^{i}Pr, $^{3}J_{H-H}$ = 6.8 Hz), 1.41 (m, 1H, CH, ^{i}Pr), 3.37 (pt, 1H, CH-O, J_{H-H}= 8.4 Hz), 3.5 (m, 2H), 3.6-3.71 (m, 2H), 6.82 (m, 2H, CH=), 6.90 (m, 2H, CH=), 7.00-7.15 (m, 3H, CH=), 7.34 (m, 3H, CH=), 7.68 (d, 1H, CH=, $^{3}J_{H-H}$ = 7.6 Hz), 7.72 (d, 1H, CH=, $^{3}J_{H-H}$ = 8.0 Hz), 8.07 (s, 1H, CH=), 8.19 (s, 1H, CH=). ^{13}C (100.6 MHz, C_6D_6): δ= 0.21 (d, CH_3, $SiMe_3$, J_{C-P}= 3.8 Hz), 0.7 (CH_3, $SiMe_3$), 19.0 (CH_3, ^{i}Pr), 19.4 (CH_3, ^{i}Pr), 29.2 (CH_2), 33.5 (CH, ^{i}Pr), 70.4 (CH_2-O), 73.1 (CH-N), 121.4-153.1 (aromatic carbons), 164.9 (C=N). MS HR-ESI [found 700.2437, $C_{39}H_{44}NO_4PSi_2$ $(M-Na)^+$ requires 700.2439].

L7a: Yield: 470.3 mg (70%); ^{31}P NMR (161.9 MHz, C_6D_6): δ = 139.2 ppm (s); ^{1}H NMR (400 MHz, C_6D_6): δ = 0.79 (s, 9H, CH_3, ^{t}Bu), 1.28 (s, 18H, CH_3, ^{t}Bu), 1.52 (s, 9H, CH_3, ^{t}Bu), 1.53 (s, 9H, CH_3, ^{t}Bu), 3.63-3.75 (m, 5H, CH_2, CH_2-O, CH-N), 6.82-6.91 (m, 2H, CH=), 7.0-7.15 (m, 1H, CH=), 7.36 (m, 2H, CH=), 7.39 (m, 1H, CH=), 7.59 (m, 2H, CH=). ^{13}C (100.6 MHz, C_6D_6): δ= 19.0 (CH_3, ^{i}Pr), 19.4 (CH_3, ^{i}Pr), 28.7 (CH_2), 31.6 (CH_3, ^{t}Bu), 31.7 (CH3, tBu), 31.9 (CH_3, ^{t}Bu), 33.9 (C, ^{t}Bu), 35.0 (C, ^{t}Bu), 36.0 (C, ^{t}Bu), 68.8 (CH_2-O), 76.6 (CH-N), 121.5-150.8 (aromatic carbons), 165.1 (C=N). MS HR-ESI [found 694.3992, $C_{42}H_{58}NO_4P$ $(M-Na)^+$ requires 694.3996].

L7b: Yield: 498.2 mg (72%); ^{31}P NMR (161.9 MHz, C_6D_6): $\delta = 144.1$ ppm (s); ^{1}H NMR (400 MHz, C_6D_6): d = 0.33 (s, 9H, CH_3, $SiMe_3$), 0.55 (s, 9H, CH_3, $SiMe_3$), 0.73 (S, 9H, CH_3, ^{t}Bu), 3.45-3.65 (m, 5H, CH_2, CH_2-O, CH-N), 6.82 (m, 2H, CH=), 6.87 (m, 2H, CH=), 7.00-7.15 (m, 4H, CH=), 7.35 (m, 2H, CH=), 7.68 (d, 1H, CH=, $^3J_{H-H}$= 8.4 Hz), 7.73 (d, 1H, CH=, $^3J_{H-H}$ = 8.4 Hz), 8.07 (s, 1H, CH=), 8.18 (s, 1H, CH=). ^{13}C (100.6 MHz, C_6D_6): δ= 0.2 (d, CH_3, $SiMe_3$, J_{C-P}= 4.6 Hz), 0.7 (CH_3, $SiMe_3$), 26.3 (CH_3, ^{t}Bu), 29.1 (CH_2), 33.4 (C, ^{t}Bu), 68.6 (CH_2-O), 76.5 (CH-N), 121.1-153.1 (aromatic carbons), 164.9 (C=N). MS HR-ESI [found 714.2591, $C_{40}H_{46}NO_4PSi_2$ $(M-Na)^+$ requires 714.2595].

L7c: Yield: 512.0 mg (74%); ^{31}P NMR (161.9 MHz, C_6D_6): $\delta = 143.1$ ppm (s); ^{1}H NMR (400 MHz, C_6D_6): d = 0.33 (s, 9H, CH_3, $SiMe_3$), 0.56 (s, 9H, CH_3, $SiMe_3$), 0.74 (CH_3, ^{t}Bu), 3.50-3.71 (m, 5H, CH_2, CH_2-O, CH-N), 6.81 (m, 2H, CH=), 6.89 (m, 2H, CH=), 7.00-7.16 (m, 3H, CH=), 7.34 (d, 2H, CH=, $^4J_{H-H}$ = 2.2 Hz), 7.39 (m, 1H, CH=), 7.68 (d, 1H, CH=, $^4J_{H-H}$ = 2.0 Hz), 7.72 (d, 1H, CH=, $^4J_{H-H}$ = 2.1 Hz), 8.07 (s, 1H, CH=), 8.19 (s, 1H, CH=). ^{13}C (100.6 MHz, C_6D_6): δ= -0.5 (d, CH_3, $SiMe_3$, J_{C-P}= 4.62 Hz), 0.0 (CH_3, $SiMe_3$), 25.6 (CH_3, tBu), 28.3 (CH_2), 33.1 (C, ^{t}Bu), 67.9 (CH_2-O), 75.7 (CH-N), 120.4-152.3 (aromatic carbons), 164.1 (C=N). MS HR-ESI [found 714.2592, $C_{40}H_{46}NO_4PSi_2$ $(M-Na)^+$ requires 714.2595].

3.3.5.5. Typical procedure for the allylic alkylation of linear (S1, S3–S8) and cyclic (S2, S9 and S10) substrates.

A degassed solution of $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (1.8 mg, 0.005 mmol) and the desired phosphite-oxazoline ligand (0.011 mmol) in dichloromethane (0.5 mL) was stirred for 30 min. After this time, a solution of substrate (1 mmol) in dichloromethane (1.5 mL), nucleophile (3 mmol), *N,O*-bis(trimethylsilyl)-acetamide (3 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 $MgSO_4$. For compounds **6**, **8**-**17**, **19**-**29** and **33**-**36**, the solvent was removed, conversions were measured by ^{1}H NMR and enantiomeric excesses were determined by HPLC[5g] (See Section 3.2). For compounds **7**, **31**-**32**, **37**-**38** and **40**-**42**, conversion and enantiomeric excesses were determined by GC[5g] (See Section 3.2). For compounds **30** and **39**, conversion was measured by ^{1}H NMR and ees were determined by ^{1}H NMR using $[Eu(hfc)_3]$.[5g]

3.3.5.6. Typical procedure for the allylic amination of S1.

A degassed solution of $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (1.8 mg, 0.005 mmol) and the desired phosphite-oxazoline ligand (0.011 mmol) in dichloromethane (0.5 mL) was stirred for 30 min. After this time, a solution of substrate (1 mmol) in dichloromethane (1.5 mL),

benzylamine (262 μL, 3 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 $MgSO_4$. Conversion of **18** was measured by ^1H NMR and enantiomeric excesses were determined by HPLC.[23]

3.3.5.7. Typical procedure for the allylic etherification and silylation of S1.

A degassed solution of $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (1.8 mg, 0.005 mmol) and the desired phosphite-oxazoline ligand (0.011 mmol) in dichloromethane (0.5 mL) was stirred for 30 min. Subsequently, a solution of **S1** (31.5 mg, 0.125 mmol) in dichloromethane (1.5 mL) was added. After 10 min, Cs_2CO_3 (122 mg, 0.375 mmol) and the corresponding alkyl alcohol or silanol (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 $MgSO_4$. Conversions were measured by ^1H NMR. HPLC was used to determine enantiomeric excesses of substrates **19**-**22**[5g].

3.3.6. References

1 For reviews, see: a) Tsuji, J. Palladium Reagents and Catalysis, *Innovations in Organic Synthesis*; Wiley: New York, **1995**; b) Trost, B. M.; van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395; c) Johannsen, M.; Jorgensen, K. A. *Chem. Rev.* **1998**, *98*, 1689; d) Pfaltz, A.; Lautens, M. in *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds.; Springer-Verlag: Berlin, **1999**; Vol. 2, Chapter 24; e) Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000**, *33*, 336; f) Masdeu-Bultó, A. M.; Diéguez, M.; Martin, E.; Gómez, M. *Coord. Chem. Rev.* **2003**, *242*, 159; g) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921; h) Martin, E.; Diéguez, M. *C. R. Chemie* **2007**, *10*, 188; i) Lu, Z.; Ma, S. *Angew. Chem. Int. Ed.* **2008**, *47*, 258; j) Diéguez, M.; Pàmies, O. *Acc. Chem. Res*. **2010**, *43*, 312. k) Trost, B. M.; Zhang, T.; Sieber, J. D. *Chem. Sci.* **2010**, *1*, 427. l) Trost, B. M. *Org. Process Res. Dev.* **2012**, *16*, 185.

2 a) Hayashi, T.; Yamamoto, A.; Hagihara, T.; Ito, Y. *Tetrahedron Lett.* **1986**, *27*, 191; b) Recently, this concept has also been used to explain the chiral induction by the Trost ligand; see Butts, C. P.; Filali, E.; Lloyd-Jones, G. C.; Norrby, P.-O.; Sale, D. A.; Schramm, Y. *J. Am. Chem. Soc.* **2009**, *131*, 9945.

3 See, for example, a) Trost, B. M.; Bunt, R. C. *J. Am. Chem. Soc.* **1994**, *116*, 4089. b) Trost, B. M.; Krueger, A. C.; Bunt, R. C.; Zambrano, J. *J. Am. Chem. Soc.* **1996**, *118*, 6520.

[4] For pioneering work, see: a) Dawson, G. J.; Frost, C. G.; Williams, J. M. J. *Tetrahedron Lett.* **1993**, *34*, 3149; b) von Matt, P.; Pfaltz, A. *Angew. Chem. Int. Ed.* **1993**, *32*, 566; c) Sennhenn, P.; Gabler, B.; Helmchen, G. *Tetrahedron Lett.* **1994**, *35*, 8595.

[5] For selected publications, see: a) Diéguez, M.; Ruiz, A.; Claver, C. *Chem. Commun.* **2001**, 2702. b) Pàmies, O.; Diéguez, M.; Claver, C. *J. Am. Chem. Soc.* **2005**, 127, 3646. c) Pàmies, O.; Diéguez, M. *Chem. Eur. J.* **2008**, *14*, 944. d) Mata, Y.; Pàmies, O.; Diéguez, M. *Adv. Synth. Catal*. **2009**, *351*, 3217. e) Mazuela, J.; Pàmies, O.; Diéguez, M. *Chem. Eur. J.* **2013**, *19*, 2416. f) Magre, M.; Biosca, M.; Pàmies, O.; Diéguez, M. *ChemCatChem* **2015**, *7*, 114. g) Bellini, R.; Magre, M.;Biosca, M.; Norrby, P.-O.; Pàmies, O.; Diéguez, M.; Moberg, C. *ACS Catalysis* **2016**, *6*, 1701.

[6] a) Yoon, T. P.; Jacobsen, E. N. *Science* **2003**, *299*, 1691–1693. b) Zhou, Q.-L. (Ed.) *Privileged Chiral Ligands and Catalysts*, Wiley-VCH, Weinheim **2011**.

[7] Murai, M.; Okamoto, K.; Miki, K.; Ohe, K. *Tetrahedron* **2015**, *71*, 4432.

[8] Yang, D.; Wang, L.; Han, F.; Li, D.; Zhao, D.; Wang, R. *Angew. Chem. Int. Ed.* **2015**, *54*, 2185.

[9] a) Kmentov, I.; Gotov, B.; Solcniov, E.; Toma, S. *Green Chem.* **2002**, *4*, 103; b) Liu, J.; Chen, G.; Xing, J.; Liao, J. *Tetrahedron: Asymmetry* **2011**, *22*, 575; c) Jin, Y.; Du, D. M. *Tetrahedron* **2012**, *68*, 3633; d) Martin, C. J.; Rawson, D. J.; Williams, J. M. J. *Tetrahedron: Asymmetry* **1998**, *9*, 3723. e) Deng, W. H.; Ye, F.; Bai, X. F.; Zheng, Z. J.; Cui, Y. M.; Xu, L. W. *ChemCatChem* **2015**, *7*, 75.

[10] For successful examples of Pd-catalysts, see: a) Trost, B. M.; Shen, H. C.; Dong, L.; Surivet, J.-P. *J. Am. Chem. Soc.* **2003**, *125*, 9276. b) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1998**, *120*, 815. c) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1999**, *121*, 4545. d) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **2000**, *122*, 11262. e) Uozumi, Y.; Kimura, M. *Tetrahedron: Asymmetry* **2006**, *17*, 161. f) Tietze, L. F.; Lohmann, J. K.; Stadler, C. *Synlett* **2004**, 1113. For successful applications of Ir-catalysts with phenols, see: g) Shu, C.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2004**, *43*, 4794. h) Fischer, C.; Defieber, C.; Suzuki, T.; Carreira, E. M. *J. Am. Chem. Soc.* **2004**, *126*, 1628. i) López, F.; Ohmura, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*. j) Lyothier, I.; Defieber, C.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 6204. k) Welter, C.; Dahnz, A.; Brunner, B.; Streiff, S.; Dübon, P.; Helmchen, G. *Org. Lett.* **2005**, *7*, 1239. l) Kimura, M.; Uozumi, Y. *J. Org. Chem.* **2007**, *72*, 707.

[11] a) Iourtchenko, A.; Sinou, D. *J. Mol. Catal. A* **1997**, *122*, 91. b) Haight, A. R.; Stoner, E. J.; Peterson, M. J.; Grover, V. K. *J. Org. Chem.* **2003**, *68*, 8092. c) Lam, F. L.; Au-Yeung, T. T.-L.; Kwong, F. Y.; Zhou, Z.; Wong, K. Y.; Chan, A. S. C. *Angew. Chem., Int. Ed.* **2008**, *47*, 1280. d) Ye, F.; Zheng, Z.-J.; Li, L.; Yang, K.-F.; Xia, C.-G.; Xu, L.-W. *Chem. Eur. J*. **2013**, *19*, 15452. e) Caldentey, X.; Pericàs, M. A. *J. Org. Chem.* **2010**, *75*, 2628. f) Liu, Z.; Du, H. *Org. Lett.* **2010**, *12*, 3054. g) Kato, M.; Nakamura, T.; Ogata, K.; Fukuzawa, S.-I. *Eur. J. Org. Chem.* **2009**, 5232. h) Feng, B.; Cheng, H.-G.; Chen, J.-R.; Deng, Q.-H.; Lu, L.-Q.; Xiao, W.-J. *Chem. Commun.* **2014**, *50*, 9550.

[12] a) Oslob, J. D.; Äkermark, B.; Helquist, P.; Norrby, P.-O. *Organometallics* **1997**, *16*, 3015; b) Hagelin, H.; Äkermark, B.; Norrby, P.-O. *Organometallics* **1999**, *18*, 2884.

[13] a) Hagelin, H.; Svensson, M.; Äkermark, B.; Norrby, P.-O. *Organometallics* **1999**, *18*, 4574; b) Moberg, C.; Bremberg, U.; Hallman, K.; Svensson, M.; Norrby, P.-O.; Hallberg, A.; Larhed, M.; Csçregh, I. *Pure Appl. Chem*. **1999**, *71*, 1477.

[14] a) Butts, C. P.; Filali, E.; Lloyd-Jones, G. C.; Norrby, P.-O.; Sale, D. A.; Schramm, Y. *J. Am. Chem. Soc.* **2009**, *131*, 9945. b) Fristrup, P.; Ahlquist, M.; Tanner, D.; Norrby, P.-O. *J. Phys. Chem.* **2008**, *112*, 12862.

[15] a) Auburn, P. R.; Mackenzie, P. B.; Bosnich, B. *J. Am. Chem. Soc.* **1985**, *107*, 2033. b) Jia, C.; Müller, P.; Mimoun, H. *J. Mol. Cat. A: Chem.* **1995**, *101*, 127. c) Lehman, J.; Lloyd-Jones, G. C. *Tetrahedron* **1995**, *51*, 8863. d) Hayashi, T.; Yamamoto, A.; Ito, Y.; Nishioka, E.; Miura, H.; Yanagi, K. *J. Am. Chem. Soc.* **1989**, *111*, 6301.

[16] Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A.; Peralta, J. E., Jr.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, O.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. Revision A.02 ed; Gaussian: Wallingford, CT, 2009.

[17] a) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev*. B **1988**, 37, 785. b) Becke, A. D. *J. Chem. Phys*. **1993**, 98, 5648.

[18] Hay, P. J.; Wadt, W. R. *J. Chem. Phys.* **1985**, 82, 299.

[19] a) Hehre, W. J.; Ditchfield, R.; Pople, J. A. *J. Chem. Phys.* **1972**, 56, 2257. b) Hariharan, P. C.; Pople, J. A. *Theor*. *Chim. Acta* **1973**, 28, 213. c) Francl, M. M.; Pietro,W. J.; Hehre,W. J.; Binkley, J. S.; Gordon, M. S.; Defrees, D. J.; Pople, J. A. *J. Chem. Phys*. **1982**, 77, 3654.

[20] a) Miertus, S.; Tomasi, *J. Chem. Phys.* **1982**, *65*, 239. b) Mennucci, B.; Tomasi, J. *J. Chem. Phys.* **1997**, 106, 5151. c) Cossi, M.; Barone, V.; Menucci, B.; Tomasi, J. *Chem. Phys. Lett*. **1998**, 286, 253.

[21] a) Krishnan, R.; Binkley, J. S.; Seeger, R.; Pople, J. A. *J. Chem. Phys.* **1980**, 72, 650. b) McLean, A. D.; Chandler, G. S. *J. Chem. Phys*. **1980**, 72, 5639.

[22] a) Grimme, S.; Antony, J.; Ehrlich, S.; Krieg, H. *J. Chem. Phys.* **2010**, 132, 15410 15417. b) Grimme, S.; Ehrlich, S.; Goerigk, L. *J. Comput. Chem.* **2011**, 32, 1456.

[23] Pàmies, O.; van Strijdonck, G. P. F.; Diéguez, M.; Deerenberg, S.; Net, G.; Ruiz, A.; Claver, C.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *J. Org. Chem.* **2001,** *66,* 8867.

3.4. Phosphite-oxazoline PHOX-based ligands containing an alkyl backbone chain for asymmetric Pd-catalyzed allylic substitution reactions. Study of the key Pd-intermediates

Magre, M.; Biosca, M.; Coll, M.; Pàmies, O.; Diéguez, M. *Manuscript to be submitted.*

Abstract: *A library of phosphite-oxazoline PHOX-based ligands **L8**-**L14a**-**c** containing an alkyl backbone chain has been synthesized and successfully applied to the Pd-catalyzed allylic substitution reactions. By carefully selecting the ligand components (i.e. substituents at both oxazoline and alkyl chain, as well as the biaryl group), high activities (TOF > 8000 mol substrate x (mol Pd x h)$^{-1}$) and excellent enantioselectivities have been achieved for hindered and unhindered substrates with a wide range of C-, N- and O-nucleophiles (ee's up to 99%). Moreover, DFT calculations and NMR studies of the key Pd-intermediates allowed us to better understand the origin of the excellent enantioselectivities observed experimentally.*

3.4.1. Introduction

The discovery of synthetic routes for the preparation of enantiomerically pure compounds is one of the most persistently pursued goals in chemistry.[1] Asymmetric catalysis is one of the most attractive approach because it can provide high reactivity and selectivity, and at the same time is environmentally friendly.[1] In this respect, the asymmetric Pd-catalyzed allylic substitution has become an efficient synthetic tool for the formation of carbon-carbon and carbon-heteroatom bonds.[2] Many chiral ligands (mainly P- and N-containing ligands), possessing either C_2 or C_1 symmetry, have provided high enatiomeric excesses for a wide range of disubstituted substrates. However, almost all reported ligands present substrate specificity. For example, ligands which provide high enantioselectivities for disubstituted linear hindered substrates, provides low enantiomeric excesses for unhindered substrates, and *vice versa*.[2] On the other hand, monosubstituted substrates still require much more attention due to the difficulty for controlling the regioselectivity of the nucleophilic attack.[2]

As mentioned in previous Sections 3.2 and 3.3, our group has demonstrated that the introduction of biaryl-phosphite moieties into the ligand backbone is highly advantageous.[3] The use of biaryl phosphite-containing ligands is beneficial because: a) reaction rates are increased due to the larger π-acceptor ability of the phosphite moiety;[5f] b) the chiral pocket created by the biaryl unit provides a flexible enough chiral pocket where all kind of substrates can be embedded,[5, 4] and c) a high regioselectivity towards the desired branched isomer for monosubstituted substrates increase thanks to the π-acceptor ability of the phosphite moiety that enhances the SN_1 character of the nucleophilic attack.[5] Thus, in Sections 3.2 and 3.3 we already

demonstrated that the replacement of the phosphine moiety by a biaryl phosphite unit could be beneficial in terms of substrate scope. PHOX-based phosphite-oxazoline ligands provided excellent enantioselectivities for hindered, unhindered and monosubstituted substrates with a wide range of C-, N- and O-nucleophiles.[5g]

In the previous Sections 3.2 and 3.3, we have already demonstrated the high potential of PHOX-based phosphite-oxazoline ligands (**L1** and **L5**-**L7**) and by just replacing the linker between the phosphite and the oxazoline moiety, complementary results in terms of substrate and nucleophile versatility were achieved.

In this Section we designed a third generation of phosphite-oxazoline PHOX-based ligands (**L8**-**L13a**-**c**) by replacing the *ortho*-phenylene tether by an alkyl backbone chain (Figure 3.4.1). In contrast to previous PHOX-phosphite-oxazoline ligands presented, with **L8**-**L13a**-**c** we could study the effect on catalytic performance of the presence of a secondary stereocentre on the ligand backbone. We also studied the effect of the substituent in the alkyl backbone chain as well as the substituents/configuration both at the oxazoline group and at the phosphite moiety.

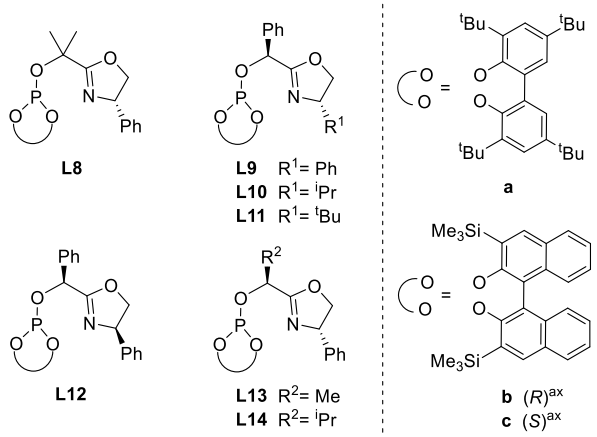


Figure 3.4.1. Phosphite-oxazoline ligands **L8**-**L14a**-**c**.

3.4.2. Results

3.4.2.1. Preparation of Ligands

The synthesis of phosphite-oxazoline ligands is shown in Scheme 3.4.1. They were easily accessible by coupling the corresponding hydroxyl-oxazoline intermediates **2** and **12**-**17** with the desired phosphorochloridites ($ClP(OR)_2$; $(OR)_2$ = **a**-**c**; step *vii*). Hydroxyl-oxazolines are straightforwardly made in multigram scale from cheap α-hydroxy acids **1**, **3**-**5**. α-Hydroxy acids **1**, **3**-**5** have been chosen because they incorporate the desired diversity in the substituents and configuration at the alkyl backbone chain. α-Hydroxyisobutyric acid **1** was condensed with (*S*)-phenylglycinol to

provide hydroxyl-oxazoline **2**. For the synthesis of hydroxyl-oxazoline **12**-**17**, the alcohol group in α-hydroxy acids **3**-**5** was first protected using acetylchloride and then the acid transformed to the corresponding acid chlorides (steps *ii* and *iii*). The latter were coupled to the desired chiral amino alcohol to afford the corresponding amides **6**-**11** (step *iv*). At this stage the desired diversity in the substituents and configuration of the oxazoline moiety is introduced. Compounds **6**-**11** were then converted to the corresponding oxazoline esters in the presence of diethylaminosulfur trifluoride (DAST; step *v*). Standard deprotection of the oxazoline esters afforded the corresponding hydroxyl-oxazolines **12**-**17** (step *vi*). All ligands were stable during purification on neutral alumina under an atmosphere of argon and they were isolated as white solids. They were stable at room temperature and very stable to hydrolysis. HRMS-ESI spectra were in agreement with the assigned structures. The ^{1}H and ^{13}C NMR spectra were as expected for these C_1 ligands. One singlet for each compound was observed in the ^{31}P NMR spectrum. Rapid ring inversions (tropoisomerization) in the biphenyl-phosphorus moiety (**a**) occurred on the NMR time scale since the expected diastereoisomers were not detected by low-temperature phosphorus NMR.

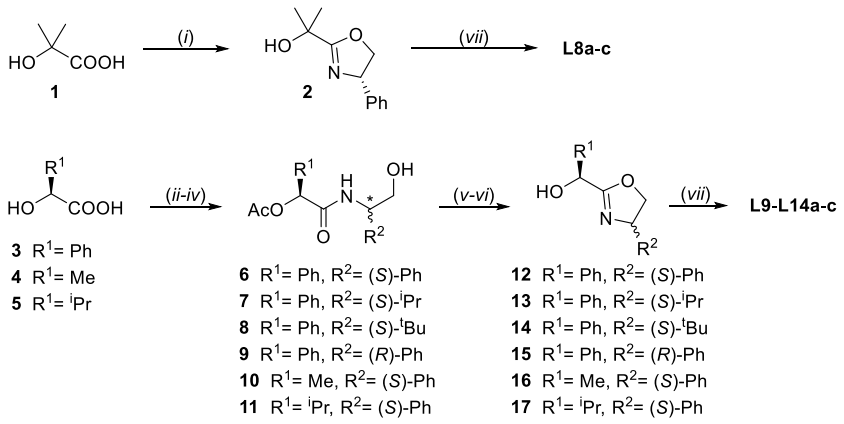


Figure 3.4.1. Synthetic route for the synthesis of phosphite-oxazoline ligand library **L8**-**L14 a**-**c**. (*i*) (*S*)-phenylglycinol, xylene, reflux, 16 h;[6] (*ii*) acetyl chloride, rt, 2 h;[7] (*iii*) CO_2Cl_2, DMF cat., CH_2Cl_2, rt, 2 h;[8] (*iv*) aminoalcohol, NEt_3, CH_2Cl_2, rt, 5 h;[8] (*v*) DAST, K_2CO_3, CH_2Cl_2, -78 ºC to rt for 3 h;[8,8] (*vi*) NaOH (aq), EtOH, 0 ºC, 2 h;[8,9] (*vii*) $ClP(OR)_2$; $(OR)_2$ = **a**-**c**, Py, toluene, 16 h.

3.4.2.2. Allylic substitution of disubstituted substrates S1-S2 using dimethyl malonate as nucleophile

In this section we studied the effectiveness of the new phosphite-oxazoline ligand library **L8**-**L14a**-**c** in the Pd-allylic alkylation of substrates *rac*-(*E*)-1,3-diphenyl-3-acetoxyprop-1-ene **S1** and *rac*-3-acetoxycyclohexene **S2**, with different steric

properties, using dimethyl malonate as nucleophile. For comparison purposes, the catalysts were generated in situ from π-allyl-palladium chloride dimer $[PdCl(\eta^3\text{-}C_3H_5)]_2$, the corresponding ligand and nucleophile using standard conditions. The results, which are shown in Table 3.4.1, indicate that enantioselectivities are affected by the substituents at both the oxazoline and at the alkyl backbone chain as well as by the biaryl phosphite group. However, the effect of these parameters on enantioselectivity is different for both substrates. Nevertheless, we have been able to identify two particular ligands (**L8c** and **L13c**) that performs exceptionally well for both substrate types, with enantioselectivities up to 99% ee and TOF's up to 8640 mol substrate×(mol Pd×h)$^{-1}$.

The results using ligands **L8a**-**c** indicated that the ligand backbone is only able to control the tropoisomerization of the biphenyl phosphite moiety (**a**) for substrate **S1**. This contrast with the perfect tropoisomerization control exerted by the ligand backbone in phosphite-based PHOX-ligands **L1** for both substrate types presented in Section 3.2. [5g] Thus, while high enantioselectivities are achieved with ligands **L8a** and **L8c** for substrate **S1** (entries 1 and 3) the use of ligand **L8c** with an enantiopure (*S*)-biaryl phosphite group is necessary to maximize enantioselectivities for substrate **S2** (entry 3 vs 1 and 2).

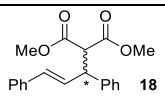
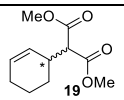
The use of ligands **L9**-**L11a** indicated that enantioselectivities are highly dependent on the oxazoline substituent. In contrast to the phosphine-oxazoline PHOX ligands the presence of bulky substituents has a negative effect one enantioselectivity. Thus, the highest enantioselectivities for both substrates were achieved using ligand **L9a**, containing a phenyl oxazoline substituent. This represents an important advantage over the traditional PHOX ligands because enantiopure phenylglycinol (used for the synthesis of **L9**) is much cheaper than *tert*-leucinol (used for the synthesis of **L11**).

The results using **L9b**-**c** and **L12b**-**c** indicated that there is a cooperative effect between the configuration of biaryl phosphite group and the configuration of the oxazoline substituent. This resulted in a matched combination for ligands **L9c** and **L12b** (entries 6 and 10). In addition, we have found that while for linear substrate **S1** the sense of enantioselectivity is controlled by the configuration of the oxazoline substituent (ligands **L9** provides the opposite enantiomer than ligands **L12**; entries 4-6 vs 9-11), the configuration of the biaryl phosphite group controls the sense of enantioselectivity in the alkylation of cyclic substrate **S2** (ligands **L8b** and **L12b** provides the opposite enantiomers than ligands **L8c** and **L12c**).

The effect of the substituent at the alkyl chain was studied using ligands **L8**, **L9**, **L13** and **L14**. The best enantioselectivities were achieved with ligands **L8** and **L13** containing two or one methyl group at the alkyl backbone chain, respectively.

In summary, by carefully selecting the ligand components we have been able to achieve excellent activities and enantioselectivities (up to 99% ee) in the Pd-catalyzed allylic substitution of both substrates types.

Table 3.4.1. Asymmetric Pd-catalyzed allylic alkylation of substrates **S1** and **S2** using phosphite-oxazoline ligands **L8**-**L14a**-**c**[a]

		 **18**		 **19**	
Entry	Ligand	% Conv[b]	% ee[c]	% Conv[d]	% ee[e]
1	**L8a**	100	96 (*S*)	100	60 (*S*)
2	**L8b**	100	86 (*S*)	100	78 (*R*)
3	**L8c**	100	96 (*S*)	100	99 (*S*)
4	**L9a**	100	93 (*S*)	100	40 (*S*)
5	**L9b**	100	40 (*S*)	100	74 (*R*)
6	**L9c**	100	90 (*S*)	100	90 (*S*)
7	**L10a**	100	92 (*S*)	100	7 (*S*)
8	**L11a**	100	73 (*S*)	100	4 (*S*)
9	**L12a**	100	90 (*R*)	100	20 (*R*)
10	**L12b**	100	94 (*R*)	100	81 (*R*)
11	**L12c**	100	55 (*R*)	100	77 (*S*)
12	**L13a**	100	92 (*S*)	100	44 (*S*)
13	**L13b**	100	89 (*S*)	100	65 (*R*)
14	**L13c**	100	99 (*S*)	100	96 (*S*)
15	**L14a**	100	84 (*S*)	100	33 (*S*)
16	**L14b**	100	91 (*S*)	100	60 (*R*)
17	**L14c**	100	90 (*S*)	100	97 (*S*)
18[f]	**L13c**	72	99 (*S*)	41	96 (*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 (3 mol%). [b] Conversion percentage determined by ^{1}H-NMR after 30 min. [c] Enantiomeric excesses determined by HPLC. Absolute configuration drawn in parentheses. [d] Conversion percentage determined by GC after 2 h. [e] Enantiomeric excesses determined by GC. Absolute configuration drawn in parentheses. [f] Reactions carried for 5 min using 0.1 mol% of catalyst precursor.

3.4.2.3. Allylic substitution of disubstituted substrates using several nucleophiles. Scope and limitations

In this section, we report the use of Pd-**L8c** and Pd-**L13c** catalytic systems in the allylic substitution of several linear and cyclic disubstituted substrates (Figure 3.4.2) using a wide range of C-, N- and O-nucleophiles, among which are the challenging functionalized malonates, β-diketones, 2-cyanoacetates, pyrroles and alkyl alcohols.

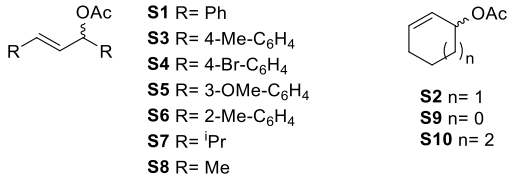


Figure 3.4.2. Substrates **S1**-**S10** used in this study.

In a first set of experiments we used the Pd-catalyzed allylic substitution of **S1** to study the nucleophile scope using **L13c** ligand. The results, which are summarized in Figure 3.4.3, indicated that a wide range C-, N- and O-nucleophiles could be efficiently used for this transformation. Several malonates, including those substituted with allyl-, butenyl, pentenyl- and propargyl-groups; reacted easily to **S1** to provide the alkylated products **20**-**26** in excellent yields and enantioselectivities (ee's ≥99%).The use of malononitrile (compound **27**) and acetylacetone (compound **29**) also afforded the desired alkylated products in excellent enantioselectivities (>99% ee). Similarly to previous reports the use of isopropyl cyanoacetate (compound **28**) as nucleophile resulted in the formation of two diastereoisomers with low diastereoselectivity,[9] albeit both diastereoisomers were obtained in almost enantiopure form (ee's up to 99%).

The reaction also worked well when pyrroles were used as nucleophiles (compounds **30** and **31**). These are important results because N-containing heterocycles are present in many relevant compounds. In this respect, an important class of electron-rich N-containing heterocycles is pyrroles, which are widely present in biologically compounds and have versatile synthetic applications.[10] Despite this, only one catalytic system has previously been successfully applied in the Pd-allylic alkylation of **S1** type substrates, however it required low temperature (-20 °C) to achieved high ee.[11] We were pleased to see that we could reach ee's up to 99% and high yield working at room temperature.

The use of benzylamine as model N-nucleophile also provided the substitution product **32** in excellent enantioselectivity (>99% ee). Interestingly, the excellent enantiocontrol also extends to the use of several benzylic and allylic alcohols (compounds **33**-**37**, ee's up to 99%). The results show that enantioselectivity is affected by electronic properties of the aryl group. In contrast to Pd-(*S*)-**L1a**, the use of (4-(trifluoromethyl)phenyl)methanol led therefore to lower enantioselectivities than when using other more electron-rich benzylic alcohols. Therefore, complementary results than Pd-(*S*)-**L1a** have been obtained for this type of nucleophiles. The effective allylic substitution with this type of O-nucleophiles is of interest for the construction of aliphatic chiral ethers which are important for the synthesis of biologically active targets.[12,13] Even more remarkable are the almost perfect enantioselectivities (ee's up to 99%) and high yields achieved in the etherification of **S1** with the triphenylsilanol

(compound **38**). The Pd-catalyzed allylic etherification of allylic substrates with silanols is an elegant route for obtaining chiral silyl ethers than can further transformed into high-value compounds such as chiral aromatic allylic alcohols.[14] Interestingly, all the results obtained up to this point are comparable to those obtained with the privileged ligands **L1**.

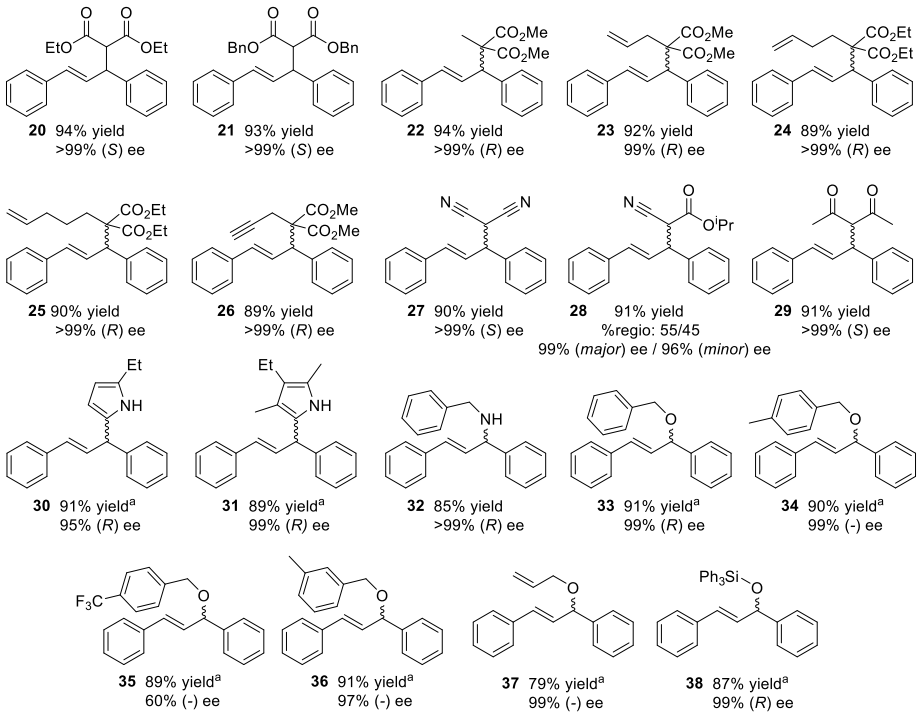


Figure 3.4.3. Allylic substitution of **S1** with C-, N- and O-nucleophiles using Pd-**L13c** catalytic system. Reactions were run at 23 °C with $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (0.5 mol %), CH_2Cl_2 as solvent, ligand (1.1 mol %), BSA (3 equiv), and KOAc. Full conversions were achieved after 2 h. [a] Reactions carried out using 2 mol % $[PdCl(\eta^3\text{-}C_3H_5)]_2$, 4 mol % ligand, and Cs_2CO_3 (3 equiv). Full conversions were achieved after 18 h.

We then decided to study other symmetrical disubstituted linear substrates **S3**-**S8** with steric and electronic requirements different from those of **S1** using Pd-**L13c** catalytic system. The results, which are collected in Figure 3.4.4, indicated that Pd-**L13c** can also be used for the alkylation of substrates **S3**–**S6**, with different substituents in the aryl groups, with various carbon nucleophiles with high yields and enantioselectivities, comparable to those of **S1** (compounds **39**-**45**, ee's ≥99%). Interestingly, Pd-**L13c** can also successfully be used for the alkylation of **S7** (compound **46**, >95% ee). This substrate is more sterically demanding than **S1** and it usually reacts with inferior

catalytic performance. Enantioselectivities as high as 83% ee were achieved in the allylic substitution of less sterically hindered substrate **S8** (compounds **47** and **48**). The enantioselectivities achieved for this latter challenging substrate are similar of those achieved using phosphite-oxazoline PHOX-ligands **L1** (Section 3.2).

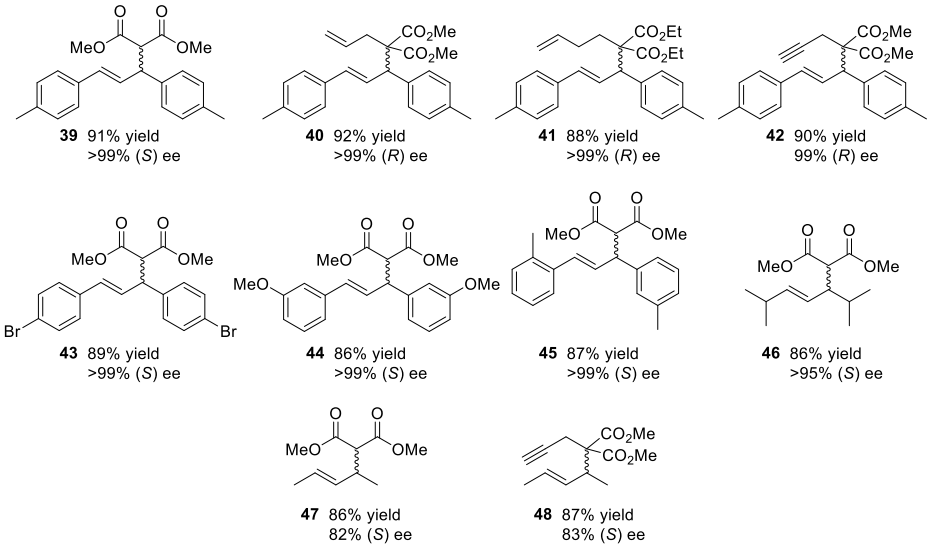


Figure 3.4.4. Allylic substitution of **S3-S8** with C-nucleophiles using Pd-**L13c** catalytic system. Reactions were run at 23 °C with $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (0.5 mol %), CH_2Cl_2 as solvent, ligand (1.1 mol %), BSA (3 equiv), and KOAc. Full conversions were achieved after 2 h (except for reactions using substrates **S6** and **S7** that were run for 12 h).

We then focused our attention to the allylic substitution of several cyclic substrates, with different ring sizes (**S2 S9** and **S10**) with a range of nucleophiles using Pd-**L8c** catalytic system. The results, which are summarized in Figure 3.4.5, indicated that high yields and excellent enantioselectivities (ee's from 95% to >99%) could be achieved in the allylic alkylation of **S2** using a wide range of C-nucleophiles, including the less studied α-functionalized malonates and acetylacetone (compounds **49**-**54**). Pd-**L8c** is also able to efficiently catalyze the alkylation of cyclic substrates **S9** and **S10** (compounds **55**-**58**; ee's up to >99%). High enantioselectivities were therefore obtained in both cases, even with **S9**, which usually provides products with much lower enantioselectivities than cyclic **S2**.

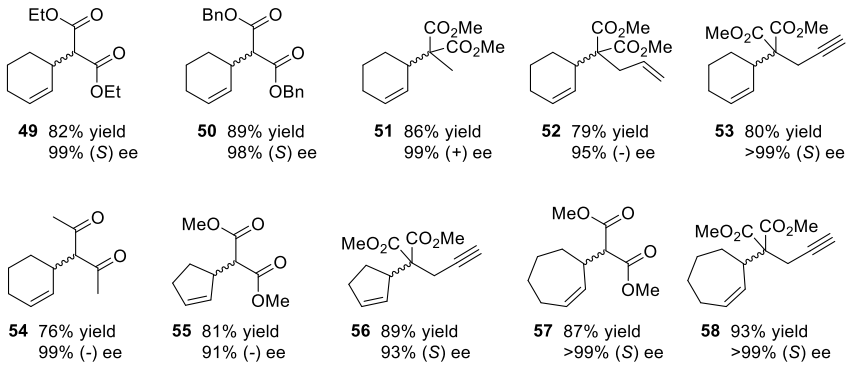
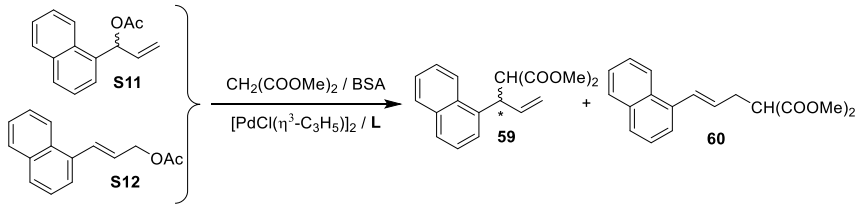


Figure 3.4.5. Allylic substitution of **S2**, **S9**-**S10** with C-nucleophiles using Pd-**L8c** catalytic system. Reactions were run at 23 °C with $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (0.5 mol %), CH_2Cl_2 as solvent, ligand (1.1 mol %), BSA (3 equiv), and KOAc. Full conversions were achieved after 2 h.

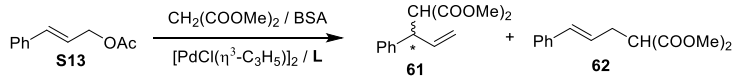
3.4.2.4. Allylic substitution of monosubstituted substrates S11-S13

To further study the potential of these readily available ligands, in this section, we tested **L8**-**L14a**-**c** in the regio- and stereoselective allylic alkylation of 1-(1-naphthyl)allyl acetate (**S11**), 1-(1-naphthyl)-3-acetoxyprop-1-ene (**S12**) and cinnamyl acetate (**S13**) with dimethyl malonate as nucleophile (Eq. 3.4.1). 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 products **60** and **62** rather than the desired branched isomer **59** and **61**.[15] The development of highly regio- and enantioselective Pd-catalysts is therefore still important.[16]

(Eq 3.4.1a)



(Eq 3.4.1b)



The results are summarized in Table 3.4.2. The results achieved under standard reaction conditions (*i.e.* using dichloromethane as solvent and at room temperature) indicated that regioselectivities are hardly affected by the ligand parameters. Thus moderate regioselectivities towards the desired branched products were achieved (up

to 65% branched). However, enantioselectivities followed a similar trend that for the allylic substitution of substrate **S1**. Thus, the sense of enantioselectivity is dictated by the configuration of the oxazoline substituent (entries 4-6 vs 7-9) and there is cooperative effect between the configurations of the biaryl phosphite group and of the oxazoline substituent, that results again in a matched combination for ligands containing either an (S)-configuration at both the biaryl phosphite group and at the oxazoline substituent (*i.e* ligand **L9c**; entry 6) or (*R*)-configuration at both the phosphite and at the oxazoline moieties (*i.e.* ligand **L12b**; entry 7). However, the effect of the substituent of the alkyl backbone on enantioselectivity is different than those observed in the alkylation of **S1**. Thus, enantioselectivities were better when using ligand **L14c**, containing an isopropyl group at the alkyl backbone chain (ee's up to 94%; entry 11).

Catalytic performance can not only be controlled by the ligand parameters, but also the reaction conditions may play a major role in improving the catalytic performance. In this context, we have achieved high regio- (up to 80% branched) and enantioselectivities (up to 98% ee) in the alkylation of substrates **S11**-**S13** using Pd-**L14c** catalytic system by carrying out the reactions at 0 °C and using benzene as solvent (entries 12-14).

Table 3.4.2. Selected results for the Pd-catalyzed allylic substitution of monosubstituted substrates **S11**-**S13**.[a]

Entry	Substrate	Ligand	% Conv[b] (%yield)	% branched[c]	% ee[d]
1	**S11**	**L8a**	100 (88)	55	60 (*S*)
2	**S11**	**L8b**	100 (89)	55	34 (*S*)
3	**S11**	**L8c**	100 (88)	60	84 (*S*)
4	**S11**	**L9a**	100 (91)	50	59 (*S*)
5	**S11**	**L9b**	100 (89)	65	30 (*S*)
6	**S11**	**L9c**	100 (90)	50	88 (*S*)
7	**S11**	**L12a**	100 (89)	55	43 (*R*)
8	**S11**	**L12b**	100 (88)	65	84 (*R*)
9	**S11**	**L12c**	100 (91)	40	42 (*R*)
10	**S11**	**L13c**	100 (90)	40	89 (*S*)
11	**S11**	**L14c**	100 (88)	65	94 (*S*)
12[e]	**S11**	**L14c**	100 (91)	80	98 (*S*)
13[e]	**S12**	**L14c**	100 (92)	80	98 (*S*)
14[e]	**S13**	**L14c**	100 (93)	70	94 (*S*)

[a] 1 mol % $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$, 2.2 mol % ligand, CH_2Cl_2 as solvent, BSA/KOAc as base, [b] % Conversion measured after 30 min. Isolated yield shown in parenthesis. [c] Regioselectivity measured by ^1H NMR. [d] Enantiomeric excesses determined by chiral HPLC. [e] Reaction carried out in benzene at 0 °C for 2 h.

It should be noted that enantioselectivities are higher than those achieved using phosphite-oxazoline PHOX ligands **L1** (Section 3.2) and therefore compares well with the best ones reported so far.

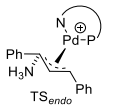
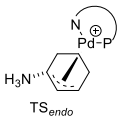
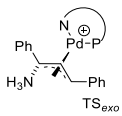
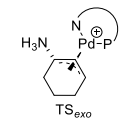
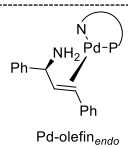
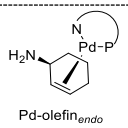
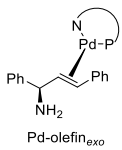
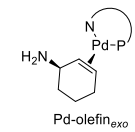
3.4.2.5. Origin of enantioselectivity

Initially, we performed a DFT computational study of the key intermediates and transition states involved in the enantiocontrol of the Pd-catalyzed allylic substitution of substrates **S1** and **S2**, using ligands **L8b**, **L8c** and **L13c**. The latter have been chosen because they will allow to study the effect of varying the configuration of the biaryl phosphite moiety (ligands **L8b** and **L8c**) as well as the effect of having a chiral center in the alkyl backbone chain (ligand **L13c**). As already mentioned, enantioselectivity is controlled in the effectively irreversible nucleophilic attack, but transition state (TS) for this step can be either early or late depending on the nature of the nucleophile, ligands, and reaction conditions. In an early transition state, the interactions leading to stereochemical differentiation can be understood from the structure of the Pd-allyl intermediate,[17] whereas the late transition state is more reminiscent of the Pd-alkene product complex.[18] For the early TS case, stereochemistry is governed by both the population of the Pd-η^3-allyl intermediates and the relative electrophilicity of the allylic carbon atoms, with an allyl terminus *trans* to a phosphorus atom generally being more reactive than one *trans* to the oxazoline group. When the TS is late, the formation of the most stable Pd-olefin complex controls enantioselectivity. Previous experience has shown that ammonia can be used as a good model nucleophile,[19] avoiding the problems related to charge separation in conjunction with a continuum solvent model. Note that the use of ammonia as nucleophile instead of dimethyl malonate results in the inversion of the CIP descriptor in the 1,3-diphenylallyl case, due to the change in priority of the groups, although the sense of stereoselectivity is maintained.

We therefore calculated the relative stability of the transition states TS_{endo} and TS_{exo}, using NH_3 as nucleophile and the Pd-olefin intermediates (Pd-$olefin_{endo}$ and Pd-$olefin_{exo}$). The results are summarized in Table 3.4.3. The energy differences of the calculated TSs using **S1** and **S2** agree with the catalytic results. Thus, for instance, the energy difference between the TSs using **S1** with **L8b** ($\Delta G^{\#}$=11.2 kJmol^{-1}) is lower than that of **L8c** ($\Delta G^{\#}$=21 kJmol^{-1}). This is in good agreement with the higher enantioselectivities achieved using **L8c** (Table 3.4.1, 96% (*S*) ee for **L8c** vs. 86% (*S*) ee for **L8b**). In addition, the TS calculations using **S2** as substrates agree with the formation of the opposite enantiomers of the substituted product **19** when **L8b** and **L8c** are used, and also with identifying Pd-**L8c** system as the most enantioselective catalyst ($\Delta G^{\#}$=15.6 kJmol^{-1} for Pd-**L8c** vs $\Delta G^{\#}$=13.6 kJmol^{-1} for Pd-**13c**). On the other hand, the calculated energies of the Pd-olefin intermediates do not correlate well with the experimental results. Thus, for instance, the calculated results of the Pd-olefin

complexes of **S1** ($\Delta G^{\#} \geq 30$ kJmol^{-1}) indicated that all three ligands should provide excellent levels of enantioselectivity (ee_{calc}>99.9% (S)). In addition, for **S2**, although the energy difference between the Pd-olefin intermediates correctly predicts the formation of opposite enantiomers of the substitution products when using ligands **L8b** and **L8c**; the calculated energy differences between Pd-olefin complexes containing **L8b** are higher than that of intermediates containing **L8c** ($\Delta G^{\#}$=15.6 kJmol^{-1} for Pd-**L8c** vs $\Delta G^{\#}$=13.6 kJmol^{-1} for Pd-**13c**), which wrongly predicts much higher enantioselectivities when using Pd-**L8b**.

Table 3.4.3. Calculated energies for the TSs and Pd-η^2-olefin complexes using **S1** and **S2** and NH_3 as nucleophile[a]

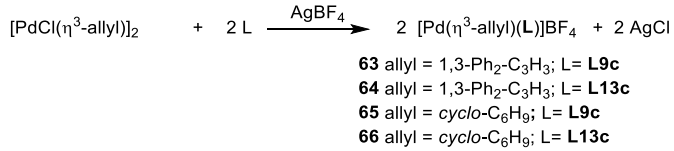
Structure	**L8b**	**L8c**	**L13c**	**Structure**	**L8b**	**L8c**	**L13c**
	16.6	21	14.2		5	0	0
	5.4	0	0		4	15.6	13.6
	36.6	33.2	30.0		4.4	6.2	0
	5.1	0	0		0	8.2	6.1

[a] Relative energies in kJ/mol.

In summary the DFT calculations indicate that the Pd-allylic substitution reactions using ligands **L8**-**L14a**-**c** proceed via an early transition state, in which the structure and the reactivity of the corresponding Pd-allyl intermediates play a major role in enantioselectivity.

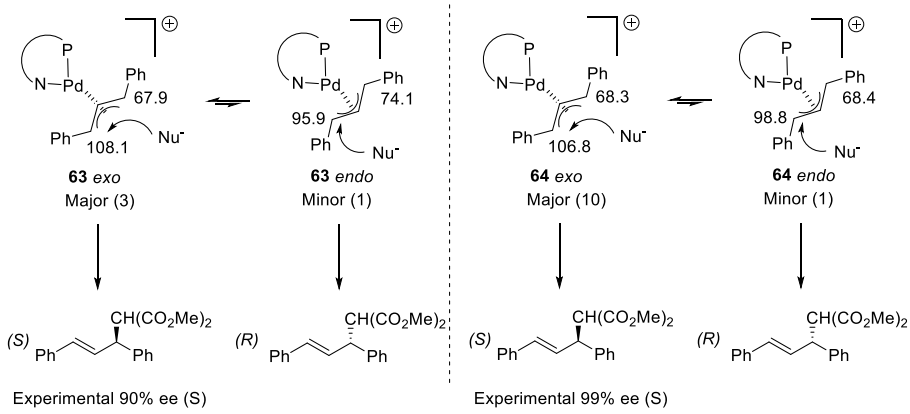
To provide further insight into how ligand parameters affect catalytic performance, we therefore studied the Pd-π-allyl compounds **63**-**66** [Pd(η^3-allyl)(**L**)]BF_4 (L= **L9c** and **L13c**). Ligands **L9c** and **L13c** have been chosen to study the effect of different substituents in the alkyl backbone chain. These ionic palladium complexes, which contain 1,3-diphenyl or cyclohexenyl allyl groups, were prepared using the previously

reported method from the corresponding Pd-allyl dimer and the appropriate ligand in the presence of silver tetrafluoroborate (Scheme 3.4.2).[20] The complexes were characterized by ^{1}H, ^{13}C and ^{31}P NMR spectroscopy. The spectral assignments were based on information from ^{1}H-^{1}H, ^{31}P-^{1}H and ^{13}C-^{1}H correlation measurements in combination with ^{1}H-^{1}H NOESY experiments. Unfortunately, we were unable to obtain crystal of sufficient quality to perform X-ray diffraction measurements.



Scheme 3.4.2. Preparation of [Pd(η^3-allyl)(**L**)]BF_4 complexes **63**-**66.**

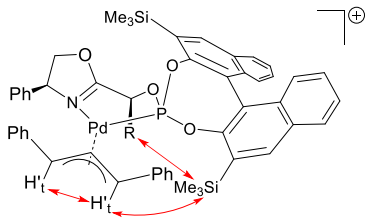
The VT-NMR study (30 ºC to -80 ºC) of Pd-1,3-diphenyl allyl intermediates **63** and **64**, showed a 3:1 and a 10:1 mixture of two isomers in equilibrium (Scheme 3.4.3).



Scheme 3.4.3. Diastereoisomer Pd-allyl intermediates for **S1** with ligands **L9c** (isomers **63**) and **L13c** (intermediates **64**). The relative amounts of each isomer are shown in parentheses. The chemical shifts (in ppm) of the allylic terminal carbons are also shown.

Both isomers were unambiguously assigned by NMR to the two *syn*/*syn* Pd-η^3-*exo* and *endo* isomer. In both isomers, the NOE indicated interactions between the two terminal protons of the allyl group, which clearly indicates a syn/syn disposition (Figure 3.4.6). Moreover, there is a NOE interaction between the terminal allyl proton trans to the oxazoline with the TMS group that shows a NOE interaction with the substituent at the alkyl backbone chain (Figure 3.4.6). These interactions can be explained by assuming a syn/syn exo disposition for the major isomer. The carbon chemical shifts of compounds **63** and **64** indicate that the most electrophilic allylic terminal carbon is located *trans* to the phosphite moiety in the major isomer ($\Delta\delta(^{13}C) \approx 12.4$ ppm for **63**

and $\Delta\delta(^{13}C)$ ≈ 8 ppm for **64**). This indicates that not only the major isomers react faster than the minor isomers but also that the relative reaction rate is higher for intermediate **63** than for **64**. The latter has been verified by studying the reactivity of the Pd-1,3-diphenyl allyl intermediates **63** and **64** with sodium malonate at low temperature by in situ NMR. Our results showed that while the major isomer of **63** reacts 8 times faster than the minor isomer, the relative reaction rate of **64** is of 6. Thus, although the use of Pd-**L9c**, with a phenyl substituent at the alkyl backbone chain, does not effectively control the population of Pd-allyl intermediates, it exerts a high electronic differentiation, which is key for achieving enantioselectivities as high as 90% ee (Table 3.4.1). Gratifyingly, the use of Pd-**L13c**, with a methyl alkyl substituents at the alkyl backbone chain, effectively controls both the population and the relative electrophilicity in the Pd-allyl intermediates.

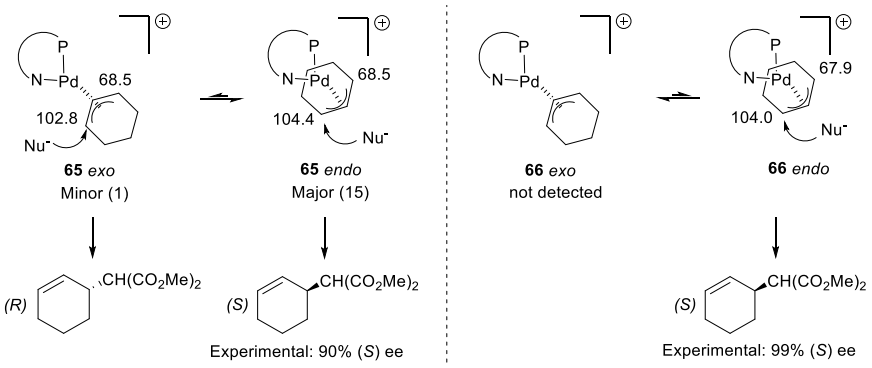


63 R= Ph
64 R= Me

Figure 3.4.6. Relevant NOE contacts from the NOESY experiments for the major isomers of [Pd(η^3-1,3-diphenylallyl)(**L**)]BF_4 **63** and **64**.

The VT-NMR study (30 ºC to -80 ºC) of Pd-1,3-cyclohexenyl allyl intermediate **65** show a 15:1 mixture of two isomers in equilibrium, while for intermediate **66** only one isomer has been isomer (Scheme 3.4.4).

The major isomers of intermediates **65** and **66** shows NOE interactions between the central allyl proton with the TMS group that shows a NOE interaction with the substituent at the alkyl backbone chain (Figure 3.4.7). These interactions can be explained by assuming an *endo* disposition for the major isomers. The carbon NMR chemical shifts indicated again that the most electrophilic allylic terminus carbon is *trans* to the phosphite moiety. For intermediate **65**, the fact that the electrophilicity of the allylic terminal carbon atom *trans* to the phosphite is rather similar in both *endo* and *exo* isomers ($\Delta\delta(^{13}C)$ ≈ 1.6 ppm) suggests that both isomers reacts at a similar rate. So, the enantioselectivity is mainly affected by the population of the *endo* and *exo* isomers. The much higher enantioselectivity obtained using Pd-**L13c** can therefore be attributed to the fact that only the *endo* isomer is detected.



Scheme 3.4.4. Diastereoisomer Pd-allyl intermediates for **S2** with ligands **L9c** (isomers **65**) and **L13c** (intermediates **66**). The relative amounts of each isomer are shown in parentheses. The chemical shifts (in ppm) of the allylic terminal carbons are also shown.

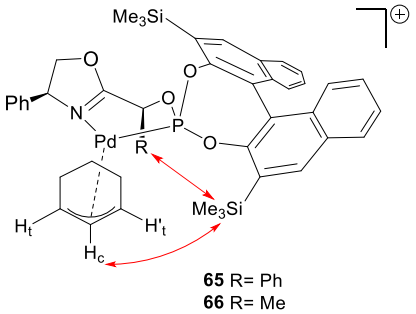


Figure 3.4.7. Relevant NOE contacts from the NOESY experiments for the major isomers of [Pd(η^3-1,3-cyclohexenylallyl)(**L**)]BF_4 **65** and **66**.

3.4.3. Conclusions

We report a new generation of phosphite-oxazoline PHOX-based ligand library for the Pd-catalyzed allylic substitution of several substrate and nucleophile types. These ligands allow us to study the influence of a second stereocentre on the ligand backbone, the substituents/configurations on the oxazoline group as well as the variation of the biaryl phosphite group, which showed to be crucial in terms of enantioselectivity. By suitable tuning the ligand parameters we have been able to achieve high activities (TOF > 8000 mol substrate×(mol Pd×h)$^{-1}$) and excellent enantioselectivities (ee's up to 99%) for a range of hindered and unhindered substrates using a wide range of C, N- and O-nucleophiles. The effect of the substituent at the alkyl chain was studied using ligands **L8**, **L9**, **L13** and **L14**, achieving the highest enantioselectivities with ligands **L8** and **L13** (ee's up to 99%) containing two or one methyl group at the alkyl backbone chain, respectively.

As for ligands **L1** and **L5-L7**, the DFT calculations agree with an early TS and the enantioselectivities can be therefore explained by both the population of the Pd-η^3-allyl intermediates and the relative electrophilicity of the allylic carbon atoms.

3.4.4. Experimental Part

3.4.4.1. General Procedures.

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 $^{13}C\{^{1}H\}$) or H_3PO_4 ($^{31}P\{^{1}H\}$) as internal standard. Racemic substrates **S1**-**S10** [21] and hydroxyl-oxazoline **1** has been prepared and characterized following a procedure already reported in the literature. Acylchlorides **5**-**7** have been synthesized and characterized following a reported procedure.[8] Acetyl hydroxyl-amides **10**-**11** and hydroxyl-oxazolines **21**-**23** have been synthesized and characterized following a reported procedure.[9-10]

3.4.4.2. Computational details.

The geometries of all intermediates were optimized using the Gaussian 09 program,[22] employing the B3LYP[23] density functional and the LANL2DZ[24] basis set for palladium and the 6-31G* basis set for all other elements.[25] Solvation correction was applied in the course of the optimizations using the PCM model with the default parameters for dichloromethane.[26] 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**[27] basis set was used for all elements except palladium, and by applying dispersion correction using DFT-D3[28] model. All energies reported are Gibbs free energies at 298.15 K and calculated as $G_{reported} = G_{6\text{-}31G^*} + (E_{6\text{-}311+G^{**}} - E_{6\text{-}31G^*}) + EDFT\text{-}D3$.

3.4.4.3. Characterization details for intermediates 6-17.

(*S*)-2-(((*S*)-2-hydroxy-1-phenylethyl)amino)-2-oxo-1-phenylethyl acetate 6. 2.66 g (85% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 2.11 (s, 3H, CH_3, OAc), 3.98 (m, 2H, CH_2-O), 5.17 (m, 1H, CH-N), 6.20 (s, 1H, CH), 6.90 (bs, 1H, NH), 7.30-7.51 (m, 10H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 21.2 (CH_3, OAc), 55.6 (CH-N), 66.2 (CH_2-O), 75.8 (CH), 126.7 (CH=), 127.5 (CH=), 127.7 (CH=), 127.8 (CH=), 128.1 (CH=),

128.9 (C=), 129.0 (CH=), 129.1 (C), 129.2 (CH=), 129.3 (CH=), 129.4 (CH=), 138.6 (C), 168.8 (C=O), 169.7 (C=O).

(*S*)-2-(((*S*)-1-hydroxy-3-methylbutan-2-yl)amino)-2-oxo-1-phenylethyl acetate 7. 2.48 g (89% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 0.90 (d, 3H, CH_3, ^{i}Pr, $^{3}J_{H-H}$= 8.0 Hz), 0.96 (d, 3H, CH_3, ^{i}Pr, $^{3}J_{H-H}$= 8.0 Hz), 1.95 (m, 1H, CH, ^{i}Pr), 2.19 (s, 3H, CH_3, OAc), 3.72 (m, 3H, CH_2-O, CH-N), 6.08 (s, 1H, CH), 6.35 (bs, 1H, NH), 7.29-7.56 (m, 5H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 19.0 (CH_3, ^{i}Pr), 19.7 (CH_3, ^{i}Pr), 21.2 (CH_3, OAc), 29.2 (CH, ^{i}Pr), 57.1 (CH-N), 63.6 (CH_2-O), 75.9 (CH), 127.5 (CH=), 129.0 (CH=), 129.2 (CH=), 135.0 (C), 168.7 (C=O), 169.8 (C=O).

(*S*)-2-(((*S*)-1-hydroxy-3,3-dimethylbutan-2-yl)amino)-2-oxo-1-phenylethyl acetate 8. ^{1}H NMR (400 MHz, $CDCl_3$): δ= 0.94 (s, 9H, CH_3, ^{t}Bu), 2.20 (s, 3H, CH_3, OAc), 3.60 (m, 1H, CH-O_{ox}), 3.80 (m, 2H, CH-O_{ox}, CH-N), 6.10 (s, 1H, CH-O), 6.34 (bs, 1H, NH), 7.34-7.47 (m, 5H, CH=).

(*S*)-2-(((*R*)-2-hydroxy-1-phenylethyl)amino)-2-oxo-1-phenylethyl acetate 9. ^{1}H NMR (400 MHz, $CDCl_3$): δ= 2.19 (s, 3H, CH_3, OAc), 3.92 (m, 2H, CH_2-O), 5.08 (m, 1H, CH-N), 6.09 (s, 1H, CH), 6.76 (bs, 1H, NH), 7.18-7.48 (m, 10H, CH=).

(*S*)-1-(((*S*)-2-hydroxy-1-phenylethyl)amino)-1-oxopropan-2-yl acetate 10. 2.0 g (90% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.38 (d, 3H, CH_3, $^{3}J_{H-H}$= 6.8 Hz), 2.03 (s, 3H, CH_3, OAc), 2.64 (bs, 1H, OH), 3.69 (m, 2H, CH_2-O), 4.94 (m, 1H, CH-N), 5.10 (q, 1H, CH, $^{3}J_{H-H}$= 6.8 Hz), 6.87 (bs, 1H, NH), 7.16-7.30 (m, 5H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 17.7 (CH_3), 20.9 (CH_3, OAc), 55.0 (CH-N), 65.3 (CH_2-O), 70.5 (CH-O), 126.5 (CH=), 127.6 (CH=), 128.6 (CH=), 138.9 (C), 169.9 (C=O), 171.0 (C=O).

(*S*)-1-(((*S*)-2-hydroxy-1-phenylethyl)amino)-3-methyl-1-oxobutan-2-yl acetate 11. 2.51 g (90% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 0.88 (m, 6H, CH_3, ^{i}Pr), 2.07 (s, 3H, CH_3, OAc), 2.19 (m, 1H, CH, ^{i}Pr), 3.23 (bs, 1H, OH), 3.66 (m, 2H, CH_2-O), 4.95 (m, 2H, CH-O, CH-N), 6.93 (bs, 1H, NH), 7.07 (d, 1H, CH=, $^{3}J_{H-H}$= 7.2 Hz), 7.21-7.29 (m, 4H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 17.1 (CH_3, ^{i}Pr), 18.6 (CH_3, ^{i}Pr), 20.7 (CH_3, OAc), 30.6 (CH, ^{i}Pr), 55.0 (CH-N), 65.3 (CH_2-O), 78.2 (CH-O), 126.6 (CH=), 127.5 (CH=), 128.6 (CH=), 139.1 (C), 169.8 (C=O), 170.4 (C=O).

(*S*)-phenyl((*S*)-4-phenyl-4,5-dihydrooxazol-2-yl)methanol 12. 1.87 g (97% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 4.18 (pt, 1H, CH-Ox, JH-H= 8.4 Hz), 4.62 (dd, 1H, CH-O_{ox}, $^{2}J_{H-H}$= 10.0 Hz, $^{3}J_{H-H}$= 8.4 Hz), 5.14 (t, 1H, CH-N, $^{3}J_{H-H}$= 9.2 Hz), 5.33 (s, 1H, CH-O), 7.18-7.45 (m, 10H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 68.8 (CH-N), 69.7 (CH-O), 76.3 (CH-O_{ox}), 126.7 (CH=), 126.8 (CH=), 126.9 (CH=), 127.9 (CH=), 128.0 (CH=), 128.6 (CH=), 128.8 (CH=), 129.0 (CH=), 139.3 (C), 141.7 (C), 170.0 (C=N).

(*S*)-((*S*)-4-isopropyl-4,5-dihydrooxazol-2-yl)(phenyl)methanol 13. ^{1}H NMR (400 MHz, $CDCl_3$): δ= 0.89 (d, 3H, CH_3, ^{i}Pr, $^{3}J_{H-H}$= 6.8 Hz), 0.98 (d, 3H, CH_3, ^{i}Pr, $^{3}J_{H-H}$= 6.8 Hz), 1.76 (m, 1H, CH, ^{i}Pr), 3.75 (bs, 1H, OH), 3.90 (m, 1H, CH-O_{ox}), 4.08 (pt, 1H, CH-O_{ox}, J_{H-H}= 8.4 Hz), 4.29 (t, 1H, CH-N, $^{3}J_{H-H}$= 8.4Hz), 5.28 (s, 1H, CH-O), 7.25-7.38 (m, 3H, CH=), 7.44-7.46 (m, 2H, CH=).

(*S*)-((*S*)-4-(*tert*-butyl)-4,5-dihydrooxazol-2-yl)(phenyl)methanol 14. ^{1}H NMR (400 MHz, $CDCl_3$): δ= 0.90 (s, 9H, CH_3, ^{t}Bu), 3.88 (m, 2H, CH-N, OH), 4.15 (m, 2H, CH_2-O), 5.30 (s, 1H, CH-O), 7.35 (m, 3H, CH=), 7.46 (m, 2H, CH=).

(*S*)-phenyl((*R*)-4-phenyl-4,5-dihydrooxazol-2-yl)methanol 15. ^{1}H NMR (400 MHz, $CDCl_3$): δ= 3.76 (bs, 1H, OH), 4.14 (pt, 1H, CH-O_{ox}, J_{H-H}= 8.8 Hz), 4.75 (dd, 1H, CH-O_{ox}, $^{2}J_{H-H}$= 10.0 Hz, $^{3}J_{H-H}$= 8.4 Hz), 5.26 (t, 1H, CH-N, $^{3}J_{H-H}$= 8.4 Hz), 5.38 (s, 1H, CH-O), 7.18 (m, 2H, CH=), -7.29-7.42 (m, 6H, CH=), 7.50 (m, 2H, CH=).

(*S*)-1-((*S*)-4-phenyl-4,5-dihydrooxazol-2-yl)ethan-1-ol 16. 1.16 g (95% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.47 (d, 3H, CH_3, $^{3}J_{H-H}$= 6.8 Hz), 3.45 (bs, 1H, OH), 4.21 (pt, 1H, CH-O_{ox}, JH-H= 8.4 Hz), 4.45 (m, 1H, CH-O), 4.72 (dd, 1H, CH-O_{ox}, $^{2}J_{H-H}$= 10.0 Hz, $^{3}J_{H-H}$= 8.4 Hz), 5.21 (t, 1H, CH-N, $^{3}J_{H-H}$= 9.2 Hz), 7.23-7.38 (m, 5H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 21.0 (CH_3), 63.7 (CH-O), 69.1 (CH-N), 76.1 (CH-O_{ox}), 126.7 (CH=), 128.0 (CH=), 129.0 (CH=), 141.8 (C), 171.5 (C=N).

(*S*)-2-methyl-1-((*S*)-4-phenyl-4,5-dihydrooxazol-2-yl)propan-1-ol 17. 1.64 g (98% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 0.96 (d, 3H, CH_3, ^{i}Pr, $^{3}J_{H-H}$= 6.4 Hz), 1.06 (d, 3H, CH^3, ^{i}Pr, $^{3}J_{H-H}$= 6.4 Hz), 2.08 (m, 1H, CH, ^{i}Pr), 2.94 (bs, 1H, OH), 4.22 (m, 2H, CH-O_{ox}, CH-O), 4.73 (t, 1H, CH-N, $^{3}J_{H-H}$= 8.4 Hz), 5.21 (pt, 1H, CH-O_{ox}, J_{H-H}= 8.4 Hz), 7.24-7.38 (m, 5H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 16.5 (CH_3, ^{i}Pr), 18.8 (CH_3, ^{i}Pr), 32.5 (CH, ^{i}Pr), 68.9 (CH_2-O_{ox}), 72.2 (CH-N), 76.1 (CH-O), 126.7 (CH=), 127.9 (CH=), 129.0 (CH=), 141.7 (C), 171.0 (C=N).

3.4.4.4. Typical procedure for the preparation of phosphite-oxazoline ligands L8-L14a-c.

To a solution of *in situ* generated phosphochloridite (1.1 mmol) in dry toluene (6 mL), pyridine (0.16 mL, 2.0 mmol) was added. Then, this solution was placed in a -78 ºC bath. After 2 min at that temperature, a solution of the alcohol-oxazoline (1.0 mmol) and pyridine (0.16 mL, 2.0 mmol) in toluene (6 mL) was added dropwise at -78 °C. The mixture was left to warm to room temperature and stirred overnight at this temperature. The precipitate formed was filtered under argon and the solvent was evaporated under vacuum. The residue was purified by flash chromatography (under argon, using neutral alumina and dry toluene as eluent system) to afford the corresponding phosphite-oxazoline **L8**-**L14a**-**c** as white solids.

L8b: Yield: 398.3 mg (60%); ^{31}P NMR (161.9 MHz, C_6D_6): δ = 153.9 (s); ^{1}H NMR (400 MHz, C_6D_6): δ = 0.52 (s, 9H, CH_3, $SiMe_3$), 0.57 (s, 9H, CH_3, $SiMe_3$), 1.57 (s, 3H, CH_3), 1.74 (s, 3H, CH_3), 3.76 (pt, 1H, CH-O, J_{H-H}= 8.4 Hz), 4.07 (dd, 1H, CH-O, $^{2}J_{H-H}$= 10.0 Hz; $^{3}J_{H-H}$= 8.4 Hz), 4.92 (dd, 1H, CH-N, $^{2}J_{H-H}$= 10.0 Hz, $^{3}J_{H-H}$= 8.4 Hz), 6.82 (m, 2H, CH=), 6.96-7.13 (m, 7H, CH=), 7.26 (d, 1H, CH=, $^{3}J_{H-H}$= 8.4 Hz), 7.27 (d, 1H, CH=, $^{3}J_{H-H}$= 8.4 Hz), 7.66 (m, 2H, CH=), 8.09 (s, 1H, CH=), 8.15 (s, 1H, CH=). ^{13}C (100.6 MHz, C_6D_6): δ= -0.3 (d, CH_3, $SiMe_3$, J_{C-P}= 4.52 Hz), 0.4 (CH_3, $SiMe_3$), 28.2 (d, CH_3, $^{3}J_{C-P}$= 3.82 Hz), 28.7 (d, CH_3, $^{3}J_{C-P}$= 7.74 Hz), 69.8 (CH-N), 74.9 (CH_2-O), 76.2 (d, C, CMe_2, $^{3}J_{C-P}$= 5.33 Hz), 122.6-152.4 (aromatic carbons), 169.1 (C=N). TOF-MS (ESI+): m/z = 686,2285, calcd. for $C_{38}H_{42}NNaO_4PSi_2$ $[M+Na]^+$: 686,2282.

L8c: Yield: 331.9 mg (50%); ^{31}P NMR (161.9 MHz, C_6D_6): δ = 153.6 (s); ^{1}H NMR (400 MHz, C_6D_6): δ = 0.53 (s, 9H, CH_3, $SiMe_3$), 0.589 (s, 9H, CH_3, $SiMe_3$), 1.62 (s, 3H, CH_3), 1.77 (s, 3H, CH_3), 3.65 (pt, 1H, CH-O, J_{H-H}= 8.0 Hz), 4.06 (dd, 1H, CH-O, $^{2}J_{H-H}$= 10.8 Hz; $^{3}J_{H-H}$= 8.8 Hz), 4.92 (dd, 1H, CH-N, $^{2}J_{H-H}$= 10.0 Hz, $^{3}J_{H-H}$= 8.0 Hz), 6.81 (m, 2H, CH=), 6.95-7.11 (m, 7H, CH=), 7.26 (m, 2H, CH=), 7.67 (m, 2H, CH=), 8.11 (s, 1H, CH=), 8.15 (s, 1H, CH=). ^{13}C (100.6 MHz, C_6D_6): δ= -0.3 (d, CH_3, $SiMe_3$, J_{C-P}= 4.62 Hz), 0.4 (CH_3, $SiMe_3$), 28.0 (d, CH_3, $^{3}J_{C-P}$= 3.92 Hz), 28.7 (d, CH_3, $^{3}J_{C-P}$= 6.94 Hz), 69.5 (CH-N), 74.8 (CH_2-O), 75,9 (d, C, CMe_2, $^{3}J_{C-P}$= 5.33 Hz), 122.5-152.4 (aromatic carbons), 169.0 (C=N). TOF-MS (ESI+): m/z = 686,2280, calcd. for $C_{38}H_{42}NNaO_4PSi_2$ $[M+Na]^+$: 686,2282.

L9a: Yield: 339.0 mg (49%); ^{31}P NMR (161.9 MHz, C_6D_6): δ = 139.2 (s); ^{1}H NMR (400 MHz, C_6D_6): δ = 1.20 (s, 18H, CH_3, ^{t}Bu), 1.27 (s, 9H, CH_3, ^{t}Bu), 1.49 (s, 9H, CH_3, ^{t}Bu), 3.64 (pt, 1H, CH-O_{ox}, J_{H-H}= 8.8 Hz), 4.07 (pt, 1H, CH-O_{ox}, J_{H-H}= 8.4 Hz), 4.90 (pt, 1H, CH-N, J_{H-H}= 8.8 Hz), 6.08 (d, 1H, CH-OP, $^{3}J_{H-P}$= 10.0 Hz), 6.89-7.11 (m, 8H, CH=), 7.27 (d, 1H, CH=, $^{4}J_{H-H}$= 2.0 Hz), 7.29 (d, 1H, CH=, $^{4}J_{H-H}$= 2.8 Hz), 7.39 (d, 2H, CH=, $^{3}J_{H-H}$= 7.2 Hz), 7.49 (d, 1H, CH=, $^{4}J_{H-H}$= 2.4 Hz), 7.57 (d, 1H, CH=, $^{4}J_{H-H}$= 2.8 Hz). ^{13}C (100.6 MHz, C_6D_6): δ= 30.7 (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), 35.1 (C, ^{t}Bu), 35.3 (C, ^{t}Bu), 69.3 (CH-N), 73.1 (CH-OP), 74.6 (CH_2-O_{ox}), 124.0-146.6 (aromatic carbons), 166.1 (C=N). TOF-MS (ESI+): m/z = 714,3682 calcd. for $C_{44}H_{54}NNaO_4P$ $[M+Na]^+$: 714,3683.

L9b: Yield: 398.7 mg (56%); ^{31}P NMR (161.9 MHz, C_6D_6): δ = 139.8 (s); ^{1}H NMR (400 MHz, C_6D_6): δ = 0.33 (s, 9H, CH_3, $SiMe_3$), 0.48 (s, 9H, CH_3, $SiMe_3$), 3.68 (pt, 1H, CH-O_{ox}, J_{H-H}= 8.0 Hz), 4.07 (dd, 1H, CH-O_{ox}, $^{2}J_{H-H}$= 10.0 Hz; $^{3}J_{H-H}$= 8.0 Hz), 4.92 (dd, 1H, CH-N, $^{2}J_{H-H}$= 10.0 Hz, $^{3}J_{H-H}$= 8.8 Hz), 5.95 (d, 1H, CH-OP, $^{3}J_{H-P}$= 9.6 Hz), 6.83 (m, 3H, CH=), 6.92-7.06 (m, 6H, CH=), 7.09-7.18 (m, 3H, CH=), 7.24 (m, 2H, CH=), 7.33 (d, 1H, CH=, $^{3}J_{H-H}$= 8.4 Hz), 7.69 (d, 1H, CH=, $^{3}J_{H-H}$= 8.4 Hz), 7.73 (d, 1H, CH=, $^{3}J_{H-H}$= 8.0 Hz), 8.04 (s, 1H, CH=), 8.13 (s, 1H, CH=). ^{13}C (100.6 MHz, C_6D_6): δ= -0.3 (CH_3, $SiMe_3$), -0.2 (CH_3, $SiMe_3$), 69.3 (CH-N), 72.9 (CH-OP), 74.6 (CH_2-O_{ox}), 122.1-152.2

(aromatic carbons), 165.8 (C=N). TOF-MS (ESI+): m/z = 734,2278 calcd. for $C_{42}H_{42}NNaO_4PSi_2$ $[M+Na]^+$: 734,2282.

L9c: Yield: 484.1 mg (68%); ^{31}P NMR (161.9 MHz, C_6D_6): $\delta = 140.7$ (s); ^1H NMR (400 MHz, C_6D_6): δ = 0.32 (s, 9H, CH_3, $SiMe_3$), 0.56 (s, 9H, CH_3, $SiMe_3$), 3.59 (pt, 1H, CH-O_{ox}, J_{H-H}= 8.4 Hz), 4.05 (dd, 1H, CH-O_{ox}, $^2J_{H-H}$= 10.0 Hz; $^3J_{H-H}$= 8.8 Hz), 4.83 (dd, 1H, CH-N, $^2J_{H-H}$= 9.6 Hz, $^3J_{H-H}$= 7.6 Hz), 5.93 (d, 1H, CH-OP, $^3J_{H-P}$= 9.6 Hz), 6.80-7.05 (m, 7H, CH=), 7.09 (m, 4H, CH=), 7.26 (d, 1H, CH=, $^3J_{H-H}$= 8.8 Hz), 7.35 (m, 3H, CH=), 7.66 (d, 1H, CH=, $^3J_{H-H}$= 7.6 Hz), 7.71 (d, 1H, CH=, $^3J_{H-H}$= 8.0 Hz), 8.06 (s, 1H, CH=), 8.22 (s, 1H, CH=). ^{13}C (C_6D_6): δ= -0.4 (CH_3, $SiMe_3$), 0.0 (CH_3, $SiMe_3$), 69.2 (CH-N), 73.6 (CH-OP), 74.5 (CH_2-O_{ox}), 122.6-152.3 (aromatic carbons), 165.3 (C=N). TOF-MS (ESI+): m/z = 734,2281, calcd. for $C_{42}H_{42}NNaO_4PSi_2$ $[M+Na]^+$: 734,2282.

L10a: Yield: 395.5 mg (52%); ^{31}P NMR (161.9 MHz, C_6D_6): $\delta = 139.2$ (s); ^1H NMR (400 MHz, C_6D_6): δ = 0.55 (d, 3H, CH_3, ^{i}Pr, $^3J_{H-H}$= 6.4 Hz), 0.76 (d, 3H, CH_3, ^{i}Pr, $^3J_{H-H}$= 6.4 Hz), 1.28 (s, 9H, CH_3, ^{t}Bu), 1.29 (s, 9H, CH_3, ^{t}Bu), 1.34 (s, 9H, CH_3, ^{t}Bu), 1.35 (m, 1H, CH, ^{i}Pr), 1.54 (s, 9H, CH_3, ^{t}Bu), 3.64 (pt, 1H, CH-O_{ox}, J_{H-H}= 8.4 Hz), 3.62 (m, 1H, CH-N), 3.85 (dd, 1H, CH-O_{ox}, $^2J_{H-H}$= 9.2 Hz, $^3J_{H-H}$= 8.0 Hz), 6.04 (d, 1H, CH-OP, $^3J_{H-P}$= 10.0 Hz), 6.99-7.15 (m, 3H, CH=), 7.27 (d, 1H, CH=, $^4J_{H-H}$= 2.8 Hz), 7.29 (d, 1H, CH=, $^4J_{H-H}$= 2.4 Hz), 7.38 (m, 2H, CH=), 7.51 (d, 1H, CH=, $^4J_{H-H}$= 2.8 Hz), 7.59 (d, 1H, CH=, $^4J_{H-H}$= 2.4 Hz). ^{13}C (100.6 MHz, C_6D_6): δ= 18.8 (CH_3, ^{i}Pr), 19.2 (CH_3, ^{i}Pr), 31.4 (CH_3, ^{t}Bu), 31.7 (CH_3, ^{t}Bu), 31.8 (CH_3, ^{t}Bu), 31.9 (CH_3, ^{t}Bu), 33.4 (CH, ^{i}Pr), 35.0 (C, ^{t}Bu), 35.8 (C, ^{t}Bu), 35.9 (C, ^{t}Bu), 71.1 (CH_2-O_{ox}), 72.9 (CH-N), 73.9 (CH-OP), 124.7-147.2 (aromatic carbons), 165.2 (C=N). TOF-MS (ESI+): m/z = 680,3839 calcd. for $C_{41}H_{56}NNaO_4P$ $[M+Na]^+$: 680,3839.

L11a: Yield: 436.0 mg (67%); ^{31}P NMR (161.9 MHz, C_6D_6): $\delta = 139.4$ (s); ^1H NMR (400 MHz, C_6D_6): δ = 0.61 (s, 9H, CH_3, ^{t}Bu), 1.28 (s, 9H, CH_3, ^{t}Bu), 1.29 (s, 9H, CH_3, ^{t}Bu), 1.37 (s, 9H, CH_3, ^{t}Bu), 1.55 (s, 9H, CH_3, ^{t}Bu), 3.69 (m, 2H, CH-O_{ox}, CH-N), 3.88 (dd, 1H, CH-O_{ox}, $^2J_{H-H}$= 9.2 Hz, $^3J_{H-H}$= 7.6 Hz), 6.07 (d, 1H, CH-OP, $^3J_{H-P}$= 9.6 Hz), 6.99-7.15 (m, 3H, CH=), 7.27 (d, 1H, CH=, $^4J_{H-H}$= 2.4 Hz), 7.31 (d, 1H, CH=, $^4J_{H-H}$= 2.4 Hz), 7.41 (m, 2H, CH=), 7.52 (d, 1H, CH=, $^4J_{H-H}$= 2.4 Hz), 7.60 (d, 1H, CH=, $^4J_{H-H}$= 2.4 Hz). ^{13}C (100.6 MHz, C_6D_6): δ= 26.0 (CH_3, ^{t}Bu), 31.4 (CH_3, ^{t}Bu), 31.6 (CH_3, ^{t}Bu), 31.7 (CH_3, ^{t}Bu), 31.9 (CH_3, ^{t}Bu), 34.2 (C, ^{t}Bu), 35.0 (C, ^{t}Bu), 35.1 (C, ^{t}Bu), 35.8 (C, ^{t}Bu), 35.9 (C, ^{t}Bu), 69.2 (CH_2-O_{ox}), 74.0 (CH-OP), 76.1 (CH-N), 124.7-147.3 (aromatic carbons), 165.2 (C=N). TOF-MS (ESI+): m/z = 694,3995 calcd. for $C_{42}H_{58}NNaO_4P$ $[M+Na]^+$: 694,3996.

L12a: Yield: 420.3 mg (60%); ^{31}P NMR (161.9 MHz, C_6D_6): $\delta = 139.2$ (s); ^1H NMR (400 MHz, C_6D_6): δ = 1.29 (s, 9H, CH_3, ^{t}Bu), 1.30 (s, 9H, CH_3, ^{t}Bu), 1.33 (s, 9H, CH_3, ^{t}Bu), 1.52 (s, 9H, CH_3, ^{t}Bu), 3.62 (pt, 1H, CH-O_{ox}, J_{H-H}= 8.4 Hz), 3.99 (dd, 1H, CH-O_{ox}, $^2J_{H-H}$= 10.4 Hz, $^3J_{H-H}$= 8.4 Hz), 4.92 (pt, 1H, CH-N, J_{H-H}= 10.0 Hz), 6.01 (d, 1H, CH-OP,

$^{3}J_{H-P}$= 9.6 Hz), 6.99-7.14 (m, 8H, CH=), 7.32 (m, 2H, CH=), 7.39 (m, 2H, CH=), 7.53 (d, 1H, CH=, $^{4}J_{H-H}$= 2.4 Hz), 7.60 (d, 1H, CH=, $^{4}J_{H-H}$= 2.0 Hz). ^{13}C (100.6 MHz, C_6D_6): δ= 31.4 (CH_3, ^{t}Bu), 31.5 (CH_3, ^{t}Bu), 31.6 (CH_3, ^{t}Bu), 31.9 (CH_3, ^{t}Bu), 35.0 (C, ^{t}Bu), 35.9 (C, ^{t}Bu), 36.0 (C, ^{t}Bu), 70.0 (CH-N), 73.8 (CH-OP), 75.3 (CH_2-O_{ox}), 124.7-147.3 (aromatic carbons), 167.0 (C=N). TOF-MS (ESI+): m/z = 714,3681 calcd. for $C_{44}H_{54}NNaO_4P$ $[M+Na]^+$: 714,3683.

L12b: Yield: 440.1 mg (65%); ^{31}P NMR (161.9 MHz, C_6D_6): δ = 137.9 (s); ^{1}H NMR (400 MHz, C_6D_6): δ = 0.30 (s, 9H, CH_3, $SiMe_3$), 0.50 (s, 9H, CH_3, $SiMe_3$), 3.61 (pt, 1H, CH-O_{ox}, J_{H-H}= 8.4 Hz), 3.92 (dd, 1H, CH-O_{ox}, $^{2}J_{H-H}$= 10.0 Hz; $^{3}J_{H-H}$= 8.0 Hz), 4.92 (m, 1H, CH-N), 5.70 (d, 1H, CH-OP, $^{3}J_{H-P}$= 9.2 Hz), 6.86 (m, 2H, CH=), 6.98-7.06 (m, 6H, CH=), 7.10-7.24 (m, 6H, CH=), 7.26 (d, 1H, CH=, $^{3}J_{H-H}$= 8.8 Hz), 7.42 (d, 1H, CH=, $^{3}J_{H-H}$= 8.8 Hz), 7.70 (d, 1H, CH=, $^{3}J_{H-H}$= 8.4 Hz), 7.77 (d, 1H, CH=, $^{3}J_{H-H}$= 8.0 Hz), 8.04 (s, 1H, CH=), 8.13 (s, 1H, CH=). ^{13}C (100.6 MHz, C_6D_6): δ= 0.3 (d, CH_3, $SiMe_3$, J_{C-P}= 3.1 Hz), 0.4 (CH_3, $SiMe_3$), 69.7 (CH-N), 73.5 (d, CH-OP, J_{C-P}= 5.33 Hz), 75.4 (CH_2-O_{ox}), 123.3-153.0 (aromatic carbons), 166.8 (C=N). TOF-MS (ESI+): m/z = 734,2280 calcd. for $C_{42}H_{42}NNaO_4PSi_2$ $[M+Na]^+$: 734,2282.

L12c: Yield: 498.6 mg (71%); ^{31}P NMR (161.9 MHz, C_6D_6): δ = 143.1 (s); ^{1}H NMR (400 MHz, C_6D_6): δ = 0.33 (s, 9H, CH_3, $SiMe_3$), 0.50 (s, 9H, CH_3, $SiMe_3$), 3.52 (dd, 1H, CH-O_{ox}, $^{2}J_{H-H}$= 9.2 Hz; $^{3}J_{H-H}$= 8.4 Hz), 3.91 (dd, 1H, CH-O_{ox}, $^{2}J_{H-H}$= 10.0 Hz; $^{3}J_{H-H}$= 8.4 Hz), 4.74 (pt, 1H, CH-N, J_{H-H}= 10.0 Hz), 5.87 (d, 1H, CH-OP, $^{3}J_{H-P}$= 8.8 Hz), 6.83-7.17 (m, 12H, CH=), 7.27 (d, 1H, CH=, $^{3}J_{H-H}$= 8.4 Hz), 7.36 (d, 1H, CH=, $^{3}J_{H-H}$= 8.4 Hz), 7.41 (m, 2H, CH=), 7.67 (d, 1H, CH=, $^{3}J_{H-H}$= 8.0 Hz), 7.77 (d, 1H, CH=, $^{3}J_{H-H}$= 8.0 Hz), 8.06 (s, 1H, CH=), 8.19 (s, 1H, CH=). ^{13}C (100.6 MHz, C_6D_6): δ= 0.7 (d, CH_3, $SiMe_3$, J_{C-P}= 4.52 Hz), 1.0 (CH_3, $SiMe_3$), 70.4 (CH-N), 74.5 (CH-OP), 75.3 (CH_2-O_{ox}), 125.9-153.4 (aromatic carbons), 166.6 (C=N). TOF-MS (ESI+): m/z = 734,2281 calcd. for $C_{42}H_{42}NNaO_4PSi_2$ $[M+Na]^+$: 734,2282.

L13a: Yield: 445.3 mg (65%); ^{31}P NMR (161.9 MHz, C_6D_6): δ = 144.6 (s); ^{1}H NMR (400 MHz, C_6D_6): δ = 1.25 (s, 9H, CH_3, ^{t}Bu), 1.27 (s, 9H, CH_3, ^{t}Bu), 1.45 (d, 3H, CH_3, $3J_{H-H}$= 6.4 Hz), 1.59 (s, 9H, CH_3, ^{t}Bu), 1.60 (s, 9H, CH_3, ^{t}Bu), 3.77 (pt, 1H, CH-O_{ox}, J_{H-H}= 8.8 Hz), 4.14 (dd, 1H, CH-O_{ox}, $^{2}J_{H-H}$= 10.4 Hz, $^{3}J_{H-H}$= 8.4 Hz), 4.92 (pt, 1H, CH-N, J_{H-H}= 10.0 Hz), 5.18 (m, 1H, CH-OP), 6.99-7.14 (m, 5H, CH=), 7.33 (m, 2H, CH=), 7.60 (m, 2H, CH=). ^{13}C (100.6 MHz, C_6D_6): δ= 20.7 (d, CH_3, $^{3}J_{C-P}$= 3.01 Hz), 31.8 (CH_3, ^{t}Bu), 31.9 (CH_3, ^{t}Bu), 32.0 (CH_3, ^{t}Bu), 32.1 (CH_3, ^{t}Bu), 35.0 (C, ^{t}Bu), 36.0 (C, ^{t}Bu), 36.1 (C, ^{t}Bu), 67.9 (d, CH-OP, $^{2}J_{C-P}$= 9.95 Hz), 70.2 (CH-N), 75.3 (CH_2-O_{ox}), 124.7-147.2 (aromatic carbons), 167.6 (C=N). TOF-MS (ESI+): m/z = 652,3525 calcd. for $C_{39}H_{52}NNaO_4P$ $[M+Na]^+$: 652,3526.

L13b: Yield: 398.0 mg (58%); ^{31}P NMR (161.9 MHz, C_6D_6): δ = 142.7 (s); ^{1}H NMR (400 MHz, C_6D_6): δ = 0.54 (s, 9H, CH_3, $SiMe_3$), 0.55 (s, 9H, CH_3, $SiMe_3$), 1.27 (d, 3H, CH_3,

$^3J_{H-H}$= 6.8 Hz), 3.76 (pt, 1H, CH-O_{ox}, J_{H-H}= 8.8 Hz), 4.15 (dd, 1H, CH-O_{ox}, $^2J_{H-H}$= 10.0 Hz; $^3J_{H-H}$= 8.8 Hz), 4.91 (pt, 1H, CH-N, J_{H-H}= 9.2 Hz), 5.13 (m, 1H, CH-OP), 6.86 (m, 2H, CH=), 6.99-7.15 (m, 7H, CH=), 7.27 (d, 1H, CH=, $^3J_{H-H}$= 8.4 Hz), 7.36 (d, 1H, CH=, $^3J_{H-H}$= 8.0 Hz), 7.70 (d, 2H, CH=, $^3J_{H-H}$= 8.4 Hz), 8.13 (s, 1H, CH=), 8.15 (s, 1H, CH=). ^{13}C (100.6 MHz, C_6D_6): δ= 0.4 (d, CH_3, $SiMe_3$, J_{C-P}= 5.33 Hz), 0.8 (CH_3, $SiMe_3$), 20.4 (d, CH_3, $^3J_{C-P}$= 1.06 Hz), 67.3 (CH-OP), 70.2 (CH-N), 75.2 (CH_2-O_{ox}), 123.3-152.9 (aromatic carbons), 167.3 (C=N). TOF-MS (ESI+): m/z = 672,2124 calcd. for $C_{37}H_{40}NNaO_4PSi_2$ $[M+Na]^+$: 672,2126.

L13c: Yield: 405.0 mg (59%); ^{31}P NMR (161.9 MHz, C_6D_6): δ = 144.7 (s); ^{1}H NMR (400 MHz, C_6D_6): δ = 0.55 (s, 9H, CH_3, $SiMe_3$), 0.56 (s, 9H, CH_3, $SiMe_3$), 1.51 (d, 3H, CH_3, $^3J_{H-H}$= 6.8 Hz), 3.67 (pt, 1H, CH-O_{ox}, J_{H-H}= 8.4 Hz), 4.01 (dd, 1H, CH-O_{ox}, $^2J_{H-H}$= 10.0 Hz; $^3J_{H-H}$= 8.4 Hz), 4.85 (dd, 1H, CH-N, $^2J_{H-H}$= 10.0 Hz, $^3J_{H-H}$= 8.4 Hz), 5.05 (m, 1H, CH-OP), 6.86 (m, 2H, CH=), 6.86 (m, 2H, CH=), 6.99-7.15 (m, 7H, CH=), 7.27 (d, 1H, CH=, $^3J_{H-H}$= 8.4 Hz), 7.34 (d, 1H, CH=, $^3J_{H-H}$= 8.0 Hz), 7.70 (pt, 2H, CH=, J_{H-H}= 7.6 Hz), 8.12 (s, 1H, CH=), 8.16 (s, 1H, CH=). ^{13}C (100.6 MHz, C_6D_6): δ= 0.5 (d, CH_3, $SiMe_3$, J_{C-P}= 4.52 Hz), 0.8 (CH_3, $SiMe_3$), 21.5 (d, CH_3, $^3J_{C-P}$= 3.02 Hz), 68.7 (d, CH-OP, $^2J_{C-P}$= 6.16 Hz), 70.0 (CH-N), 75.2 (CH_2-O_{ox}), 122.6-153.0 (aromatic carbons), 166.9 (C=N). TOF-MS (ESI+): m/z = 672,2125 calcd. for $C_{37}H_{40}NNaO_4PSi_2$ $[M+Na]^+$: 672,2126.

L14a: Yield: 429.0 mg (60%); ^{31}P NMR (161.9 MHz, C_6D_6): δ = 146.2 (s); ^{1}H NMR (400 MHz, C_6D_6): δ = 0.95 (d, 3H, CH_3, ^{i}Pr, $^3J_{H-H}$= 7.2 Hz), 1.00 (d, 3H, CH_3, ^{i}Pr, $^3J_{H-H}$= 7.2 Hz), 1.26 (s, 18H, CH_3, ^{t}Bu), 1.59 (s, 9H, CH_3, ^{t}Bu), 1.62 (s, 9H, CH_3, ^{t}Bu), 2.26 (m, 1H, CH, ^{i}Pr), 3.775 (pt, 1H, CH-O_{ox}, J_{H-H}= 8.8 Hz), 4.15 (dd, 1H, CH-O_{ox}, $^2J_{H-H}$= 10.0 Hz, $^3J_{H-H}$= 8.0 Hz), 4.97 (m, 2H, CH-N, CH-OP), 6.98-7.14 (m, 5H, CH=), 7.32 (m, 2H, CH=), 7.58 (m, 2H, CH=). ^{13}C (100.6 MHz, C_6D_6): δ= 18.6 (CH_3, ^{i}Pr), 18.7 (CH_3, ^{i}Pr), 31.7 (CH_3, ^{t}Bu), 31.8 (CH_3, ^{t}Bu), 31.9 (CH_3, ^{t}Bu), 32.0 (CH_3, ^{t}Bu), 32.7 (d, CH, ^{i}Pr, $^3J_{C-P}$= 2.3 Hz), 35.0 (C, ^{t}Bu), 35.1 (C, ^{t}Bu), 36.0 (C, ^{t}Bu), 36.1 (C, ^{t}Bu), 70.2 (CH-N), 75.0 (CH_2-O_{ox}), 76.3 (d, CH-OP, $^2J_{C-P}$= 8.34 Hz), 124.6-147.2 (aromatic carbons), 166.1 (C=N). TOF-MS (ESI+): m/z = 680,3842 calcd. for $C_{41}H_{56}NNaO_4P$ $[M+Na]^+$: 680,3839.

L14b: Yield: 480.3 mg (68%); ^{31}P NMR (161.9 MHz, C_6D_6): δ = 149.0 (s); ^{1}H NMR (400 MHz, C_6D_6): δ = 0.56 (s, 9H, CH_3, $SiMe_3$), 0.60 (s, 9H, CH_3, $SiMe_3$), 0.72 (d, 3H, CH_3, ^{i}Pr, $^3J_{H-H}$= 6.8 Hz), 0.82 (d, 3H, CH_3, ^{i}Pr, $^3J_{H-H}$= 6.8 Hz), 2.20 (m, 1H, CH, ^{i}Pr), 3.80 (pt, 1H, CH-O_{ox}, J_{H-H}= 8.8 Hz), 4.22 (dd, 1H, CH-O_{ox}, $^2J_{H-H}$= 10.4 Hz; $^3J_{H-H}$= 8.8 Hz), 4.77 (dd, 1H, CH-OP, $^3J_{H-P}$= 9.6 Hz; $^3J_{H-H}$= 6.8 Hz), 5.03 (pt, 1H, CH-N, J_{H-H}= 10.4 Hz), 6.86 (m, 2H, CH=), 6.99-7.15 (m, 7H, CH=), 7.28 (d, 1H, CH=, $^3J_{H-H}$= 8.8 Hz), 7.33 (d, 1H, CH=, $^3J_{H-H}$= 8.4 Hz), 7.71 (t, 2H, CH=, $^3J_{H-H}$= 7.2 Hz), 8.12 (s, 1H, CH=), 8.18 (s, 1H, CH=). ^{13}C (100.6 MHz, C_6D_6): δ= 0.5 (d, CH_3, $SiMe_3$, J_{C-P}= 3.82 Hz), 0.8 (CH_3, $SiMe_3$), 18.4 (CH_3, ^{i}Pr), 18.6 (CH_3, ^{i}Pr), 32.6 (CH, ^{i}Pr), 70.3 (CH-N), 75.2 (CH_2-O_{ox}),

75.8 (CH-OP), 123.3-153.0 (aromatic carbons), 165.9 (C=N). TOF-MS (ESI+): m/z = 700,2441 calcd. for $C_{39}H_{44}NNaO_4PSi_2$ $[M+Na]^+$: 700,2439.

L14c: Yield: 481.0 mg (69%); ^{31}P NMR (161.9 MHz, C_6D_6): $\delta = 147.3$ (s); ^1H NMR (400 MHz, C_6D_6): δ = 0.56 (s, 9H, CH_3, $SiMe_3$), 0.60 (s, 9H, CH_3, $SiMe_3$), 0.93 (d, 3H, CH_3, ^iPr, $^3J_{H-H}$= 6.8 Hz), 1.06 (d, 3H, CH_3, ^iPr, $^3J_{H-H}$= 6.8 Hz), 2.33 (m, 1H, CH, ^iPr), 3.52 (pt, 1H, CH-O_{ox}, J_{H-H}= 8.8 Hz), 3.81 (dd, 1H, CH-O_{ox}, $^2J_{H-H}$= 10.4 Hz; $^3J_{H-H}$= 8.4 Hz), 4.05 (pt, 1H, CH-N, J_{H-H}= 9.2 Hz), 4.96 (pt, 1H, CH-OP, J_{H-H}= 7.6 Hz), 6.83 (m, 2H, CH=), 6.96-7.15 (m, 7H, CH=), 7.24 (d, 1H, CH=, $^3J_{H-H}$= 8.8 Hz), 7.30 (d, 1H, CH=, $^3J_{H-H}$= 8.4 Hz), 7.69 (t, 2H, CH=, $^3J_{H-H}$= 8.8 Hz), 8.18 (s, 2H, CH=). ^{13}C (100.6 MHz, C_6D_6): δ= 0.5 (d, CH_3, $SiMe_3$, J_{C-P}= 4.60 Hz), 0.8 (CH_3, $SiMe_3$), 18.7 (CH_3, ^iPr), 19.5 (CH_3, ^iPr), 32.7 (d, CH, ^iPr, $^3J_{H-P}$= 4.62 Hz), 69.7 (CH-N), 74.7 (CH_2-O_{ox}), 77.0 (CH-OP), 123.2-153.1 (aromatic carbons), 165.2 (C=N). TOF-MS (ESI+): m/z = 700,2438 calcd. for $C_{39}H_{44}NNaO_4PSi_2$ $[M+Na]^+$: 700,2439.

3.4.4.5. General procedure for the preparation of [Pd(η³-allyl)(P-N)]BF_4 complexes 63-66

The corresponding ligand (0.05 mmol) and the complex [Pd(μ-Cl)(η³-1,3-allyl)]$_2$ (0.025 mmol) were dissolved in CD_2Cl_2 (1.5 mL) at room temperature under argon. $AgBF_4$ (9.8 mg, 0.05 mmol) was added after 30 minutes and the mixture was stirred for 30 minutes. The mixture was then filtered over celite under argon and the resulting solutions were analyzed by NMR. After the NMR analysis, the complexes were precipitated as pale yellow solids by adding hexane.

Pd-Ph-allyl-L9c (63). Major isomer (75%). ^{31}P NMR (161.9 MHz, CD_2Cl_2): $\delta = 139.1$ ppm (s); ^1H NMR (400 MHz, CD_2Cl_2): d = 0.30 (s, 9H, CH_3, $SiMe_3$), 0.54 (s, 9H, CH_3, $SiMe_3$), 4.38 (m, 1H, CH_2), 4.47 (m, 1H, CH= *trans* to N), 5.01 (m, 2H, CH_2, CH-N), 5.96 (m, 1H, CH^c=), 6.15 (m, 2H, CH-O, CH= *trans* to P), 7.1-8.2 (m, 30H, CH=). ^{13}C (100.6 MHz, CD_2Cl_2): δ= -0.1 (CH_3, $SiMe_3$), 0.6 (CH_3, $SiMe_3$), 67.7 (CH-N), 67.9 (d, CH= *trans* to N, J_{C-P}= 10.7 Hz), 76.3 (CH-OP), 78.0 (CH_2), 108.1 (d, CH= *trans* to P, J_{C-P}= 29.8 Hz), 112.6 (d, CH^c=, J_{C-P}= 9.9 Hz), 120.0-150.0 (aromatic carbons), 169.5 (C=N). Minor isomer (25%).^{31}P NMR (161.9 MHz, CD_2Cl_2): $\delta = 140.2$ ppm (s); ^1H NMR (400 MHz, CD_2Cl_2): d = 0.20 (s, 9H, CH_3, $SiMe_3$), 0.39 (s, 9H, CH_3, $SiMe_3$), 4.35 (m, 1H, CH_2), 4.74 (m, 1H, CH-N), 5.01 (m, 1H, CH_2), 5.23 (m, 1H, CH= *trans* to N), 5.27 (m, 1H, CH= *trans* to P), 5.60 (m, 1H, CH^c=), 6.15 (m, 1H, CH-OP), 7.1-8.2 (m, 25H, CH=). ^{13}C (100.6 MHz, CD_2Cl_2): δ= -0.5 (CH_3, $SiMe_3$), -0.2 (CH_3, $SiMe_3$), 68.9 (CH-N), 74.1 (d, CH= *trans* to N, J_{C-P}= 10.7 Hz), 75.9 (CH-OP), 77.6 (CH_2), 95.9 (d, CH= *trans* to P, J_{C-P}= 42 Hz), 109.2 (d, CH^c=, J_{C-P}= 13 Hz), 120.0-150.0 (aromatic carbons), 170.2 (C=N).

Pd-Ph-allyl-L13c (64). Major isomer (91%). ^{31}P NMR (161.9 MHz, CD_2Cl_2): δ = 140.3 ppm (s); ^{1}H NMR (400 MHz, CD_2Cl_2): d = 0.46 (s, 9H, CH_3, $SiMe_3$), 0.74 (s, 9H, CH_3, $SiMe_3$), 1.96 (d, 3H, CH_3, $^3J_{H-H}$= 6.8 Hz), 4.33 (dd, 1H, CH_2, $^2J_{H-H}$= 8.8 Hz, $^3J_{H-H}$= 4.8 Hz), 4.51 (m, 1H, CH= *trans* to N), 4.88 (m, 1H, CH-N), 5.00 (m, 1H, CH_2), 5.12 (m, 1H, CH-OP), 6.02 (m, 2H, CH^c=, CH= *trans* to P), 6.3-8.4 (m, 25H, CH=). ^{13}C (100.6 MHz, CD_2Cl_2): δ= -0.1 (CH_3, $SiMe_3$), 0.8 (CH_3, $SiMe_3$), 22.6 (b, CH_3), 67.3 (CH-N), 68.3 (d, CH= *trans* to N, J_{C-P}= 9.9 Hz), 71.5 (CH-OP), 78.2 (CH_2), 106.8 (d, CH= *trans* to P, J_{C-P}= 30.4 Hz), 112.2 (d, CH^c=, J_{C-P}= 9.8 Hz), 121.0-150.0 (aromatic carbons), 172.1 (C=N). Minor isomer (9%).^{31}P NMR (161.9 MHz, CD_2Cl_2): δ = 142.9 ppm (s); ^{1}H NMR (400 MHz, CD_2Cl_2): d = 0.41 (s, 9H, CH_3, $SiMe_3$), 0.62 (s, 9H, CH_3, $SiMe_3$), 1.75 (d, 3H, CH_3, $^3J_{H-H}$= 6.8 Hz), 4.39 (dd, 1H, CH_2, $^2J_{H-H}$= 8.8 Hz, $^3J_{H-H}$= 4.4 Hz), 4.53 (m, 1H, CH= *trans* to N), 4.71 (m, 1H, CH_2), 4.88 (m, 1H, CH-N), 5.12 (m, 1H, CH-OP), 5.98 (m, 1H, CH= *trans* to P), 6.09 (m, 1H, CH^c=), 6.3-8.4 (m, 25H, CH=). ^{13}C (100.6 MHz, CD_2Cl_2): δ= 0.1 (CH_3, $SiMe_3$), 0.3 (CH_3, $SiMe_3$), 22.4 (b, CH_3), 68.1 (CH-N), 68.4 (d, CH= *trans* to N, J_{C-P}= 9.2 Hz), 70.9 (CH-OP), 78.0 (CH_2), 98.8 (d, CH= *trans* to P, J_{C-P}= 32.4 Hz), 112.7 (d, CH^c=, J_{C-P}= 9.2 Hz), 121.0-150.0 (aromatic carbons), 172.3 (C=N).

Pd-Cy-allyl-L9c (65). Major isomer (95%). ^{31}P NMR (161.9 MHz, CD_2Cl_2): δ = 143.3 ppm (s); ^{1}H NMR (400 MHz, CD_2Cl_2): d = 0.10 (m, 1H, CH_2), 0.61 (s, 9H, CH_3, $SiMe_3$), 0.81 (m, 1H, CH_2), 0.89 (s, 9H, CH_3, $SiMe_3$), 1.0-1.3 (m, 4H, CH_2), 4.05 (b, 1H, CH= *trans* to N), 4.53 (dd, 1H, CH_2, $^2J_{H-H}$= 9.6 Hz, $^3J_{H-H}$= 7.2 Hz), 5.18 (m, 1H, CH_2),5.33 (m, 1H, CH^c=), 5.95 (m, 2H, CH-N, CH= *trans* to P), 6.36 (d, 1H, CH-OP, J_{C-P}= 26 Hz), 7.10 (d, 1H, CH=, $^3J_{H-H}$= 8.8 Hz) , 7.1-7.3 (m, 2H, CH=), 7.4-7.6 (m, 14H, CH=), 8.02 (d, 2H, CH=, $^3J_{H-H}$= 8.4 Hz), 8.24 (s, 1H, CH=).^{13}C (100.6 MHz, CD_2Cl_2): δ= -0.4 (CH_3, $SiMe_3$), 0.0 (CH_3, $SiMe_3$), 19.9 (CH_2), 27.0 (b, CH_2), 68.5 (d, CH= *trans* to N, J_{C-P}= 9.1 Hz), 74.5 (CH-OP), 76.4 (CH-N), 78.2 (CH_2), 104.4 (d, CH= *trans* to P, J_{C-P}= 39.5 Hz), 111.6 (d, CH^c=, J_{C-P}= 10.7 Hz), 122.7-151.0 (aromatic carbons), 169.4 (C=N). Minor isomer (5%).^{31}P NMR (161.9 MHz, CD_2Cl_2): δ = 139.5 ppm (s); ^{1}H NMR (400 MHz, CD_2Cl_2): d = 0.10 (m, 1H, CH_2), 0.42 (s, 9H, CH_3, $SiMe_3$), 0.81 (m, 1H, CH_2), 0.89 (s, 9H, CH_3, $SiMe_3$), 1.0-1.3 (m, 4H, CH_2), 3.94 (b, 1H, CH= *trans* to N), 4.42 (m, 1H, CH_2), 5.21 (m, 1H, CH_2), 5.33 (m, 1H, CH^c=), 5.89 (m, 1H, CH= *trans* to P), 6.06 (m, 1H, CH-N), 6.34 (d, 1H, CH-OP, J_{C-P}= 21 Hz), 7.0-8.2 (m, 20H, CH=).

Pd-Cy-allyl-L13c (66). ^{31}P NMR (161.9 MHz, CD_2Cl_2): δ = 143.7 ppm (s); ^{1}H NMR (400 MHz, CD_2Cl_2): d = 0.11 (m, 1H, CH_2), 0.47 (s, 9H, CH_3, $SiMe_3$), 0.54 (s, 9H, CH_3, $SiMe_3$), 0.68 (m, 1H, CH_2), 1.0-1.3 (m, 4H, CH_2), 1.89 (d, 1H, CH_3, $^3J_{H-H}$= 6.8 Hz), 4.04 (b, 1H, CH= *trans* to N), 4.51 (dd, 1H, CH_2, $^2J_{H-H}$= 9.2 Hz, $^3J_{H-H}$= 8 Hz), 5.15 (dd, 1H, CH_2, $^2J_{H-H}$= 9.2 Hz, $^3J_{H-H}$= 10.8 Hz), 5.33 (m, 1H, CH^c=), 5.36 (q, 1H, CH, $^3J_{H-H}$= 6.8 Hz), 5.71 (dd, 1H, CH_{-N}, $^3J_{H-H}$= 8 Hz, $^3J_{H-H}$= 10.8 Hz), 5.95 (m, 1H, CH= *trans* to P), 6.99 (d, 1H, CH=, $^3J_{H-H}$= 8.8 Hz), 7.12 (d, 1H, CH=, $^3J_{H-H}$= 8.8 Hz), 7.28 (m, 2H,

CH=), 7.4-7.5 (m, 7H, CH=), 8.02 (t, 1H, CH=, $^3J_{H-H}$= 8.8 Hz), 8.23 (d, 1H, CH=, $^3J_{H-H}$= 7.2 Hz).^{13}C (100.6 MHz, CD_2Cl_2): δ= -0.1 (CH_3, $SiMe_3$), 0.0 (CH_3, $SiMe_3$), 19.5 (CH_2), 22.9 (d, CH_3, J_{C-P}= 4.5 Hz), 27.1 (b, CH_2), 67.9 (d, CH= *trans* to N, J_{C-P}= 9.2 Hz), 71.6 (CH-OP), 74.3 (CH-N), 78.2 (CH_2), 104.0 (d, CH= *trans* to P, J_{C-P}= 40 Hz), 111.7 (d, CH^c=, J_{C-P}= 10.7 Hz), 121.0-151.0 (aromatic carbons), 171.8 (C=N).

3.4.4.6. Typical procedure for the allylic alkylation of linear (S1, S3–S8) and cyclic (S2, S9 and S10) substrates.

A degassed solution of $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (1.8 mg, 0.005 mmol) and the desired phosphite-oxazoline ligand (0.011 mmol) in dichloromethane (0.5 mL) was stirred for 30 min. After this time, a solution of substrate (1 mmol) in dichloromethane (1.5 mL), nucleophile (3 mmol), *N,O*-bis(trimethylsilyl)-acetamide (3 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 $MgSO_4$. For compounds **6**, **8**-**17**, **19**-**29** and **33**-**36**, the solvent was removed, conversions were measured by ^{1}H NMR and enantiomeric excesses were determined by HPLC[5g] (See Section 3.2). For compounds **7**, **31**-**32**, **37**-**38** and **40**-**42**, conversion and enantiomeric excesses were determined by GC[5g] (See Section 3.2). For compounds **30** and **39**, conversion was measured by ^{1}H NMR and ees were determined by ^{1}H NMR using $[Eu(hfc)_3]$.[5g]

3.4.4.7. Typical procedure for the allylic amination of S1.

A degassed solution of $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (1.8 mg, 0.005 mmol) and the desired phosphite-oxazoline ligand (0.011 mmol) in dichloromethane (0.5 mL) was stirred for 30 min. After this time, a solution of substrate (1 mmol) in dichloromethane (1.5 mL), benzylamine (262 μL, 3 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 $MgSO_4$. Conversion of **18** was measured by ^{1}H NMR and enantiomeric excesses were determined by HPLC.[29]

3.4.4.8. Typical procedure for the allylic etherification and silylation of S1.

A degassed solution of $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (1.8 mg, 0.005 mmol) and the desired phosphite-oxazoline ligand (0.011 mmol) in dichloromethane (0.5 mL) was stirred for 30 min. Subsequently, a solution of **S1** (31.5 mg, 0.125 mmol) in dichloromethane (1.5 mL) was added. After 10 min, Cs_2CO_3 (122 mg, 0.375 mmol) and the corresponding alkyl alcohol or silanol (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 $MgSO_4$. Conversions were measured by ^1H NMR. HPLC was used to determine enantiomeric excesses of substrates **19**-**22.**[5g]

3.4.5. References

1 a) *Asymmetric Catalysis in Industrial Scale: Challenges, Approaches and Solutions* (Eds.: H. U. Blaser, E. Schmidt), Wiley-VCH, Weinheim, **2003**; b) *Comprehensive Asymmetric Catalysis* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **1999**; c) *Asymmetric Catalysis in Organic Synthesis* (Ed. R. Noyori), Wiley, New York, **1994**; d) *Applied Homogeneous Catalysis with Organometallics Compounds*, 2nd ed. (Eds.: B. Cornils, W. A. Hermann), WileyVCH, Weinheim, **2002**; e) *Catalytic Asymmetric Synthesis* (Eds.: I. Ojima), Wiley, Hobocken, **2010**.

2 For reviews, see: a) *Palladium Reagents and Catalysis: Innovations in Organic Synthesis* (Ed.: J. Tsuji), Wiley, New York, **1995**; b) Trost, B.M.; van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395; c) Johannsen, M.; Jorgensen, K. A. *Chem. Rev.* **1998**, *98*, 1689; d) Pfaltz, A.; Lautens, M. in *Comprehensive Asymmetric Catalysis.* Vol. 2 (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **1999**, Chapter 24; e) Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000**, *33*, 336; f) Masdeu-Bultó, A. M.; Diéguez, M.; Martín, E.; Gómez, M. *Coord. Chem. Rev.* **2003**, *242*, 159; g) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921; h) Martín, E.; Diéguez, M. *C. R. Chemie* **2007**, *10*, 188; i) Lu, Z.; Ma, S. *Angew. Chem. Int. Ed.* **2008**, *47*, 258.

3 See, for instance: a) Pàmies, O.; Diéguez, M. *Acc. Chem. Res.* **2010**, *43*, 312; b) van Leeuwen, P.W. N. M.; Kamer, P. C. J.; Claver, C.; Pàmies, O.; Diéguez, M. *Chem. Rev.* **2011**, *111*, 2077. c) Diéguez, M.; Pàmies, O. *Chem. Eur. J.* **2008**, *14*, 3653. d) Mata, Y.; Pàmies, O.; Diéguez, M. *Adv. Synth. Catal.* **2009**, *351*, 3217. E) Coll, M.; Pàmies, O.; Diéguez, M. *Org. Lett.* **2014**, *16*, 1892. f) Pàmies, O.; Diéguez, M.; Claver, C. *J. Am. Chem. Soc.* **2005**, *127*, 3646. g) Bellini, R.; Magre, M.; Biosca, M.; Norrby, P.-O.; Pàmies, O.; Diéguez, M.; Moberg, C. *ACS Catalysis* **2016**, *6*, 1701, h) Magre, M.; Biosca, M.; Pàmies, O.; Diéguez, M. *ChemCatChem* **2015**, *7*, 114.

4 The flexibility that offers the biphenyl moiety can be used to fine tune the chiral pocket formed upon complexation. See for example: a) ref. [5]; b) Mata, Y.; Diéguez, M.; Pàmies, O.; Claver, C. *Adv. Synth. Catal.* **2005**, *347*, 1943.

5 Prétot, R.; Pfaltz, A. *Angew. Chem. Int. Ed.* **1998**, *37*, 323.

6 Alen, J. V.; Williams, J. M. J. *Tetrahedron: Asymmetry* **1994**, *5*, 277.

7 a) Bolm, C.; Zani, L.; Rudolph, J.; Schiffers, I. *Synthesis* **2004**, *13*, 2173. b) Buisson, D.; Azerad, R. *Tetrahedron: Asymmetry* **1999**, *10*, 2997. c) Kardassi, G.; Brungs, P.; Nothelfer, C.; Eberhard, S. *Tetrahedron* **1998**, *54*, 3479.

8 Li, Z.-T.; Li, X.-S.; Li, L.-C.; Xu, D.-C. *Russian Journal of Organic Chemistry* **2006**, *42*, 545.

[9] a) Kmentov, I.; Gotov, B.; Solcniovc, E.; Toma, S. *Green Chem.* **2002**, *4*, 103; b) Liu, J.; Chen, G.; Xing, J.; Liao, J. *Tetrahedron: Asymmetry* **2011**, *22*, 575; c) Jin, Y.; Du, D. M.; *Tetrahedron* **2012**, *68*, 3633; d) Martin, C. J.; Rawson, D. J.; Williams, J. M. J. *Tetrahedron: Asymmetry* **1998**, *9*, 3723. e) Deng, W. H.; Ye, F.; Bai, X. F.; Zheng, Z. J.; Cui, Y. M.; Xu, L. W. *ChemCatChem* **2015**, *7*, 75.

[10] For a recent review, see: d'Ischia, M.; Napolitano, A.; Pezzella, A. In *Comprehensive Heterocyclic Chemistry III: Pyrroles and their Benzo Derivatives: Applications*; Katritzky, A. R., Ramsden, C. A., Scriven, E. F. V., Taylor, R. J. K., Eds.; Elsevier: Amsterdam, **2008**; Vol. 3, pp 353.

[11] Liu, Y.; Cao, Z.; Du, H. *J. Org. Chem.* **2012**, *77*, 4479.

[12] a) *Dictionary of Natural Products*; Buckingham, J., Ed.; Cambridge University Press.: Cambridge, **1994**. b) Lumbroso, A.; Cooke, M. L.; Breit, B. *Angew. Chem. Int. Ed.* **2013**, *52*, 1890.

[13] The use of aliphatic alcohols has been much less studied than those using phenols. See: a) Iourtchenko, A.; Sinou, D. *J. Mol. Catal. A* **1997**, *122*, 91. b) Haight, A. R.; Stoner, E. J.; Peterson, M. J.; Grover, V. K. *J. Org. Chem.* **2003**, *68*, 8092. c) Lam, F. L.; Au-Yeung, T. T.-L.; Kwong, F. Y.; Zhou, Z.; Wong, K. Y.; Chan, A. S. C. *Angew. Chem. Int. Ed.* **2008**, *47*, 1280. d) Ye, F.; Zheng, Z.-J.; Li, L.; Yang, K.-F.; Xia, C.-G.; Xu, L.-W. *Chem.–Eur. J.* **2013**, *19*, 15452. e) Caldentey, X.; Pericàs, M. A. *J. Org. Chem.* **2010**, *75*, 2628. f) Liu, Z.; Du, H. *Org. Lett.* **2010**, *12*, 3054. g) Kato, M.; Nakamura, T.; Ogata, K.; Fukuzawa, S.-I. *Eur. J. Org. Chem.* **2009**, 5232. h) Feng, B.; Cheng, H.-G.; Chen, J.-R.; Deng, Q.-H.; Lu, L.-Q.; Xiao, W.-J. *Chem. Commun.* **2014**, *50*, 9550.

[14] Silanols have been less studied than other type of nucleophile and there is only one catalytic system, Pd/CycloN_2P_2-Phos, that has provided high levels of enantioselectivity (up to 94%), see ref. 13d

[15] In contrast to Pd-catalytic systems, Ir-, Ru- and Mo-catalysts provide very high selectivity in order for the attack at the non-terminal carbon to give the chiral product. See, for instance: a) Bruneau, C.; Renaud, J. L.; Demersemen, B. *Chem. Eur. J.* **2006**, *12*, 5178; b) Malkov, A. V.; Gouriou, L.; Lloyd-Jones, G. C.; Starý, I.; Langer, V.; Spoor, P.; Vinader, V.; Kočovský, P. *Chem. Eur. J.* **2006**, *12*, 6910; c) Trost, B. M.; Hildbrand, S.; Dogra, K. *J. Am. Chem. Soc.* **1999**, *121*, 10416; d) Alexakis, A.; Polet, D. *Org. Let.* **2004**, *6*, 3529. e) Hartwig, J. F.; Pouy, M. J. in *Top. Organomet. Chem*. **2011**, 34, 169. f) Moberg, C. *Org. React* **2014**, 84, 1.

[16] For successful applications of Pd-catalysts, see: a) ref 7; b) You, S.-L.; Zhu, X.-Z.; Luo, Y.-M.; Hou, X.-L.; Dai, L.-X. *J. Am. Chem. Soc.* **2001**, *123*, 7471; c) Hilgraf, R.; Pfaltz, A. *Synlett* **1999**, 1814. d) Hilgraf, R.; Pfaltz, A. *Adv. Synth. Catal*. **2005**, *347*, 61.

[17] a) Oslob, J. D.; Äkermark, B.; Helquist, P.; Norrby, P.-O. *Organometallics* **1997**, *16*, 3015; b) Hagelin, H.; Äkermark, B.; Norrby, P.-O. *Organometallics* **1999**, *18*, 2884.

[18] a) Hagelin, H.; Svensson, M.; Äkermark, B.; Norrby, P.-O. *Organometallics* **1999**, *18*, 4574; b) Moberg, C.; Bremberg, U.; Hallman, K.; Svensson, M.; Norrby, P.-O.; Hallberg, A.; Larhed, M.; Csçregh, I. *Pure Appl. Chem*. **1999**, *71*, 1477.

[19] a) Butts, C. P.; Filali, E.; Lloyd-Jones, G. C.; Norrby, P. O.; Sale, D. A.; Schramm, Y. *J. Am. Chem. Soc.* **2009**, *131*, 9945. b) Fristrup, P.; Ahlquist, M.; Tanner, D.; Norrby, P.-O. *J. Phys. Chem.* **2008**, *112*, 12862.

[20] a) Deerenberg, S.; Schrekker, H. S.; van Strijdonck, G. P. F.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Fraanje, J.; Goubitz, K. *J. Org. Chem.* **2000**, *65*, 4810. b) Fernández, F.; Gómez, M.; Jansat, S.; Muller, G.; Martín, E.; Flores Santos, L.; García, P. X.; Acosta, A.; Aghmiz, A.; Jiménez-Pedrós, M.; Masdeu-Bultó, A. M.; Diéguez, M.; Claver, C.; Maestro, M. A. *Organometallics* **2005**, *24*, 3946.

[21] a) Auburn, P. R.; Mackenzie, P. B.; Bosnich, B. *J. Am. Chem. Soc.* **1985**, *107*, 2033. b) Jia, C.; Müller, P.; Mimoun, H. *J. Mol. Cat. A: Chem.* **1995**, *101*, 127. c) Lehman, J.; Lloyd-Jones, G. C. *Tetrahedron* **1995**, *51*, 8863. d) Hayashi, T.; Yamamoto, A.; Ito, Y.; Nishioka, E.; Miura, H.; Yanagi, K. *J. Am. Chem. Soc.* **1989**, *111*, 6301.

[22] Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A.; Peralta, J. E., Jr.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, O.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. Revision A.02 ed; Gaussian: Wallingford, CT, 2009.

[23] a) Lee, C.; Yang,W.; Parr, R. G. *Phys. Rev*. B **1988**, 37, 785. b) Becke, A. D. *J. Chem. Phys*. **1993**, 98, 5648.

[24] Hay, P. J.; Wadt, W. R. *J. Chem. Phys.* **1985**, 82, 299.

[25] a) Hehre, W. J.; Ditchfield, R.; Pople, J. A. *J. Chem. Phys.* **1972**, 56, 2257. b) Hariharan, P. C.; Pople, J. A. *Theor*. *Chim. Acta* **1973**, 28, 213. c) Francl, M. M.; Pietro,W. J.; Hehre,W. J.; Binkley, J. S.; Gordon, M. S.; Defrees, D. J.; Pople, J. A. *J. Chem. Phys*. **1982**, 77, 3654.

[26] a) Miertus, S.; Tomasi, *J. Chem. Phys.* **1982**, *65*, 239. b) Mennucci, B.; Tomasi, J. *J. Chem. Phys.* **1997**, 106, 5151. c) Cossi, M.; Barone, V.; Menucci, B.; Tomasi, J. *Chem. Phys. Lett*. **1998**, 286, 253.

[27] a) Krishnan, R.; Binkley, J. S.; Seeger, R.; Pople, J. A. *J. Chem. Phys.* **1980**, 72, 650. b) McLean, A. D.; Chandler, G. S. *J. Chem. Phys*. **1980**, 72, 5639.

[28] a) Grimme, S.; Antony, J.; Ehrlich, S.; Krieg, H. *J. Chem. Phys.* **2010**, 132, 15410. b) Grimme, S.; Ehrlich, S.; Goerigk, L. *J. Comput. Chem.* **2011**, 32, 1456.

[29] Pàmies, O.; van Strijdonck, G. P. F.; Diéguez, M.; Deerenberg, S.; Net, G.; Ruiz, A.; Claver, C.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *J. Org. Chem.* **2001,** *66,* 8867.

3.5. Alternating theoretical and experimental optimization of a new amino-phosphite ligand library for asymmetric Pd-catalyzed allylic substitution

Magre, M.; Biosca, M.; Norrby, P.-O.; Pàmies, O.; Diéguez, M. *ChemCatChem*, **2015**, 7, 4091.

Abstract: *A new library of modular amino-phosphite ligands* ***L15*****-*****L20a*****-*****g*** *obtained in a few synthetic steps from enantiopure aminoalcohols has been tested in the asymmetric Pd-catalyzed allylic substitution. The modular ligand design has been shown to be crucial in finding highly selective catalysts for each substrate type using a wide range of C, N and O-nucleophiles. A DFT study of the species responsible for the enantiocontrol was used for optimizing the ligand structure. By selecting the ligand components, we were able to identify unprecedented catalytic systems that can create new chiral C-C, C-N and C-O bonds in a variety of substrate types (hindered and unhindered) in high yields and enantioselectivities (ee's up to 99%). Further studies on the Pd-π-allyl intermediates provided a deep understanding of the effect of ligand structure in the origin of enantioselectivity. Potential applications of the new Pd-amino-phosphite catalysts were demonstrated by the practical synthesis of a range of chiral carbocycles by simple tandem reactions, with no loss of enantioselectivity*.

3.5.1. Introduction

The synthesis of chiral C-X bonds, where X is a C atom or an heteroatom, are the most significant processes in the preparation of complex chiral molecules from simple ones. Of all the C-X bond forming strategies, enantioselective Pd-catalyzed allylic substitution is among the most studied. Some advantages include a high functional group tolerance, mild reaction conditions and high versatility of the alkene functionality of the substrate for further stereoselective functionalization.[1] Most of the top ligands reported to date for Pd-allylic substitution use the capacity of the ligand to direct the nucleophilic attack to one of the allylic terminal atoms, by means of either a secondary ligand-nucleophile interaction[2] or an electronic discrimination[3].[1] The latter approach uses heterodonor ligands to electronically differentiate between the two allylic terminal carbon atoms because of the different *trans* influences of the donor groups. Mixed phosphine/phosphinite-oxazoline ligands have played a dominant role among heterodonor.[1] Our group has also contributed in the Pd-catalyzed allylic substitution with an improved generation of ligands. We have shown that some common limitations of this process, such as low reaction rates and high substrate specificity are overcome by introducing biaryl-phosphite moieties into the ligand design.[4] As a result increased reaction rates are achieved thanks to the larger π-acceptor ability of the phosphite groups and substrate versatility is increased because the flexibility of the phosphite moieties allows the catalyst chiral pocket to adapt to both hindered and unhindered

substrates. We have therefore reported several phosphite-oxazolines as extremely effective ligands for this process.[5] Despite the important advances, the application of P-oxazoline ligands is mainly limited to the use of few nucleophiles, mainly dimethyl malonate and benzylamine. The use of functionalized malonates and alkyl alcohols has scarcely been reported.[1] In addition, only a few catalysts have been efficiently applied in the allylic substitution of a several type of substrates, with different electronic and steric proprieties, using a broad range of nucleophiles.[6] More efforts have therefore to be made to expand the range of nucleophiles and substrates with the aim to synthesize more complex chiral organic molecules.

To expand the range of ligands and improve performance, we have recently moved our research towards developing heterodonor ligands that contain groups more robust than oxazolines (Sections 3.2, 3.3 and 3.4). In this context, we reported the application of Pd-phosphite-pyridine/thioether catalytic systems in the allylic substitution of several substrate types using a large variety of nucleophiles.[7] A part from this, the successful use in this process of other heterodonor P-X ligands where X are more robust groups than oxazoline has not been reported yet, and a systematic study of the scope of this family of ligands is still missing. Although other researchers have developed heterodonor phosphine/phosphinite-ligands, containing groups more robust than oxazoline (such as amine,[8] imine,[9] pyridine,[10] thioether,[11] etc.), only a few of them have been successfully applied and these are limited in substrate and nucleophile scope (enantioselectivities are mainly high in the allylic substitution of hindered standard substrate *rac*-(*E*)-1,3-diphenyl-3-acetoxyprop-1-ene **S1** using dimethylmalonate as nucleophile). To be of practical interest, substantial improvements in terms of enantioselectivity, chemical yield and substrate and nucleophile versatility are still needed.

To address this point, in this study we prepared and tested a new family of chiral ligands that are readily accessible, easier to handle and that expand the application range. We therefore report a highly modular amino-phosphite ligand library (Figure 3.5.1) for the Pd-allylic substitution of hindered and unhindered substrates with a large number of nucleophiles. These ligands are easily prepared in few steps from readily available enantiopure aminoalcohols. They also incorporate the advantages of the robustness of the amine moiety and the additional control provided by either the adaptability of the chiral cavity due to the biaryl-phosphite groups and the flexibility of the chiral pocket through a highly modular ligand scaffold. In a simple two/three step procedure (Scheme 3.5.1), several ligand parameters could be easily tuned to maximize the catalyst performance so that we could investigate the effect of systematically changing the substituents (ligands **L15**, **L19** and **L20**) and configuration (ligands **L15** and **L18**) at the ligand backbone, the amine substituents (ligands **L15**-**L17**) and the substituents and configurations in the biaryl phosphite moiety (**a**-**g**). By judicious choice of the ligand components, we achieved high enantioselectivities and activities in a number of substrates using a wide range of C-, N- and O-nucleophiles. The potential application of

these new Pd/amino-phosphite catalytic systems has also been demonstrated by the practical synthesis of chiral carbocycles by simple sequential reactions, with no loss in enantiomeric excess.

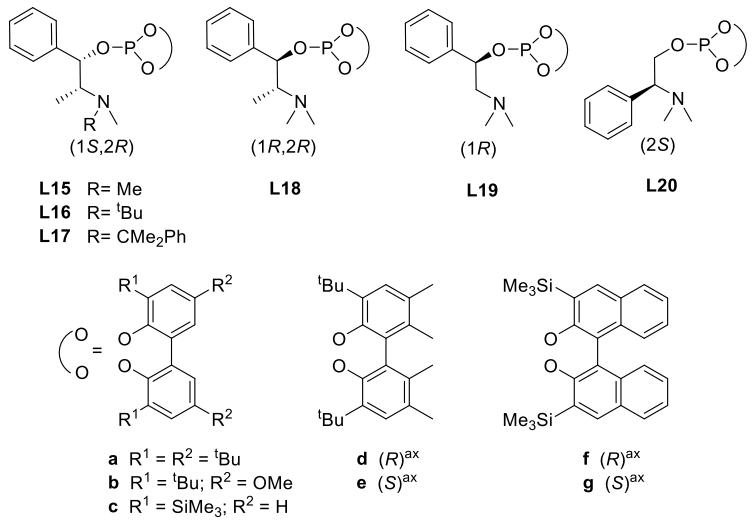


Figure 3.5.1. Amino-phosphite ligand library **L15**-**L20a**-**g**.

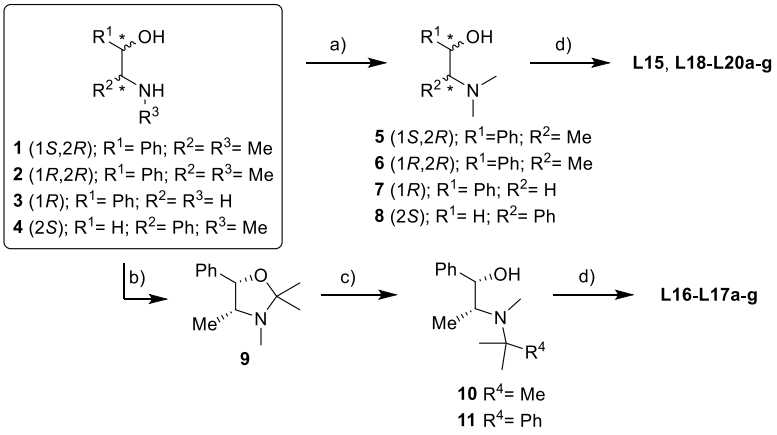
Despite the recent success of Pd/phosphite-nitrogen catalyst systems, the mechanistic aspects of these ligands are not sufficiently understood to predict, a priori, the type of ligand needed to obtain a high selectivity. To address this important point, in this paper we also carried out DFT calculations and the synthesis and characterization of the Pd-π-allyl intermediates in order to explain the origin of enantioselectivity using these highly versatile catalytic systems. It should be noted that these DFT calculations have also been crucial in the optimization of the ligand design.

3.5.2. Results and discussion

3.5.2.1. Synthesis of ligand library

Ligands **L15**-**L20a**-**g** were synthesized from the corresponding easily accessible enantiopure aminoalcohols (**1**-**4**, Scheme 3.5.1). Amino-alcohols **1**-**4** already incorporate the desired diversity in the substituents and in the configurations of the aminoalcohol backbone. The diversity at the amino group was achieved by either direct methylation of **1**-**4** using formic acid and formaldehyde to afford compounds **5**-**8**[12] (Scheme 3.5.1, step a) or by formation of oxazolidine **9**[13] (Scheme 3.5.1, step b) from **1**, followed by ring-opening with the corresponding Grignard reagents (compounds **10**-**11**, step c)[14]. Finally, reaction of amino-alcohols **5**-**8**, **10** and **11** with one equivalent of

the desired *insitu* formed phosphorocholoridite gave access to amino-phosphite ligands **L15**-**L20a**-**g** (step d) with the desired substituents and configurations of the biaryl phosphite group (**a**-**g**).



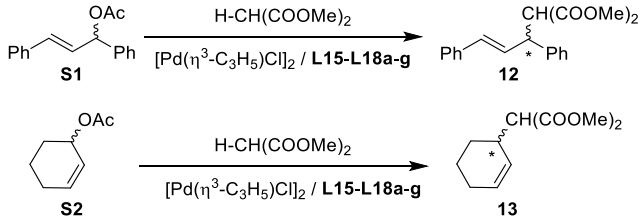
Scheme 3.5.1. Synthesis of amino-phosphites **L15-L20a**-**g.** a) Formic acid /formaldehyde / H_2O (yields 90-95%);[12] b) 2,2-dimethoxypropane/toluene (yield 72%);[13] c) MeMgBr /Et_2O or PhMgBr/THF (yields 87-93%)[14] and d) $ClP(OR)_2$; $(OR)_2$ = **a**-**g**/Py/toluene (yields 30-95%).

Ligands **L15**-**L20a**-**g** were isolated in moderate-to-excellent yields as white solids after purification on neutral alumina under an atmosphere of argon. Advantageously, they were stable in air and very stable to hydrolysis, so further manipulation/storage was carried out in air. The HRMS-ESI spectra were in agreement with the assigned structure. Ligands **L15**-**L20a**-**g** were also characterized by ^1H, ^{13}C and ^{31}P NMR spectroscopy. The spectral assignments, made using ^1H–^1H and ^{13}C–^1H correlation measurements, were as expected for these C_1-symmetric ligands. One singlet for each compound was observed in the ^{31}P NMR spectrum. Rapid ring inversions (tropoisomerization) in the biphenyl-phosphorus moieties (**a**-**c**) occurred on the NMR time scale because the expected diastereoisomers were not detected by low-temperature ^{31}P NMR (in CD_2Cl_2 +35 to -85 °C).[15]

3.5.2.2. Allylic substitution of *rac*-1,3-diphenyl-3-acetoxyprop-1-ene S1 and *rac*-3-acetoxycyclohexene S2 with ephedrine-based ligands L15-L18a-g. Computational study for ligand optimization

First, we tested the efficiency of the ephedrine-based amino-phosphite ligands **L15**-**L18a**-**g**. As mentioned previously, the asymmetric Pd-catalyzed allylic alkylation is highly dependent on the olefin geometry. [1] The effectiveness of the catalyst in transferring the chiral information to the alkylated product mainly depends on its ability to adapt to the variation of the steric demands of the substrate. In order to assess the

performance of ligands **L15**-**L18a**-**g** in the allylic alkylation of substrates with different steric requirements, we initially evaluated them in the asymmetric Pd-catalyzed allylic alkylation of the model substrates *rac*-(*E*)-1,3-diphenyl-3-acetoxyprop-1-ene (**S1**) and *rac*-3-acetoxycyclohexene (**S2**) (Scheme 3.5.2). Because of the presence of less bulky anti substituents, the enantioselectivity for cyclic substrate **S2** is more difficult to control.[1] There are, therefore, fewer successful catalysts for **S2**. In all the cases, the catalysts were generated *in situ* from $[PdCl(\eta^3\text{-}C_3H_5)]_2$ and the corresponding ligand.



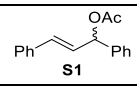
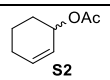
Scheme 3.5.2. Pd-allylic alkylation of model substrates **S1** and **S2**.

The results, summarized in Table 3.5.1, indicate that enantioselectivity is mainly affected by the substituents/configuration at the biaryl phosphite moiety (**a**-**g**) and by the amine substituents, while the configuration of the ephedrine-backbone affects less. The sense of the enantioselectivity is therefore mostly controlled by the biaryl phosphite moiety, regardless of the configuration of the ephedrine-backbone. The effect of the substituents/configuration of the biaryl phosphite moiety was studied with ligands **L15a-g** (Table 3.5.1, entries 1-7). Results indicate that the presence of trimethylsilyl groups at the *ortho* positions of the biaryl phosphite moiety affects negatively both the activity and the enantioselectivity (entry 3 vs 1-2 and entries 6-7 vs 4-5).

Also, by comparing the results from using ligand **L15a** with the related enantiopure biaryl ligands **L15d** and **L15e** (entry 1 vs 4 and 5), we can conclude that the tropoisomeric biphenyl moiety in ligands **L15a**-**c** is not controlled when coordinated in the Pd-π-allyl intermediate species. The best enantioselectivities are therefore obtained with ligands containing enantiopure biaryl phosphite moieties, with *tert*-butyl groups at the *ortho* positions (**d** and **e**; entries 4 and 5).

We then evaluated the effect of the amine substituents with ligands **L15**-**L17**. In general, the use of ligands **L15**, with a dimethyl amine group, yielded higher enantioselectivities than ligands **L16** and **L17** (*i.e.* entries 4 vs 9 and 12). A plausible explanation may be the formation of mixtures of diastereomeric amino complexes with ligands **L16** and **L17** (note that the N atom in ligands **L16** and **L17** becomes a stereogenic center when coordinated to the metal). In addition, **L15** have the advantage that can be synthesized in fewer steps than **L16**-**L17** (Scheme 3.5.1).

Table 3.5.1. Pd-catalyzed allylic alkylation of substrates **S1**-**S2** with dimethyl malonate as nucleophile using ephedrine-based amino-phosphite ligands **L15-L18a-g**.[a]

		 **S1**		 **S2**	
Entry	Ligand	% Conv (% Yield)[b]	% ee[c]	% Conv (% Yield)[d]	% ee[e]
1	**L15a**	100 (94)	31 (*R*)	100 (93)	9 (*R*)
2	**L15b**	100 (92)	29 (*R*)	100 (94)	8 (*R*)
3	**L15c**	51 (48)	11 (*R*)	98 (91)	3 (*R*)
4	**L15d**	100 (94)	81 (*R*)	100 (90)	60 (*R*)
5	**L15e**	100 (93)	75 (*S*)	100 (93)	60 (*S*)
6	**L15f**	50 (45)	64 (*R*)	95 (89)	39 (*R*)
7	**L15g**	36 (31)	27 (*S*)	97 (91)	58 (*S*)
8	**L16a**	29 (24)	6 (*S*)	100 (92)	9 (*S*)
9	**L16d**	100 (96)	42 (*R*)	100 (88)	36 (*R*)
10	**L16e**	70 (66)	33 (*S*)	100 (93)	56 (*S*)
11	**L17a**	56 (51)	0	100 (91)	9 (*S*)
12	**L17d**	100 (93)	42 (*R*)	100 (92)	53 (*S*)
13	**L17e**	84 (80)	29 (*S*)	100 (89)	68 (*S*)
14	**L18a**	62 (57)	8 (*R*)	100 (93)	7 (*R*)
15	**L18d**	100 (96)	81 (*R*)	100 (91)	45 (*R*)
16	**L18e**	89 (85)	60 (*S*)	100 (93)	70 (*S*)

[a] Reactions were run at 23 °C with $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (0.5 mol%), ligand (1 mol%), CH_2Cl_2 as solvent, BSA (3 eq), dimethyl malonate (3 eq), KOAc. [b] Conversions and yields determined after 6 h. [c] Enantiomeric excesses determined by HPLC. [d] Conversions and yields determined after 18 h. [e] Enantiomeric excesses determined by GC.

Finally, the configuration of the ephedrine backbone was studied by comparing ligands **L15** and **L18**. A cooperative effect between the configurations of both the ephedrine-backbone and the biaryl phosphite moiety was observed. Such a cooperative effect depends of the steric demands of the substrate.

While for **S1** the cooperative effect results in a matched combination for ligands **L15d** and **L18d** (81% ee, entries 4 and 15), containing a *R*-biphenyl moiety, the matched combination for substrate **S2**, was achieved using *pseudo*-ephedrine ligand **L18e** (70% ee, entry 16), containing a *S*-biphenyl phosphite moiety.

To find what ligand parameters should be further modified to increase enantioselectivity, we performed a DFT computational study of the key intermediates and transition states

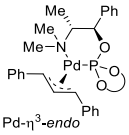
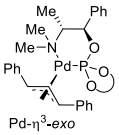
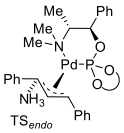
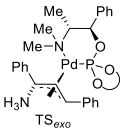
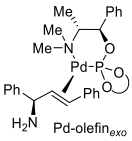
involved in the enantiocontrol of the Pd-catalyzed allylic substitution of substrate **S1**, using ligands **L18d** and **L18e** as models. The mechanistic studies found in the literature have shown that enantioselectivity is controlled in the effectively irreversible nucleophilic attack, but transition state (TS) for this step can be either early or late depending on the nature of the nucleophile, ligands, and reaction conditions. In an early transition state, the interactions leading to stereochemical differentiation can be understood from the structure of the Pd-allyl intermediate,[16] whereas the late transition state is more reminiscent of the Pd-alkene product complex.[17] A sterically encumbered ligand can in fact be employed to push the allyl into a more product-like orientation, strongly affecting the regiochemical preference in the nucleophilic attack.[18] In our experience, a diffuse anion like malonate, or a neutral nucleophile like amine, would be expected to give relatively early transition states, whereas a highly concentrated charge like a fluoride anion gives a late TS.[19]

For the early TS case, stereochemistry is governed by both the population of the Pd-η^3-allyl intermediates and the relative electrophilicity of the allylic carbon atoms, with an allyl terminus *trans* to a phosphorus atom generally being more reactive than one *trans* to a nitrogen. When the TS is late, the formation of the most stable Pd-olefin complex controls enantioselectivity. Calculation were carried out using the B3LYP functional, the 6-31G*/LANL2DZ basis set, and the PCM solvent model with parameters for CH_2Cl_2, as implemented in Gaussian 09. The energies were further refined by performing single-point calculations at the 6-311+G** level, and by dispersion correction with the DFT-D3 model. Previous experience has shown that ammonia can be used as a good model nucleophile,[2b,20] avoiding the problems related to charge separation in conjunction with a continuum solvent model. Note that the use of ammonia as nucleophile instead of dimethyl malonate results in the inversion of the CIP descriptor in the 1,3-diphenylallyl case, due to the change in priority of the groups, although the sense of stereoselectivity is maintained.

We initially calculated the relative stability of the Pd-η^3-diphenylallyl complexes. Only the two *syn-syn* η^3-allyl complexes (named Pd-η^3-*endo* and the Pd-η^3-*exo*, Table 3.5.2) were calculated. The contribution of the other allylic species of higher energy (*anti-anti* and *syn-anti* Pd-η^3) was neglected. In line with the catalytic results (Table 3.5.1), the DFT results indicate that the configuration of the biaryl-phosphite moiety controls the preferential formation of one of the *syn-syn* Pd-allyl intermediates.

Thus, while for ligand **L18d** the formation of the Pd-η^3-*exo* is preferred (ΔG = 7.6 kJ/mol), the most stable Pd-allyl intermediate for **L18e** is Pd-η^3-*endo* (ΔG = 8.2 kJ/mol). Assuming that the allyl intermediates are in rapid equilibrium [21] and that the nucleophile will always attack *trans* to phosphorus, we can see that the preferred intermediate leads to the preferred product in this case.

Table 3.5.2. Calculated energies for the *endo* and *exo* Pd-η^3-allyl intermediates, TSs and Pd-η-olefin complexes using **S1** and NH_3 as nucleophile[a]

	L18d	**L18e**
 Pd-η^3-*endo*	0	8.2
 Pd-η^3-*exo*	7.6	0
 TS_{endo}	0	2
 TS_{exo}	4	0
 Pd-olefin$_{endo}$	0	0
 Pd-olefin$_{exo}$	1.8	5

[a] Relative energies in kJ/mol.

We then calculated the transition states TS_{endo} and TS_{exo}, using NH_3 as nucleophile (Table 3.5.2). The energy differences of the calculated TSs agree with the catalytic results. The energy difference between both TSs of ligand **L18d** ($\Delta G^{\#}$= 4 kJ/mol) is higher than for ligand **L18e** ($\Delta G^{\#}$= 2 kJ/mol). This is in good agreement with the higher enantioselectivities achieved using ligand **L18d** (Table 3.5.1, 81% ee for **L18d** vs 60% ee for **L18e**). In addition, the formation of opposite enantiomers of the substituted product is predicted when using ligands **L18d** and **L18e**.

Finally, we calculated the Pd-olefin intermediates (Pd-olefin$_{endo}$ and Pd-olefin$_{exo}$). The results (Table 3.5.2) indicated that the larger energy difference of the Pd-olefin complexes is achieved with ligand **L18e** ($\Delta G^{\#}$= 5 kJ/mol for **L18e** vs 1.8 kJ/mol for **L18d**). Thus, in the current case, the product complex energies do not correlate with the transition state energies or with the experimental selectivities. The structural elucidation

of the Pd-allyl intermediates and the determination of their relative reactivity towards the nucleophile are therefore crucial to understand their catalytic behavior.

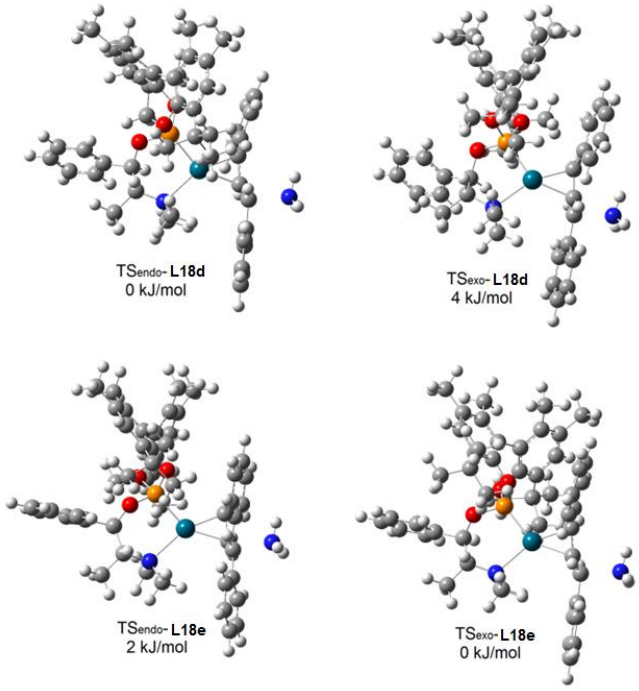


Figure 3.5.2. Calculated transition states using ephedrine-based ligands **L18d** and **L18e**.

Figure 3.5.2 shows the calculated TSs for the major and the minor pathway with both ligands. A special feature of all these TSs is that the methyl substituent of the ephedrine-backbone is pointing in the opposite direction to the coordination sphere. This finding suggests that the methyl group should have little impact on the enantioselectivity. To prove this, we recalculated the TSs by removing the methyl substituent of the ephedrine-backbone (new ligand **L19e**; Figure 3.5.1). Surprisingly, the calculated energy difference between the two TSs for the formation of both enantiomers of the alkylated product (Figure 3.5.3a) was 8.5 kJ/mol (ligand **L19e**) surpassing the values for ligands **L18d** and **L18e** (4 kJ/mol and 2 kJ/mol, respectively), indicating that ligand **L19e** should provide higher enantioselectivity than the ephedrine-based ligands **L18d** and **L18e**.
To study the effect of the other stereogenic center of the ephedrine-backbone (C-2), the phenyl substituent was switched from C-1 to C-2 (new ligand **L20e**, Figure 3.5.1). Slightly lower energy difference between the TSs were achieved than using Pd-**L18e** (Figure 3.5.3b), which suggest that this modification should provide lower enantioselectivities than **L18e**.

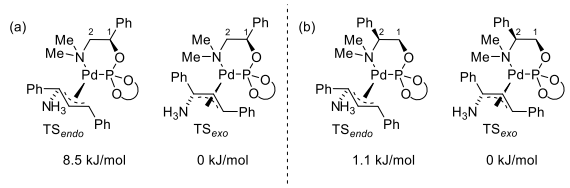


Figure 3.5.3. Calculated energies of transition states (TSs) using (a) ligands **L19e** and (b) **L20e**.

These theoretical results prompted us to prepare and screen amino-phosphite ligands **L19-L20d**-**e** (Scheme 3.5.1) in the asymmetric allylic substitution of substrates **S1** and **S2**. The experimental results are shown in Table 3.5.3. As predicted by the theoretical calculations, the use of ligand **L19e**, without the methyl substituent at stereogenic C-2 of the ephedrine backbone, in the allylic alkylation of **S1** provided the highest enantioselectivities (Table 3.5.3, entry 2, 94% (*S*) ee), while the use of ligand **L20e** led to similar enantioselectivities to **L18e** (entry 4). The same behavior is observed in the allylic alkylation of cyclic substrate **S2**. Using ligand **L19e** we could therefore increase enantioselectivity from 70% ee to 82% ee (Table 3.5.3, entry 2).

Table 3.5.3. Pd-catalyzed allylic alkylation of substrates **S1** and **S2** with dimethyl malonate using amino-phosphite ligands **L19**-**L20d**-**e**.[a]

		OAc Ph Ph **S1**		OAc **S2**	
Entry	Ligand	% Conv (% Yield)[b]	% ee[c]	% Conv (% Yield) [d]	% ee[e]
1	**L19d**	100 (94)	92 (*R*)	100 (90)	70 (*R*)
2	**L19e**	100 (96)	94 (*S*)	100 (89)	82 (*S*)
3	**L20d**	100 (92)	41 (*R*)	100 (91)	46 (*R*)
4	**L20e**	100 (93)	62 (*S*)	100 (92)	62 (*S*)
5[f]	**L19e**	100 (95)	97 (*S*)	100 (91)	86 (*S*)
6[g]	**L19e**	38 (32)	89 (*S*)	56 (49)	74 (*S*)

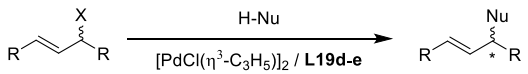
[a] Reactions were run at 23 °C with $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (0.5 mol%), ligand (1 mol%), CH_2Cl_2 as solvent, BSA (3 eq), dimethyl malonate (3 eq), KOAc. [b] Conversions and yields determined after 6 h. [c] Enantiomeric excesses determined by HPLC. [d] Conversions and yields determined after 18 h. [e] Enantiomeric excesses determined by GC. [f] Reactions carried out at 5 °C. [g] Reactions carried out at -15 °C.

Interestingly, for substrate **S1**, ligand **L19d** provided similar high enantioselectivities like **L19e** did, but in the opposite enantiomer of the substitution product (92% (*R*) ee, entry 1). Both enantiomers of the substitution products can be therefore obtained by

simply changing the configuration of the biaryl phosphite moiety in ligands **L19**. All these results show the importance of using modular scaffold to build new ligand systems. Enantioselectivity can be improved by controlling not only the structural but also the reaction parameters. We therefore studied these reactions at a low reaction temperature (entries 5 and 6). Enantioselectivity was further improved (ee's up to 97% for **S1** and 86% for **S2**) by lowering the reaction temperature to 5 ºC (Table 3.5.3, entry 5).

3.5.2.3. Allylic substitution of symmetrical 1,3-disubstituted allylic substrates S1-S7 with other C-, N- and O-nucleophiles. Scope and limitations

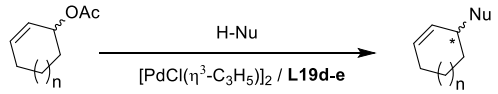
With the optimal amino-phosphite ligands **L19e** and **L19d** we investigated the substrate and nucleophile scope. The following linear and cyclic disubstituted substrates with different steric properties were studied (Scheme 3.5.3): *rac*-(*E*)-1,3-diphenyl-3-acetoxyprop-1-ene (**S1**), *rac*-(*E*)-1,3-ditolyl-3-acetoxyprop-1-ene (**S3**), *rac*-(*E*)-1,3-dimethyl-3-acetoxyprop-1-ene (**S4**), *rac*-(*E*)-ethyl-2,5-dimethyl-3-hex-4-enylcarbonate (**S5**), *rac*-3-acetoxycyclohexene (**S2**), *rac*-3-acetoxycyclopentene (**S6**) and *rac*-3-acetoxycycloheptene (**S7**).



S1 R= Ph; X= OAc
S3 R= *p*Me-C_6H_4; X= OAc
S4 R= Me; X= OAc
S5 R= ^{i}Pr; X= OCO_2Et

14 R= Ph; H-Nu= H-CH(CO_2Et)$_2$
15 R= Ph; H-Nu= H-CH(CO_2Bn)$_2$
16 R= Ph; H-Nu= H-CMe(CO_2Me)$_2$
17 R= Ph; H-Nu= H-CAllyl(CO_2Me)$_2$
18 R= Ph; H-Nu= H-CButenyl(CO_2Et)$_2$
19 R= Ph; H-Nu= H-CPentenyl(CO_2Et)$_2$
20 R= Ph; H-Nu= H-Propargyl(CO_2Me)$_2$
21 R= Ph; H-Nu= H-CH(COMe)$_2$
22 R= Ph; H-Nu= H-$NHCH_2$Ph
23 R= Ph; H-Nu= H-OCH_2Ph

24 R= Ph; H-Nu= H-OCH_2(*p*Me-C_6H_4)
25 R= Ph; H-Nu= H-OCH_2(*p*CF_3-C_6H_4)
26 R= Ph; H-Nu= H-OCH_2(*m*Me-C_6H_4)
27 R= *p*Me-C_6H_4; H-Nu= H-CH(CO_2Me)$_2$
28 R= *p*Me-C_6H_4; H-Nu= H-CAllyl(CO_2Me)$_2$
29 R= *p*Me-C_6H_4; H-Nu= H-CButenyl(CO_2Et)$_2$
30 R= Me; H-Nu= H-CH(CO_2Me)$_2$
31 R= Me; H-Nu= H-CMe(CO_2Me)$_2$
32 R= Me; H-Nu= H-CAllyl(CO_2Me)$_2$
33 R= ^{i}Pr; H-Nu= H-CH(CO_2Me)$_2$



S2 n=1
S6 n=0
S7 n=2

34 n=1; H-Nu= H-CH(CO_2Et)$_2$
35 n=1; H-Nu= H-CMe(CO_2Me)$_2$
36 n=1; H-Nu= H-CAllyl(CO_2Me)$_2$
37 n=1; H-Nu= H-CPropargyl(CO_2Me)$_2$
38 n=1; H-Nu= H-CH(COMe)$_2$

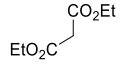
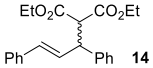
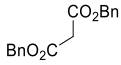
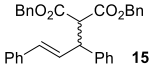
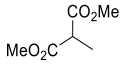
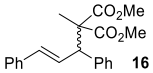
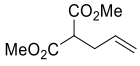
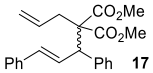
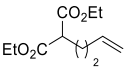
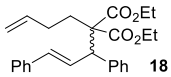
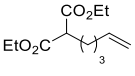
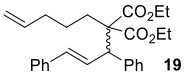
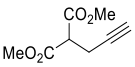
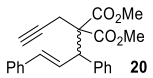
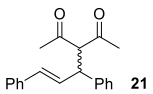
39 n=0; H-Nu= H-CH(CO_2Me)$_2$
40 n=0; H-Nu= H-CPropargyl(CO_2Me)$_2$
41 n=2; H-Nu= H-CH(CO_2Me)$_2$
42 n=2; H-Nu= H-CPropargyl(CO_2Me)$_2$

Scheme 3.5.3. Pd-catalyzed allylic substitution of several allylic substrates **S1**-**S7** and a wide range of C-, N- and O-nucelophiles.

The range of nucleophiles was also expanded, compared to previous work, with special attention to the more challenging and interesting, from a synthetic point of view,

functionalized malonates and β-diketones. The results of Pd/**L19e** and Pd/**L19d** in the allylic substitution of **S1** using a wide range of C-nucleophiles are shown in Table 3.5.4. It can be observed that enantioselectivity was relatively unaffected by a change in the steric nature of the ester groups and in the substituents of the malonate nucleophiles (entries 1-13). Therefore, a variety of malonates, including those α-substituted, reacted cleanly with **S1** to afford products **14**-**20** in high yields, and with enantioselectivities that were as high as or higher than those obtained with dimethyl malonate (ee's up to 99% ee, entries 1-13). Among them, it should be stressed the high enantioselectivities using allyl-, butenyl, pentenyl- and propargyl-substituted malonates (entries 7-13, between 95-99% ee).

Table 3.5.4. Allylic substitution of **S1** with other several C-nucleophiles using Pd/**L19d**-**e** catalytic systems.[a]

			L19d		**L19e**	
Entry	H-Nu	Product	% Y.[b]	% ee[c]	% Y.[b]	% ee[c]
1		 **14**	91	92 (*R*)	92	93 (*S*)
2[d]			88	94 (*R*)	87	95 (*S*)
3		 **15**	93	92 (*R*)	91	94 (*S*)
4[d]			91	94 (*R*)	93	96 (*S*)
5		 **16**	92	95 (*S*)	90	96 (*R*)
6[d]			91	98 (*S*)	92	99 (*R*)
7		 **17**	94	96 (*S*)	93	97 (*R*)
8[d]			92	99 (*S*)	91	99 (*R*)
9[d]		 **18**	95	94 (*S*)	92	95 (*R*)
10		 **19**	93	95 (*S*)	94	97 (*R*)
11[d]			94	97 (*S*)	91	99 (*R*)
12		 **20**	91	94 (*S*)	90	96 (*R*)
13[d]			92	97 (*S*)	93	98 (*R*)
14		 **21**	93	96 (*R*)	94	96 (*S*)
15[d]			91	98 (*R*)	93	99 (*S*)

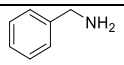
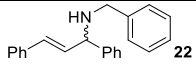
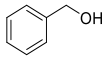
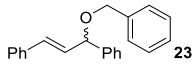
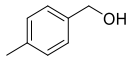
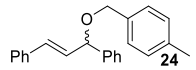
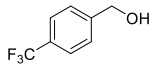
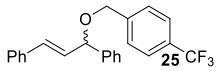
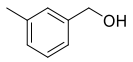
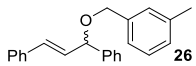
[a] Reactions were run at 23 °C with $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (0.5 mol%), CH_2Cl_2 as solvent, ligand (1 mol%), BSA (3 eq), KOAc. [b] Full conversions were achieved after 12 h. [c] Enantiomeric excess determined by chiral HPLC or GC. [d] Reactions carried out at 5 °C for 24 h. Full conversions were achieved in all cases.

This is advantageous because the resulting products are important precursors for more complex chiral molecules (see section 3.5.2.4). Excellent enantiocontrol was also

achieved when the β-diketone acetophenone, affording product **21** in high yield and enantioselectivity (entries 14-15).

It should be pointed out that the excellent results achieved using benzylamine validates the use of ammonia as nucleophile for the computational model. In all cases, both enantiomers of the substituted product can be obtained in high yields and enantioselectivities (Table 3.5.5, entry 1). We then went on to study the allylic substitution of **S1** using alkyl alcohols as a challenging class of *O*-nucleophiles. The stereoselective construction of compounds with ether groups next to a chiral carbon is important for the preparation of biologically active compounds. [22]

Table 3.5.5. Allylic substitution of **S1** with other several N- and O-nucleophiles using Pd/**L19d**-**e** catalytic systems.[a]

			L19d		**L19e**	
Entry	H-Nu	Product	% Y.[b]	% ee[c]	% Y.[b]	% ee[c]
1		 **22**	89	97 (*S*)	92	99 (*R*)
2[d]		 **23**	92	53 (*S*)	95	56 (*R*)
3[d]		 **24**	91	28 (+)	94	30 (-)
4[d]		 **25**	92	91 (+)	94	94 (-)
5[d]		 **26**	93	68 (+)	91	70 (-)

[a] Reactions were run at 23 °C with $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (0.5 mol%), CH_2Cl_2 as solvent, ligand (1 mol%), BSA (3 eq), KOAc. [b] Full conversions were achieved after 12 h. [c] Enantiomeric excess determined by chiral HPLC or GC. [d] Reactions carried out using 2 mol% $[PdCl(\eta^3\text{-}C_3H_5)]_2$, 4 mol% ligand, Cs_2CO_3 (3 eq). Full conversions were achieved in all cases.

Although the enantioselective Pd-allylic etherification is currently studied by important research groups, few successful examples have been reported. Among them phenols have been the most studied, [23] while the aliphatic alcohols have been explored less. [11f,24] The reaction of Pd/**L19e** and Pd/**L19d** with several substituted benzylic alcohols also proceeded smoothly to afford both enantiomers of the desired products in high yields (Table 3.5.5, entries 2-5). Furthermore, the enantioselectivity was seen to be influenced by the electronic nature of the substituted benzylic alcohol. The highest enantioselectivity (ee's up to 94%, entry 4) was obtained when the benzylic alcohol contained an electron deficient *para* CF_3 substituent, and the selectivity diminished gradually as the substituent was more electron-rich. This behaviour is opposite to that observed in the etherification reaction with Pd/(*S*,*R*p)-FerroNPS catalytic system,[18c] which is one of the few Pd-catalysts that has been specially designed for this purpose

and successfully applied. The Hammet plot of this electronic effect shows a linear free-energy relationship (Figure 3.5.4; ρ = 1.78) between enantioselectivity and the electronic character of the substituent.[25] This plot could therefore be used for predicting the enantioselectivity of asymmetric allylic substitution when *para*-substituted benzylic alcohols are used.

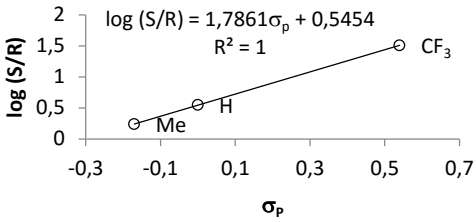


Figure 3.5.4. Hammet plot for the Pd-catalyzed allylic etherification of **S1** with ligand **L19e**.

The scope of Pd/**L19e**-**L19d** catalytic systems was further studied by using other linear substrates (Scheme 3.5.3) with different electronic (*rac*-(*E*)-1,3-ditolyl-3-acetoxyprop-1-ene **S3**) and steric requirements (*rac*-(*E*)-1,3-dimethyl-3-acetoxyprop-1-ene **S4** and *rac*-(*E*)-ethyl-2,5-dimethyl-3-hex-4-enylcarbonate **S5**) than substrate **S1** (Figure 3.5.5, compounds **27**-**33**).

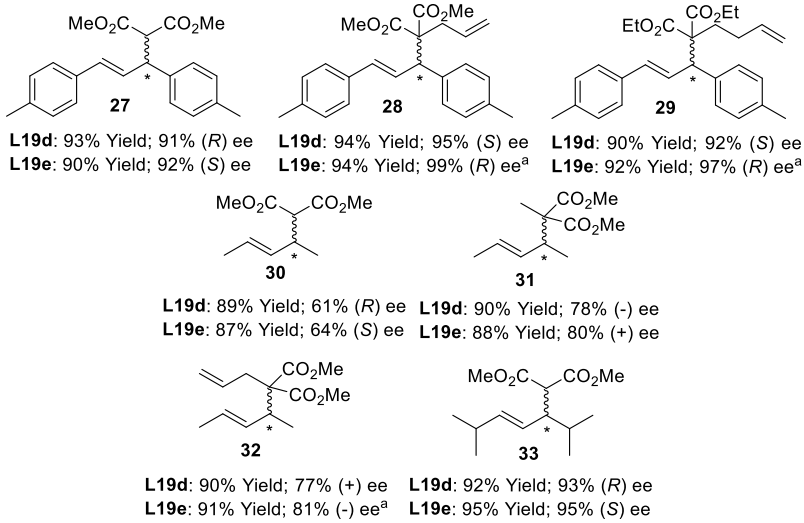


Figure 3.5.5. Asymmetric Pd-catalyzed allylic substitution of substrates **S3**-**S5** using several C-nucleophiles. Full conversions were achieved in all cases. 0.5 mol% $[PdCl(\eta^3\text{-}C_3H_5)]_2$, CH_2Cl_2 as solvent, ligand (1 mol%), 23 °C, 18 h. [a] Reaction carried out at 5 °C for 24 h.

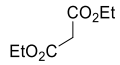
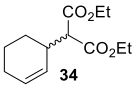
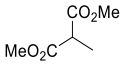
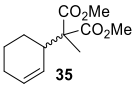
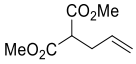
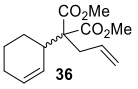
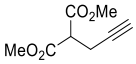
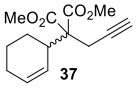
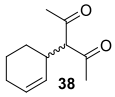
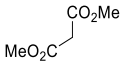
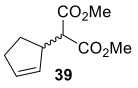
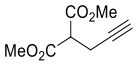
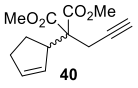
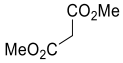
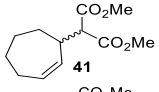
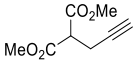
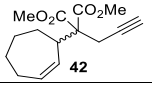
The results using **S3** followed the same trend than for **S1**. High enantioselectivities, in both enantiomers of the substituted product, were obtained in the alkylation of **S3** using several malonates, including those α-substituted with allyl- and butenyl-groups (ee's up to 99%, compounds **27**-**29**). The allylic substitution of substrate **S4**, which is less sterically demanding and is substituted much less enantioselectively than **S1**,[26] also proceeded smoothly (compounds **30**-**32**). Although enantioselectivity depended on the steric properties of the nucleophile, we were pleased to see that for the more challenging α-substituted malonates enantioselectivities were higher (compounds **31**-**32**, ee up to 81%) than for the standard dimethyl malonate. Finally, we were pleased to find out that Pd/**L19d**-**e** also provided high enantioselectivity, in both enantiomers of the alkylated product, of the more demanding substrate **S5** (95% ee) which usually reacts with lower yields and enantioselectivities than model substrate **S1**.

Finally, the good performance of Pd/**L19e** was also seen in the allylic substitution of cyclic substrates using a range of C-nucleophiles, including the less studied α-substituted malonates and β-diketones.

For substrate **S2**, enantioselectivities were as high as those obtained with dimethyl malonate (Table 3.5.6, entries 1-5, products **34**-**38**). Even more interesting is the high enantioselectivity achieved using other cyclic substrates with different ring size (*rac*-acetoycyclopentene **S6** and *rac*-acetoxycycloheptene **S7**). The enantiocontrol was high in both cases, even in the allylic substitution of *rac*-3-acetoxycyclopentene (products **39** and **40**), which is usually alkylated much less enantioselectively than 6- and 7-membered cyclic substrates.

In summary, by a theoretically-guided optimization of the crucial stereodefining moieties in this new family of modular amino-phosphite ligand library, we have been able to identified one of the very few catalytic systems that can create new C-C, C-N and C-O bonds, in a number of substrate types, with different electronic and steric proprieties, using a wide range of nucleophiles, in high activities and enantioselectivities.

Table 3.5.6. Allylic substitution of cyclic substrates **S2**, **S6** and **S7** with other several C-nucleophiles using the Pd/**L19e** catalytic system.[a]

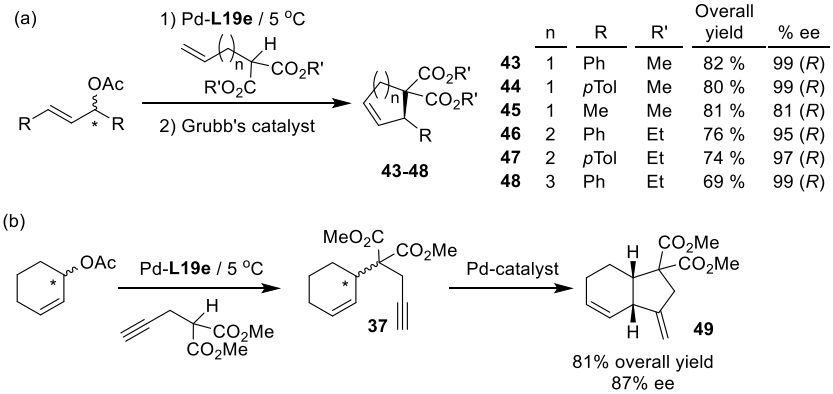
Entry	Substrate	Nucleophile	Product	% Yield[b]	% ee[c]
1	**S2**		 **34**	89	83 (*S*)
2	**S2**		 **35**	91	86 (+)
3	**S2**		 **36**	94	90 (-)
4	**S2**		 **37**	93	87 (*S*)
5	**S2**		 **38**	92	76 (-)
6	**S6**		 **39**	88	75 (-)
7	**S6**		 **40**	92	84 (*S*)
8	**S7**		 **41**	93	91 (*S*)
9	**S7**		 **42**	94	93 (*S*)

[a] Reactions were run at 5 °C with $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (0.5 mol%), CH_2Cl_2 as solvent, ligand (1 mol%), BSA (3 eq), KOAc. [b] Full conversions were achieved after 24 h. [c] Enantiomeric excess determined by chiral HPLC or GC.

3.5.2.4. Synthetic applications of the allylic substitution compounds. Preparation of chiral carbocycles

Asymmetric allylic alkylation (AAA) is a relevant method for creating chiral C-C and C-heteroatom bonds. Furthermore, functionalized substrates (see for example the above compounds **17**-**19**, **28**-**29** and **32**, formed by Pd-AAA with nucleophiles containing allyl-, butenyl- and pentenyl groups), open up new pathways to easily build up more complex molecules. To illustrate these aspects, we have prepared a range of chiral carbocycles (**43**-**49**) by simple tandem reactions involving allylic substitution of the substrate and ring-closing metathesis reactions (Scheme 3.5.4a) or the sequential allylic substitution and cycloisomerization of 1,6-enyne (Scheme 3.5.4b) reactions. Thus, the allylic substitution compounds (**17**-**19**, **28**-**29** and **32**; Scheme 3.5.3), bearing a terminal

alkene, can undergo clean ring-closing metathesis with no loss in enantiomeric excess. A range of 5-, 6- and 7-membered carbocycles with different R substituents (R= Me, Ph, *p*Tol) were therefore prepared in good yields and high enantioselectivities (compounds **43**-**48**; Scheme 3.5.4a). Also, the carbobicycle hyndrindane **49** is obtained by cycloisomerization of the 1,6-enyne **37**, produced from the AAA of **S2** with dimethyl propargylmalonate, using the methodology described by Uozumi *et al.* (Scheme 3.5.4b).

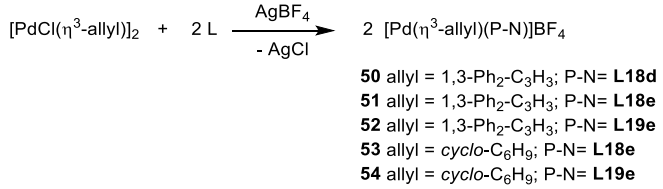


	n	R	R'	Overall yield	% ee
43	1	Ph	Me	82 %	99 (*R*)
44	1	*p*Tol	Me	80 %	99 (*R*)
45	1	Me	Me	81 %	81 (*R*)
46	2	Ph	Et	76 %	95 (*R*)
47	2	*p*Tol	Et	74 %	97 (*R*)
48	3	Ph	Et	69 %	99 (*R*)

Scheme 3.5.4. Preparation of chiral carbocycles via sequential allylic substitution of functionalized olefins/cyclisation reactions.

3.5.2.5. NMR study of key Pd-η^3-allyl intermediates

Our DFT studies have shown that enantioselectivity is determined during the nucleophilic attack (Table 3.5.2). Consequently, structural elucidation of the Pd-allyl intermediates and the determination of their relative reactivity towards the nucleophile are essential to understand their catalytic behavior. For this purpose we studied the Pd-η^3-allyl compounds **50**-**54** [Pd(η^3-allyl)(P-N)]BF_4 (P-N = **L18**-**L19d**-**e**) (Scheme 3.5.5) to obtain further insight into how ligand parameters affect catalytic performance.



Scheme 3.5.5. Preparation of [Pd(η^3-allyl)(P-N)]BF_4 complexes **50**-**54**.

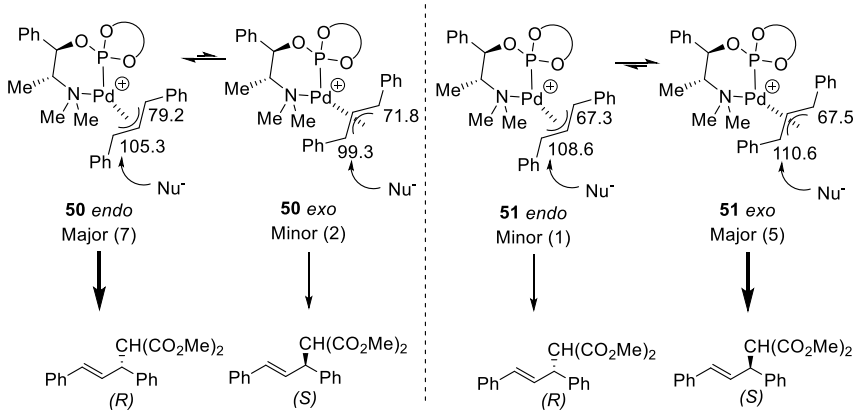
These ionic palladium complexes, which contain 1,3-diphenyl or cyclohexenyl allyl groups, were prepared using the previously reported method from the corresponding Pd-

allyl dimer and the appropriate ligand in the presence of silver tetrafluoroborate (Scheme 3.5.5).[27]

The complexes were characterized by elemental analysis and by ^{1}H, ^{13}C and ^{31}P NMR spectroscopy. The spectral assignments were based on information from ^{1}H-^{1}H, ^{31}P-^{1}H and ^{13}C-^{1}H correlation measurements in combination with ^{1}H-^{1}H NOESY experiments. Unfortunately, we were unable to obtain crystal of sufficient quality to perform X-ray diffraction measurements.

Palladium 1,3-diphenyl-allyl complexes

The VT-NMR study (30 ºC to -80 ºC) of Pd-allyl intermediates **50** and **51**, which respectively contains ephedrine-based ligands **L18d** and **L18e**, showed a mixture of two isomers in equilibrium at a ratio of 7:2 and 1:5, respectively.[28] Both isomers were unambiguously assigned by NMR to the two syn/syn Pd-η^3-endo and exo isomers (Scheme 3.5.6).



Scheme 3.5.6. Diastereoisomer Pd-allyl intermediates for **S1** with ligands **L18d** and **L18e**. The relative amounts of each isomer are shown in parentheses. The chemical shifts (in ppm) of the allylic terminal carbons are also shown.

In all cases, the NOE indicated interactions between the two terminal protons of the allyl group, which clearly indicates a *syn*/*syn* disposition (Figure 3.5.6). In addition, for the major isomer of **50** and the minor isomer of **51**, one of the methyl substituents of the amino group (the one that shows NOE interaction with the hydrogen attached to C-2) showed NOE between the terminal allyl proton *trans* to the phosphite moiety, while this interaction appeared with the central allyl proton in the minor isomer **50** and major isomer of **51** (Figure 3.5.6). Moreover, the other methyl substituent of the amino group (the one that shows NOE with the hydrogen attached to C-1) also shows NOE interaction with the central allyl proton in major isomer **50** and the minor isomer of **51**, while this interaction appears with the terminal allyl proton *trans* to the phosphite moiety for minor

and major isomers of **50** and **51**, respectively. Finally, the minor isomer of **50** and major isomer of **51** also showed NOE interactions between the terminal allyl proton *trans* to the amino group with one of the *tert*-butyl substituents at the biaryl phosphite moiety (the one that shows NOE contacts with the hydrogen attached to C-1). These interactions can be explained by assuming a *syn*/*syn* endo disposition for major and minor isomers of **50** and **51**, and a *syn*/*syn* exo disposition for minor and major isomers of **50** and **51** (Scheme 3.5.6). Although the population of the Pd-allyl intermediates obtained by DFT calculations is different than those find by NMR, the general trend is reproduced well. Thus, while for Pd/**L18d** the major isomer is Pd-η^3-*endo*, for Pd-**L18e** the major isomer is Pd-η^3-*exo*.

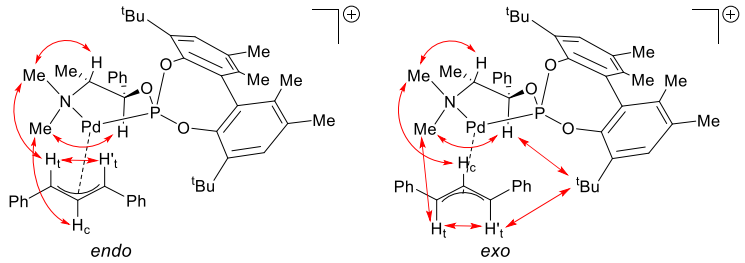
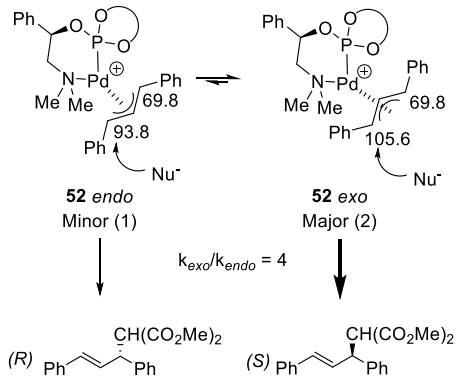


Figure 3.5.6. Relevant NOE contacts from the NOESY experiment of [Pd(η^3-1,3-diphenyl allyl)(**L18d**)]BF_4 (**50**) isomers are shown as example. The same NOE contacts were observed for [Pd(η^3-1,3-diphenylallyl)(**L18e**)]BF_4 (**51**) isomers.

In all isomers, the carbon NMR chemical shifts indicate that the most electrophilic allyl carbon terminus is *trans* to the phosphite moiety (Scheme 3.5.6). Assuming that the nucleophilic attack takes place at the more electrophilic allyl carbon terminus,[1] and in line with the DFT calculations, the stereochemical outcome of the reaction is not fully controlled by the population of the Pd-allyl intermediates (note that the diastereomeric excesses differ from the enantiomeric excesses). So, the relative electrophilicity of the terminal allylic carbons of each isomer plays an important role and have to been taken into account. In this respect, Pd/**L18d** catalyst shows higher electronic differentiation between the more electrophilic allylic terminal carbon atoms of both isomers ($\Delta(\delta^{13}C)$= 6 ppm) than in Pd/**L18e** ($\Delta(\delta^{13}C)$= 2 ppm). This higher electronic differentiation makes the major isomer of Pd/**L18d** to react faster than the major isomer of Pd/**L18e** and fully accounts for the higher enantioselectivity achieved with Pd/**L18d** than with Pd/**L18e**.
The VT-NMR study of Pd-allyl intermediate **52** containing ligand **L19e**, which differs from previous Pd/**L18d**-**e** catalysts in that the methyl substituent of the ephedrine ligand backbone has been removed, also had a mixture of two *syn*/*syn* Pd-η^3-*endo* and *exo* isomers, at a ratio 1:2 (Scheme 3.5.7).



Scheme 3.5.7. Diastereoisomer Pd-allyl intermediates for **S1** with ligand **L19e**. The relative amounts of each isomer are shown in parentheses. The chemical shifts (in ppm) of the allylic terminal carbons are also shown.

Also, the most electrophilic allyl carbon terminus was *trans* to the phosphite moiety. However, an important difference between complexes **50** and **51** is the higher electronic differentiation between the more electrophilic allylic terminus carbon atoms of both isomers in complex **52** ($\Delta(\delta^{13}C)$= 11 ppm) than in previous complexes **50** and **51** ($\Delta(\delta^{13}C)$= 6 and 2 ppm, respectively).

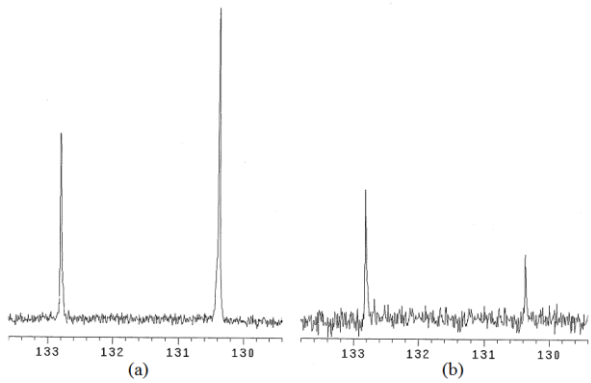
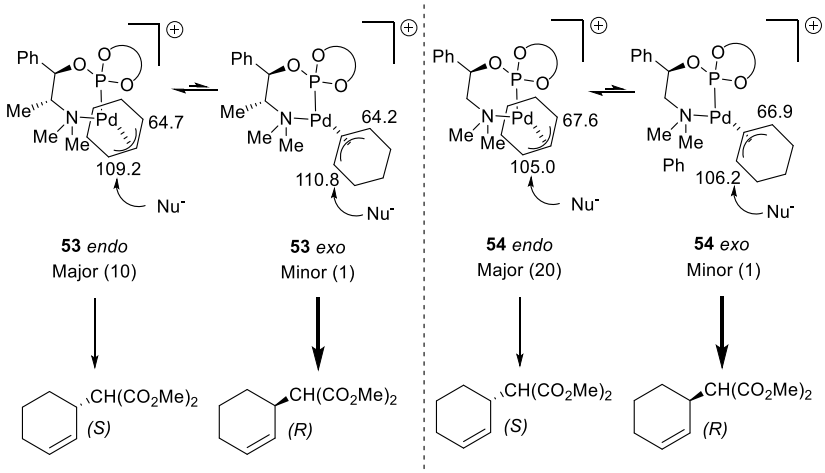


Figure 3.5.7. ^{31}P-{^{1}H}NMR spectra of [Pd(η^3-1,3-diphenylallyl)(**L19e**)]BF_4 (**52**) in CD_2Cl_2 at -80 ºC (a) before the addition of sodium malonate and (b) after the addition of sodium malonate.

This higher electronic differentiation may explain the higher enantioselectivity obtained with Pd/**L19e** than with Pd/**L18d**-**e**. Accordingly, the reactivity of the Pd-intermediates with sodium malonate at low temperature by in situ NMR indicates that the major Pd-η^3-exo isomer reacts 4 times faster than minor Pd-η^3-endo isomer (Figure 3.5.7), which fully agrees with the ee obtained experimentally.

Palladium 1,3-cyclohexenyl-allyl complexes

Finally, in an attempt to provide further information about the positive effect on enantioselectivity observed in the allylic substitution of the unhindered cyclic substrate **S2** when the methyl substituent of the ephedrine backbone was removed, we also studied the Pd-1,3-cyclohexenyl-allyl intermediate **53**, which contains ephedrine-based amino-phosphite ligand **L18e**, and compared it with its related amino-phosphite counterpart (Pd/**L19e**). The VT-NMR (35 °C to –80 °C) of Pd intermediates **53** and **54** showed a mixture of the two possible isomers at a ratio of 10:1 and 20:1, respectively (Scheme 3.5.8).



Scheme 3.5.8. Diastereoisomer Pd-allyl intermediates for **S2** with ligands **L18e** and **L19e**. The relative amounts of each isomer are shown in parentheses. The chemical shifts (in ppm) of the allylic terminal carbons are also shown.

The major isomers were unambiguously assigned by NOE to Pd-η^3-*endo* isomers (Figure 3.5.8). In both cases, the NOE indicates interactions between the central allyl proton and one of the methyl substituents of the amino group (the one that shows NOE with the hydrogen attached to C-1 of the ligand backbone) and with one of the *tert*-butyl substituents at the biaryl phosphite moiety (the one that also shows NOE contact with the hydrogen attached to C-1) (Figure 3.5.8). The carbon NMR chemical shifts indicated that the most electrophilic allylic terminus carbon is *trans* to the phosphite moiety. Assuming that the nucleophilic attack takes place at the most electrophilic allyl carbon terminus, and taking into account the observed stereochemical outcome of the reaction (70% (*S*) for complex **53** and 82% (*S*) for **54**), and the fact that the enantiomeric excesses of alkylation product **13** are different from the diastereoisomeric excesses of the Pd-intermediates (de = 81% (*S*) for **53** and de= 90% (*S*) for **54**), the minor isomers must react slightly faster than major isomers. This is in agreement with the slightly

higher electrophilicity of the allylic terminus carbon *trans* to the phosphite moiety located at the minor isomers (*i.e.* $\Delta(\delta^{13}C)$ around 1 ppm for Pd/**L18e**). The lower enantioselectivities obtained with Pd/ephedrine-based amino-phosphite ligand **L18e** than with related Pd/**L19e** catalytic system can therefore be attributed to the increase in the relative amount of fast reacting isomer *exo* with respect to isomer *endo* compared with the population of *endo* and *exo* isomers in Pd/**L19e**.

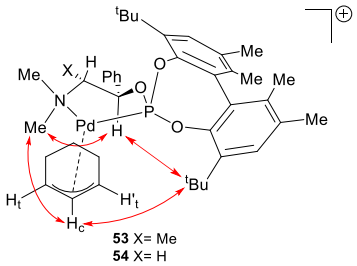


Figure 3.5.8. Relevant NOE contacts from the NOESY experiments for the major isomers of [Pd(η^3-1,3-cyclohexenylallyl)(**L**)]BF_4 (**53** and **54**; L= **L18e** and **L19e**, respectively).

3.5.3. Conclusions

A new library of modular amino-phosphite ligands **L15**-**L20a**-**g** has been successfully tested in the asymmetric Pd-catalyzed allylic substitution of substrates with different steric and electronic requirements applying a large variety of nucleophiles. These ligands, which are prepared in a few steps from readily available enantiopure aminoalcohols, include the benefits of a high stability of the amine moiety and the additional control provided by both the adaptability of the chiral cavity due to the biaryl-phosphite groups and the flexibility of the chiral pocket through a highly modular ligand scaffold. Other advantages of these ligands are that they are solid, stable to air and other oxidizing agents and therefore easy to handle and can be manipulated and stored in air. In simple two or three steps, several ligand parameters have been tuned to maximize the catalyst performance. Enantioselectivity is mainly controlled by the substituents/configuration at the biaryl phosphite moiety and by the amine substituents, while the configuration of the ephedrine-backbone affects less. Theoretically-guided optimization based on DFT studies allowed rationalizing the modifications required in the ligand for improving selectivity. Their results led to identifying one of the very few catalytic systems that can create C-C, C-N and C-O bonds in substrates with a variety of electronic and steric proprieties, using a wide range of nucleophiles, in high yields and enantioselectivities (ee's up to 99%). Further studies on the Pd-π-allyl intermediates provided a deep understanding of the effect of ligand parameters on the origin of enantioselectivity. Potential applications of the new Pd-amino-phosphite catalysts were demonstrated by the synthesis of a range of chiral 5-, 6- and 7-carbocycles by simple tandem reactions

with no loss in the enantioselectivity. These results open up the asymmetric Pd-catalyzed allylic substitution of several substrate types with a wide range of nucleophiles to the potential effective use of readily available and highly modular amino-phosphite ligands.

3.5.4. Experimental section

3.5.4.1. General Considerations

All reactions were carried out using standard Schlenk techniques under an atmosphere of argon. Solvents were purified and dried by standard procedures. Phosphorochloridites were easily prepared in one step from the corresponding biaryls.[29] Enantiopure amino-alcohol compounds **5**-**8**[12] and oxazolidine **9**[13] were prepared as previously described. Racemic substrates **S1**-**S7** were prepared as previously reported.[30] [Pd(η^3-1,3-Ph_2-C_3H_3)(μ-Cl)][31] and [Pd(η^3-cyclohexenyl)(μ-Cl)]$_2$[32] were prepared as previously described. Carbocyclic compound **49** was prepared following the methodology described by Uozumi et al.[33] ^{1}H, ^{13}C{^{1}H}, and ^{31}P{^{1}H} NMR spectra were recorded using a 400 MHz spectrometer. Chemical shifts are relative to that of $SiMe_4$ (^{1}H and ^{13}C) as internal standard or H_3PO_4 (^{31}P) as external standard. ^{1}H, ^{13}C and ^{31}P assignments were made on the basis of ^{1}H-^{1}H gCOSY, ^{1}H-^{13}C gHSQC and ^{1}H-^{31}P gHMBC experiments.

3.5.4.2. Preparation and characterization details of N-dimethyl aminoalcohols 5-8

In a round-bottom flask, corresponding aminoalcohol (**1**-**4**) (10 mmol) was dissolved in distilled water (100 mL) and paraformaldehyde (20 eq.) was added followed by the addition of formic acid (20 eq., 85% v/v in water). The reaction was stirred at reflux for 6 hours and NaOH (1M solution) was added to neutralise the reaction. Then, the aqueous solution was extracted with AcOEt (3 x 25 mL) and the organic phases were dried over $MgSO_4$. Removal of organic solvent provided dimethyl aminoalcohols (**5**-**8**) as yellowish oils which were precipitated with hexane to provided compounds **5**-**8** as white solids.

(1*S*,2*R*)-2-(Dimethylamino)-1-phenylpropan-1-ol (5): Yield: 1.63 g (91%); ^{1}H NMR ($CDCl_3$): δ = 0.75 (d, 3H, CH_3, $^3J_{H-H}$= 6.4 Hz), 2.26 (s, 6H, CH_3, NMe_2), 2.45 (m, 1H, CH-N), 4.86 (d, 1H, CH-O, $^3J_{H-H}$= 3.6Hz), 7.15-7.26 (m, 4H, CH=); ^{13}C NMR ($CDCl_3$): δ = 10.2 (CH_3), 43.2 (CH_3, NMe_2), 65.5 (CH-N), 72.3 (CH-O), 126.1 (CH=), 126.8 (CH=), 128.1 (CH=), 141.9 (C).

(1*R*,2*R*)-2-(Dimethylamino)-1-phenylpropan-1-ol (6): Yield: 1.63 g (90%); ^{1}H NMR ($CDCl_3$): δ = 0.71 (d, 3H, CH_3, $^3J_{H-H}$= 6.4 Hz), 2.3 (s, 6H, CH_3, NMe_2), 2.55 (m, 1H, CH-N), 4.2 (d, 1H, CH-O, $^3J_{H-H}$= 10 Hz), 7.34 (m, 4H, CH=); ^{13}C NMR ($CDCl_3$): δ = 6.3 (CH_3), 39.9 (CH_3, NMe_2), 65.9 (CH-N), 74.9 (CH-O), 127.3 (CH=), 127.6 (CH=), 128.2 (CH=), 142.0 (C).

(*R*)-2-(Dimethylamino)-1-phenylethan-1-ol (7): Yield: 1.53 g (93%); ^{1}H NMR ($CDCl_3$): δ = 2.34 (s, 6H, CH_3, NMe_2), 2.35-2.51 (m, 2H, CH_2-N), 4.7 (dd, 1H, CH-O, $^{3}J_{H-H}$= 10.8 Hz, $^{3}J_{H-H}$= 10.4 Hz), 7.37 (m, 4H, CH=); ^{13}C NMR (CDCl3): δ = 45.3 (CH_3, NMe_2), 67.6 (CH_2-N), 69.6 (CH-O), 125.8 (CH=), 127.4 (CH=), 128.3 (CH=), 142.3 (C).

(*S*)-2-(Dimethylamino)-2-phenylethan-1-ol (8): Yield: 1.56 g (95%); ^{1}H NMR ($CDCl_3$): δ = 2.18 (s, 6H, CH_3, NMe_2), 3.0 (bs, OH), 3.55 (m, 1H, CH-N), 3.66 (m, 1H, CH_2-O), 3.93 (m, 1H, CH_2-O), 7.18-7.36 (m, 4H, CH=); ^{13}C NMR ($_{CDCl3}$): δ = 41.4 (CH_3, NMe_2), 61.3 (CH-N), 70.2 (CH_2-O), 127.8 (CH=), 128.1 (CH=), 128.9 (CH=), 135.7 (C).

3.5.4.3. Preparation and characterization details of oxazolidine 9

Azeotropically dried *p*-TSA (450 mg, 0.5 mmol) was dissolved in toluene (50 mL). Then, ephedrine derivative **1** (1.65 g, 10 mmol) was added, followed by 2,2-dimethoxypropane (2.5 mL, 20 mmol). The resulting mixture was stirred 72 hours under reflux. The reaction mixture was quenched with $NaHCO_3$. Aqueous layer was washed with CH_2Cl_2 (3 x 20 mL) and dried over $MgSO_4$. Removal of organic solvent by rotary evaporator afforded yellow oil, which was dissolved in hexane. Filtration and evaporation of solvent provided (4*R*,5*S*)-2,2,3,4-tetramethyl-5-phenyloxazolidine **9** as a yellow-pale solid. Yield: 1.5 g (72%). ^{1}H NMR ($CDCl_3$): δ = 1.1 (d, 3H, CH_3, $^{3}J_{H-H}$= 6.0 Hz), 1.33 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 2.28 (s, 3H, CH_3, NMe), 2.55 (m, 1H, CH-N), 4.46 (d, 1H, CH-O, $^{3}J_{H-H}$= 9.2 Hz), 7.29-7.37 (m, 4H, CH=); ^{13}C NMR ($CDCl_3$): δ = 14.5 (CH_3), 21.6 (CH_3), 27.7 (CH_3), 32.8 (CH_3, NMe), 65.1 (CH-N), 84.9 (CH-O), 95.2 (CMe_2), 126.6 (CH=), 127.8 (CH=), 128.3 (CH=), 139.9 (C).

3.5.4.4. Preparation of (1*S*,2*R*)-2-(*tert*-butyl(methyl)amino)-1-phenylpropan-1-ol 10

Compound **9** (1g, 4.88 mmol) was dissolved in dry ether (20 mL). The solution was stirred in an ice-bath for 5 minutes. Then, MeMgBr (3 M in diethyl ether) (4.96 mL, 14.64 mmol) was added dropwise. The solution was warmed up to reflux and the reaction was kept at that temperature for 8 hours. The reaction was quenched with saturated NH_4Cl (20 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over $MgSO_4$ and the removal of solvents provided **10** as a yellow-pale solid. Yield: 1.0 g (93%). ^{1}H NMR ($CDCl_3$): δ = 0.94 (d, 3H, CH_3, $^{3}J_{H-H}$ = 7.2 Hz), 1.06 (s, 9H, ^{t}Bu), 2.0 (s, 3H, CH_3-N), 3.35 (m, 1H, CH-N), 4.50 (m, 1H, CH-O), 7.21-7.32 (m, 4H, CH=). ^{13}C NMR ($CDCl_3$): δ = 12.9 (CH_3), 27.1 (CH_3, ^{t}Bu), 30.9 (CH_3, NMe), 55.1 (C, ^{t}Bu), 55.2 (CH-N), 75.3 (CH-O), 126.7 (CH=), 126.8 (CH=), 127.5 (CH=), 143.1 (C).

3.5.4.5. Preparation of (1*S*,2*R*)-2-(methyl(2-phenylpropan-2-yl)amino)-1-phenyl propan-1-ol 11

Compound **9** (1g, 4.88 mmol) was dissolved in dry THF (20 mL). The solution was stirred in an ice-bath for 5 minutes. Then, PhMgBr (1.M in THF) (14.7 mL, 14.64 mmol) was added dropwise. Then, the reaction was warmed up to reflux and the reaction was kept at that temperature for 8 hours. The reaction was quenched with saturated NH_4Cl (20 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over $MgSO_4$. The organic solvents were removed and the crude was purified by silica flash chromatography (AcOEt:light petroleum:NEt_3 6:2:0.1) to afford **11** as a white solid. Yield: 1.2 g (87%). ^{1}H NMR ($CDCl_3$): δ = 0.95 (d, 3H, CH_3, $^3J_{H-H}$ = 7.1 Hz), 1.34 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 2.13 (s, 3H, CH_3-N), 3.20 (m, 1H, CH-N), 4.50 (d, 1H, CH-O, $^3J_{H-H}$ = 4.8 Hz), 7.10-7.38 (m, 10H, CH=). ^{13}C NMR ($CDCl_3$): δ = 11.7 (CH_3), 24.8 (CH_3), 25.6 (CH_3), 30.9 (CH_3, NMe), 56.4 (C, CMe_2Ph), 61.0 (CH-N), 77.6 (CH-O), 126.2 (CH=), 126.3 (CH=), 126.4 (CH=), 126.8 (CH=), 127.7 (CH=), 127.9 (CH=), 143.3 (C), 149.0 (C).

3.5.4.6. General procedure for the preparation of amino-phosphite ligands L15-L20a-g

Phosphorochloridite (1.1 mmol) produced *in situ* was dissolved in toluene (5 mL) and pyridine (0.18 mL, 2.3 mmol) was added. Amino-alcohol (1 mmol) was azeotropically dried with toluene (3 x 1 mL) and then dissolved in toluene (5 mL), to which pyridine (0.18 mL, 2.3 mmol) was added. The phosphorochloridite solution was transferred slowly to the solution of amino-alcohol. The reaction mixture was stirred at room temperature for 90 minutes (ligands **L15**, **L18**-**L20a**-**g**) or 15 hours (ligands **L16**-**L17a**-**g**), and the pyridine salts were removed by filtration. Evaporation of the solvent gave a white foam, which was purified by flash chromatography in alumina (toluene/NEt_3 100:1) to produce the corresponding ligand as white solid.

L15a: Yield: 303 mg (49%). ^{31}P NMR (C_6D_6): δ = 150.5 (s). ^{1}H NMR (C_6D_6): δ = 0.98 (d, 3H, CH_3, $^3J_{H-H}$ = 6.8 Hz), 1.29 (s, 9H, CH_3, ^{t}Bu), 1.3 (s, 9H, CH_3, ^{t}Bu), 1.48 (s, 9H, CH_3, ^{t}Bu), 1.62 (s, 9H, CH_3, ^{t}Bu), 2.14 (s, 6H, CH_3, NMe_2), 2.59 (m, 1H, CH-N), 5.55 (dd, 1H, CH-O, $^3J_{H-P}$= 8 Hz, $^3J_{H-H}$ = 4 Hz,), 7.03-7.25 (m, 7H, CH=), 7.33 (d, 1H, CH=, $^4J_{H-H}$ = 2.4 Hz), 7.37 (d, 1H, CH=, $^4J_{H-H}$ = 2.4 Hz), 7.58 (d, 1H, CH=, $^4J_{H-H}$ = 2.0 Hz), 7.61 (d, 1H, CH=, $^4J_{H-H}$ = 2.8Hz). ^{13}C NMR (C_6D_6): δ = 8.4 (CH_3), 28.8 (CH_3,^{t}Bu), 28.9 (CH_3, ^{t}Bu), 29.9 (CH_3,^{t}Bu), 30.2 (CH_3,^{t}Bu), 33.2 (C, ^{t}Bu), 34.1 (C, ^{t}Bu), 34.3 (C, ^{t}Bu), 40.9 (CH_3, NMe), 41.0 (CH_3, NMe), 64.7 (d, CH-N, $^3J_{C-P}$= 9.2 Hz), 76.6 (d, CH-O, $^2J_{C-P}$ = 9.2 Hz), 122.6-145.4 (aromatic carbons). TOF-MS (ESI+): m/z = 618.4101, calcd. for $C_{39}H_{56}NO_3P$ $[M+H]^+$: 618.4071.

L15b: Yield: 170 mg (30%). ^{31}P NMR (C_6D_6): δ = 150.2 (s). ^{1}H NMR (C_6D_6): δ = 1.00 (d, 3H, CH_3, $^{3}J_{H-H}$ = 6.4 Hz), 1.38 (s, 9H, CH_3, ^{t}Bu), 1.56 (s, 9H, CH_3, ^{t}Bu), 2.14 (s, 6H, CH_3, NMe_2), 2.57 (m, 1H, CH-N), 3.33 (s, 3H, CH_3, OMe), 3.34 (s, 3H, CH_3, OMe), 5.5 (dd, 1H, CH-O, $^{3}J_{H-P}$= 8.0 Hz, $^{3}J_{H-H}$ = 4.0 Hz), 6.67 (d, 1H, CH=, $^{4}J_{H-H}$ = 2.8 Hz), 6.72 (d, 1H, CH=, $^{4}J_{H-H}$ = 3.2 Hz), 7.01-7.26 (m, 7H, CH=). ^{13}C NMR (C_6D_6): δ = 9.5 (CH_3), 30.6 (CH_3, ^{t}Bu), 30.7 (CH_3, ^{t}Bu), 35.1(C, ^{t}Bu), 35.2 (C, ^{t}Bu), 41.9 (CH_3, NMe), 42.1 (CH_3, NMe), 54.7 (CH_3, OMe), 65.8 (CH-N), 77.6 (d, CH-O, $^{2}J_{C-P}$ = 9.9 Hz), 112.6-155.9 (aromatic carbons). TOF-MS (ESI+): m/z = 566.3028, calcd. for $C_{33}H_{44}NO_5P$ $[M+H]^+$: 566.3030.

L15c: Yield: 194 mg (32%). ^{31}P NMR (C_6D_6): δ = 152.4 (s). ^{1}H NMR (C_6D_6): δ = 0.33 (s, 9H, CH_3-Si), 0.44 (s, 9H, CH_3-Si), 0.95 (d, 3H, CH_3, $^{3}J_{H-H}$ = 6.8 Hz), 2.10 (s, 6H, CH_3, NMe_2), 2.68 (m, 1H, CH-N), 5.45 (dd, 1H, CH-O, $^{3}J_{H-P}$= 8.8 Hz, $^{3}J_{H-H}$ = 5.6 Hz), 7.03-7.46 (m, 11H, CH=). ^{13}C NMR (C_6D_6): δ = 0.0 (CH_3-Si), 0.1 (CH_3-Si), 9.7 (CH_3), 42.1 (CH_3, NMe_2), 65.8 (d, CH-N, $^{3}J_{C-P}$= 2.3 Hz), 78.1 (d, CH-O, $^{2}J_{C-P}$ = 4.8 Hz), 124.7-155.2 (aromatic carbons). TOF-MS (ESI+): m/z = 538.2354, calcd. for $C_{29}H_{40}NO_3PSi_2$ $[M+H]^+$: 538.2357.

L15d: Yield: 188 mg (32%). ^{31}P NMR (C_6D_6): δ = 141.1 (s). ^{1}H NMR (C_6D_6): δ = 1.12 (d, 3H, CH_3, $^{3}J_{H-H}$ = 7.2 Hz), 1.46 (s, 9H, CH_3, ^{t}Bu), 1.63 (s, 9H, CH_3, ^{t}Bu), 1.69 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 2.14 (s, 3H, CH_3), 2.15 (s, 3H, CH_3), 2.16 (s, 6H, CH_3, NMe_2), 2.82 (m, 1H, CH-N), 5.4 (dd, 1H, CH-O, $^{3}J_{H-P}$= 8.0 Hz, $^{3}J_{H-H}$ = 5.6 Hz), 7.0-7.3 (m, 7H, CH=). ^{13}C NMR (C_6D_6): δ = 8.1 (CH_3), 15.1 (CH_3), 15.3 (CH_3), 19.0 (CH_3), 19.1 (CH_3), 29.9 (d, CH_3, ^{t}Bu, J_{C-P}= 5.4 Hz), 30.4 (CH_3, ^{t}Bu), 33.2 (C, ^{t}Bu), 33.7 (C, ^{t}Bu), 40.5 (CH_3, NMe), 40.6 (CH_3, NMe), 63.9 (d, CH-N, $^{3}J_{C-P}$= 6.1 Hz), 77.3 (d, CH-O, $^{2}J_{C-P}$ = 6.2 Hz), 124.3-144.6 (aromatic carbons). TOF-MS (ESI+): m/z = 562.3452, calcd. for $C_{35}H_{48}NO_3P$ $[M+H]^+$: 562.3445.

L15e: Yield: 182 mg (31%). ^{31}P NMR (C_6D_6): δ =144.9 (s). ^{1}H NMR (C_6D_6): δ = 0.78 (d, CH_3, 3H, $^{3}J_{H-H}$ = 6.4 Hz), 1.41 (s, 9H, CH_3, ^{t}Bu), 1.59 (s, 9H, CH_3, ^{t}Bu), 1.66 (s, 3H, CH_3), 1.72 (s, 3H, CH_3), 2.03 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 2.11 (s, 6H, CH_3, NMe_2), 2.37 (m, 1H, CH-N), 5.41 (dd, 1H, CH-O, $^{3}J_{H-P}$= 8.0 Hz, $^{3}J_{H-H}$ = 4.0 Hz), 6.95-7.22 (m, 7H, CH=). ^{13}C NMR (C_6D_6): δ = 9.7 (CH_3), 16.2 (CH_3), 16.4 (CH_3), 20.0 (CH_3), 20.1(CH_3), 30.9 (d, CH_3, ^{t}Bu, J_{C-P}= 4.6 Hz), 31.2 (CH_3, ^{t}Bu), 34.5 (C, ^{t}Bu), 34.7 (C, ^{t}Bu), 42.0 (CH_3, NMe), 42.3 (CH_3, NMe), 62.2 (CH-N), 77.2 (d, CH-O, $^{2}J_{C-P}$ = 10.7 Hz), 125.3-146.2 (aromatic carbons). TOF-MS (ESI+): m/z = 562.3448, calcd. for $C_{35}H_{48}NO_3P$ $[M+H]^+$: 562.3445.

L15f: Yield: 439 mg (69%). ^{31}P NMR (C_6D_6): δ = 155.8 (s). ^{1}H NMR (C_6D_6): δ = 0.40 (s, 9H, CH_3, $SiMe_3$), 0.51 (s, 9H, CH_3, $SiMe_3$), 0.72 (d, CH_3, 3H, $^{3}J_{H-H}$ = 6.8 Hz), 1.96 (s, 6H, CH_3, NMe_2), 2.50 (m, 1H, CH-N), 5.43 (dd, 1H, CH-O, $^{3}J_{H-P}$= 8.4 Hz, $^{3}J_{H-H}$ = 4.8 Hz), 6.82-7.4 (m, 5H, CH=), 7.4 (d, 1H, CH=, $^{3}J_{H-H}$ = 8.4Hz), 7.70 (d, 1H, CH=, $^{3}J_{H-H}$ = 8.0 Hz), 7.8 (d, 1H, CH=, $^{3}J_{H-H}$ = 8.4 Hz), 8.1 (s, 1H, CH=), 7.9 (s, 1H, CH=). ^{13}C NMR (C_6D_6):

δ = -0.4 (d, CH_3, $SiMe_3$, J_{C-P}= 4.6 Hz), -0.1 (CH_3, $SiMe_3$), 9.3 (CH_3), 41.8 (CH_3, NMe_2), 66.0 (CH-N), 77.5 (d, CH-O, $^2J_{C-P}$ = 5.3 Hz), 122.8-152.6 (aromatic carbons). TOF-MS (ESI+): m/z = 638.2673, calcd. for $C_{37}H_{44}NO_3PSi_2$ $[M+H]^+$: 638.2670.

L15g: Yield: 400 mg (63%). ^{31}P NMR (C_6D_6): δ = 148.5 (s). ^1H NMR (C_6D_6): δ = 0.51 (s, 9H, CH_3, $SiMe_3$), 0.52 (s, 9H, CH_3, $SiMe_3$), 1.09 (d, 3H, CH_3, $^3J_{H-H}$ = 6.4 Hz), 2.05 (s, 6H, CH_3, NMe_2), 2.87 (m, 1H, CH-N), 5.35 (dd, 1H, CH-O, $^3J_{H-P}$= 8.4 Hz, $^3J_{H-H}$ = 6.5 Hz), 6.7-7.3 (m, 6H, CH=), 7.68 (m, 2H, CH=), 7.95 (s, 1H; CH=), 8.05 (s, 1H, CH=). ^{13}C NMR (C_6D_6): δ = -0.2 (d, CH_3, $SiMe_3$, J_{C-P} = 4.6 Hz), -0.1 (CH_3, $SiMe_3$), 9.2 (CH_3), 41.3 (CH_3, NMe_2), 64.3 (d, CH-N, $^3J_{C-P}$= 4.6 Hz), 78.9 (d, CH-O, $^2J_{C-P}$ = 2.3 Hz), 122.4-152.3 (aromatic carbons). TOF-MS (ESI+): m/z = 638.2669, calcd. for $C_{37}H_{44}NO_3PSi_2$ $[M+H]^+$: 638.2670.

L16a: Yield: 330 mg (50%). ^{31}P NMR (C_6D_6): δ = 148.4 (s). ^1H NMR (C_6D_6): δ = 0.83 (s, 9H, CH_3, ^tBu, N^tBu), 1.21 (d, 3H, CH_3, $^3J_{H-H}$= 6.4 Hz), 1.31 (s, 9H, CH_3, ^tBu), 1.33 (s, 9H, CH_3, ^tBu), 1.56 (s, 9H, CH_3, ^tBu), 1.61 (s, 9H, CH_3, ^tBu), 2.11 (s, 3H, NMe), 3.4 (m, 1H, CH-N), 5.25 (m, 1H, CH-O), 7.0-7.2 (m, 6H, CH=), 7.37 (m, 2H, CH=), 7.60 (d, 1H, CH=, $^4J_{H-H}$= 2Hz). ^{13}C NMR (C_6D_6): δ = 12.8 (CH_3), 26.8 (CH_3, ^tBu), 29.3 (NMe), 31.0 (CH_3, ^tBu), 31.1 (CH_3, ^tBu), 31.2 (CH_3, ^tBu), 31.3 (CH_3, ^tBu), 34.3 (C, ^tBu), 35.2 (C, ^tBu), 35.3 (C, ^tBu), 54.1 (C, ^tBu, N^tBu), 56.6 (d, CH-N, $^3J_{C-P}$ = 3.1 Hz), 81.3 (d, CH-O, $^2J_{C-P}$= 5.43 Hz), 123.8-146.7 (aromatic carbons). TOF-MS (ESI+): m/z = 660.5438, calcd. for $C_{42}H_{62}NO_3P$ $[M+H]^+$: 660.4540.

L16d: Yield: 422.6 mg (70%). ^{31}P NMR (C_6D_6): δ = 141.1 (s). ^1H NMR (C_6D_6): δ = 0.84 (s, 9H, CH_3, ^tBu, N^tBu), 2.15 (d, 3H, CH_3, $^3J_{H-H}$= 6.4 Hz), 1.51 (s, 9H, CH_3, ^tBu), 1.63 (s, 9H, CH_3, ^tBu), 1.69 (s, 3H, CH_3), 1.71 (s, 3H, CH_3,) , 2.04 (s, 3H, CH_3), 2.11 (s, 3H, CH_3), 2.16 (s, 3H, NMe), 3.4 (m, 1H, CH-N), 5.1 (m, 1H, CH-O), 7.0-7.3 (m, 7H, CH=). ^{13}C NMR (C_6D_6): δ = 12.7 (CH_3), 16.1 (CH_3), 16.3 (CH_3), 20.0 (CH_3), 20.1 (CH_3), 26.8 (CH_3, ^tBu), 29.4 (NMe), 31.1 (d, CH_3, ^tBu, J_{C-P} = 5.3 Hz), 31.4 (CH_3, ^tBu), 34.4(C, ^tBu), 34.7 (C, ^tBu), 54.2 (C, ^tBu, N^tBu), 56.4 (d, CH-N, $^3J_{C-P}$ = 5.6 Hz), 81.6 (d, CH-O, $^2J_{C-P}$= 3.0 Hz), 125.3-145.6 (aromatic carbons). TOF-MS (ESI+): m/z = 604.3917, calcd. for $C_{39}H_{56}NO_3P$ $[M+H]^+$: 604.3914.

L16e: Yield: 392 mg (65%). ^{31}P NMR (C_6D_6): δ = 142.9 (s). ^1H NMR (C_6D_6): δ = 0.60 (s, 9H, CH_3, ^tBu, N^tBu), 1.0 (d, 3H, CH_3, $^3J_{H-H}$= 6.8 Hz), 1.51 (s, 9H, CH_3, ^tBu), 1.60 (s, 9H,CH_3, ^tBu), 1.66 (s, 3H, CH_3), 1.75 (s, 3H, CH_3,) , 1.95 (s, 3H, NMe), 2.0 (s, 3H, CH_3), 2.1 (s, 3H, CH_3), 3.2 (m, 1H, CH-N), 5.0 (m, 1H, CH-O), 7.0-7.45 (m, 7H, CH=). ^{13}C NMR (C_6D_6): δ = 13.8 (CH_3), 16.2 (CH_3), 16.4 (CH_3), 20.0 (CH_3), 20.1 (CH_3), 26.8 (CH_3, ^tBu), 28.7 (NMe), 31.2 (d, CH_3, ^tBu, J_{C-P} = 5.4 Hz), 31.6 (CH_3, ^tBu), 34.5 (C, ^tBu), 34.8 (C, ^tBu), 53.7 (C, ^tBu, N^tBu), 56.7 (d, CH-N, $^3J_{C-P}$ = 2.3 Hz), 80.3 (d, CH-O, $^2J_{C-P}$= 5.3 Hz), 125.9-145.6 (aromatic carbons). TOF-MS (ESI+): m/z = 604.3912, calcd. for $C_{39}H_{56}NO_3P$ $[M+H]^+$: 604.3914.

L17a: Yield: 262 mg (37%). ^{31}P NMR (C_6D_6): δ = 148.90 (s). ^{1}H NMR (C_6D_6): δ = 1.01 (d, 3H, CH_3, $^{3}J_{H-H}$= 6.8 Hz), 1.09 (s, 3H, CH_3), 1.23 (s, 3H, CH_3), 1.28 (s, 9H, CH_3, ^{t}Bu), 1.39 (s, 9H, CH_3, ^{t}Bu), 1.55 (s, 9H, CH_3, ^{t}Bu), 1.86 (s, 9H, CH_3, ^{t}Bu), 2.2 (s, 3H, NMe), 3.2 (m, 1H, CH-N), 5.4 (dd, 1H, CH-O, $^{3}J_{H-P}$= 9.6 Hz, $^{3}J_{H-H}$ = 4.4 Hz), 7.0-7.4 (m, 12H, CH=), 7.58 (d, 1H, CH=, $^{4}J_{H-H}$ = 2.8 Hz), 7.62 (d, 1H, CH=, $^{4}J_{H-H}$ = 2.8 Hz). ^{13}C NMR (C_6D_6): δ = 9.9 (CH_3), 22.3 (CH_3), 25.2 (CH_3), 28.9 (NMe), 29.9 (CH_3, ^{t}Bu), 30.0 (CH_3, ^{t}Bu), 30.1 (CH_3, ^{t}Bu), 30.2 (CH_3, ^{t}Bu), 33.2 (C, ^{t}Bu), 34.2(C, ^{t}Bu), 34.3 (C, ^{t}Bu), 56.4 (d, CH-N, $^{3}J_{C-P}$ = 3.8 Hz), 59.8 (C, N-CMe_2Ph), 81.2 (d, CH-O, $^{2}J_{C-P}$ = 6.9 Hz), 122.7-148.7 (aromatic carbons). TOF-MS (ESI+): m/z = 722.4694, calcd. for $C_{47}H_{64}NO_3P$ $[M+H]^+$: 722.4697.

L17d: Yield: 244 mg (37%). ^{31}P NMR (C_6D_6): δ = 143.4 (s). ^{1}H NMR (C_6D_6): δ = 1.01 (d, 3H, CH_3, $^{3}J_{H-H}$= 6.9 Hz), 1.03, (s, 3H, CH_3), 1.15 (s, 3H, CH_3), 1.59 (s, 9H, CH_3, ^{t}Bu), 1.65 (s, 9H, CH_3, ^{t}Bu), 1.71 (s, 3H, CH_3), 1.8 (s, 3H, CH_3), 1.91 (s, 3H, NMe), 2.06 (s, 3H, CH_3), 2.14 (s, 3H, CH_3), 3.3 (m, 1H, CH-N), 5.3 (m, 1H, CH-O), 7.0-7.3 (m, 12H, CH=). ^{13}C NMR (C_6D_6): δ = 10.9 (CH_3), 15.2 (CH_3), 15.4 (CH_3), 19.0 (CH_3) 23.4 (CH_3), 24.7 (CH_3), 28.2 (NMe), 30.2 (d, CH_3, ^{t}Bu, J_{C-P}= 5.3 Hz), 30.5 (CH_3, ^{t}Bu), 33.4 (C, ^{t}Bu), 33.7 (C, ^{t}Bu), 56.3 (d, CH-N, $^{3}J_{C-P}$= 2.3 Hz), 59.4 (C, N-CMe_2Ph), 80.7 (d, CH-O, $^{2}J_{C-P}$ = 6.1 Hz), 124.3-148.8 (aromatic carbons). TOF-MS (ESI+): m/z = 666.4068, calcd. for $C_{43}H_{56}NO_3P$ $[M+H]^+$: 666.4071.

L17e: Yield: 331.0 mg (50%). ^{31}P NMR (C_6D_6): δ = 148.90 (s). ^{1}H NMR (C_6D_6): δ = 1.02 (d, 3H, CH_3, $^{3}J_{H-H}$= 6.8 Hz), 1.03 (s, 3H, CH_3), 1.16 (s, 3H, CH_3), 1.59 (s, 9H, CH_3, ^{t}Bu), 1.65 (s, 9H, CH_3, ^{t}Bu), 1.71 (s, 3H, CH_3), 1.79 (s, 3H, CH_3), 2.01 (s, 3H, CH_3, NMe), 2.06 (s, 3H, CH_3), 2.15 (s, 3H, CH_3), 3.31 (m, 1H, CH-N), 5.3 (m, 1H, CH-O), 7.0-7.4 (m, 12H, CH=). ^{13}C NMR (C_6D_6): δ = 11.9 (CH_3), 16.2 (CH_3), 16.5 (CH_3), 20.1 (CH_3) 24.6 (CH_3), 25.7 (CH_3), 29.2 (NMe), 31.2 (d, CH_3, ^{t}Bu, J_{C-P}= 5.3 Hz), 31.5 (CH_3, ^{t}Bu), 34.5 (C, ^{t}Bu), 34.8(C, ^{t}Bu), 57.3 (CH-N), 60.5 (C, N-CMe_2Ph), 81.7 (d, CH-O, $^{2}J_{C-P}$ = 6.1 Hz), 125.3-149.9 (aromatic carbons). TOF-MS (ESI+): m/z = 666.4072, calcd. for $C_{43}H_{56}NO_3P$ $[M+H]^+$: 666.4071.

L18a: Yield: 276 mg (43%). ^{31}P NMR (C_6D_6): δ = 148.4 (s). ^{1}H NMR (C_6D_6): δ = 0.47 (d, 3H, CH_3, $^{3}J_{H-H}$ = 6.8 Hz), 1.24 (s, 9H, CH_3, ^{t}Bu), 1.25 (s, 9H, CH_3, ^{t}Bu), 1.35 (s, 9H, CH_3, ^{t}Bu), 1.62 (s, 9H, CH_3, ^{t}Bu), 2.09 (s, 6H, CH_3, NMe_2), 2.78 (m, 1H, CH-N), 5.06 (dd, 1H, CH-O, $^{3}J_{H-P}$ = 8 Hz, $^{3}J_{H-H}$ = 4 Hz), 6.9-7.1 (m, 7H, CH=), 7.27 (d, 1H, CH=, $^{4}J_{H-H}$ = 2.4 Hz), 7.33 (d, 1H, CH=, $^{4}J_{H-H}$ = 2.8 Hz), 7.46 (d, 1H, CH=, $^{4}J_{H-H}$ = 2.4 Hz), 7.57 (d, 1H, CH=, $^{4}J_{H-H}$ = 2.4 Hz). ^{13}C NMR (C_6D_6): δ = 7.9 (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), 33.2 (C, ^{t}Bu), 34.3 (C, ^{t}Bu), 40.9 (CH_3, NMe), 41.0 (CH_3, NMe), 64.7 (d, CH-N, $^{3}J_{C-P}$= 1.5 Hz), 76.6 (d, CH-O, $^{2}J_{C-P}$ = 9.2Hz), 123.6-145.8 (aromatic carbons). TOF-MS (ESI+): m/z = 618.4070, calcd. for $C_{39}H_{56}NO_3P$ $[M+H]^+$: 618.4071.

L18d: Yield: 344 mg (61%). ^{31}P NMR (C_6D_6): δ = 139.0 (s). ^{1}H NMR (C_6D_6): δ = 0.62 (d, 3H, CH_3, $^{3}J_{H-H}$ = 7.2 Hz), 1.48 (s, 9H, CH_3, ^{t}Bu), 1.6 (s, 9H, CH_3, ^{t}Bu), 1.66 (s, 3H, CH_3), 1.67 (s, 3H, CH_3), 2.04 (s, 3H, CH_3), 2.1 (s, 3H, CH_3), 2.15 (s, 6H, CH_3, NMe_2), 3.0 (m, 1H, CH-N), 5.1 (dd, 1H, CH-O, $^{3}J_{H-H}$ = 5.6 Hz, $^{3}J_{H-P}$= 8.0 Hz), 6.9-7.2 (m, 7H, CH=). ^{13}C NMR (C_6D_6): δ = 7.4 (CH_3), 15.1 (CH_3), 15.3 (CH_3), 19.0 (CH_3), 30.0 (d, CH_3, ^{t}Bu, J_{C-P}= 5.4 Hz), 30.4 (CH_3, ^{t}Bu), 33.3 (C, ^{t}Bu), 33.7 (C, ^{t}Bu), 40.1 (CH_3, NMe), 40.2 (CH_3, NMe), 63.9 (d, CH-N, $^{3}J_{C-P}$= 3.8 Hz), 77.6 (d, CH-O, $^{2}J_{C-P}$ = 10.7 Hz), 126.3-144.6 (aromatic carbons). TOF-MS (ESI+): m/z = 562.3440, calcd. for $C_{35}H_{48}NO_3P$ $[M+H]^+$: 562.3445.

L18e: Yield: 324 mg (58%). ^{31}P NMR (C_6D_6): δ = 144.7 (s). ^{1}H NMR (C_6D_6): δ = 0.4 (d, 3H, CH_3, $^{3}J_{H-H}$ = 7.2 Hz), 1.29 (s, 9H, CH_3, ^{t}Bu), 1.67 (s, 9H, CH_3, ^{t}Bu), 1.68 (s, 3H, CH_3), 1.72 (s, 3H, CH_3), 2.07 (s, 3H, CH_3), 2.09 (s, 3H, CH_3), 2.11 (s, 6H, CH_3, NMe_2), 2.65 (m, 1H, CH-N), 4.95 (m, 1H, CH-O), 7.05-7.25 (m, 7H, CH=). ^{13}C NMR (C_6D_6): δ = 7.5 (CH_3), 16.2 (CH_3), 16.3 (CH_3), 19.9 (CH_3), 20.1 (CH_3), 30.9 (d , CH_3, ^{t}Bu, J_{C-P}= 4.6 Hz), 31.4 (CH_3, ^{t}Bu), 34.5 (C, ^{t}Bu), 34.6 (C, ^{t}Bu), 42.0 (CH_3, NMe), 42.3 (CH_3, NMe), 64.8 (CH-N), 78.7 (d, CH-O, $^{2}J_{C-P}$ = 13.9 Hz), 127.3-146.7 (aromatic carbons). TOF-MS (ESI+): m/z = 562.3442, calcd. for $C_{35}H_{48}NO_3P$ $[M+H]^+$: 562.3445.

L18f: Yield: 467 mg (73%). ^{31}P NMR (C_6D_6): δ = 143.7 (s). ^{1}H NMR (C_6D_6): δ = 0.47 (s, 9H, CH_3, $SiMe_3$) , 0.52 (s, 9H, CH_3, $SiMe_3$), 0.64 (d, 3H, CH_3, $^{3}J_{H-H}$ = 6.8 Hz), 2.02 (s, 6H, CH_3, NMe_2), 3.0 (m, 1H, CH-N), 5.1 (dd, 1H, CH-O, $^{3}J_{H-H}$ = 6.8 Hz; $^{3}J_{H-P}$= 10.4 Hz), 6.82-7.27 (m, 5H, CH=), 7.7 (m, 2H, CH=), 8.0 (s, 1H, CH=), 8.1 (s, 1H, CH=). ^{13}C NMR (C_6D_6): δ = -0.0 (CH_3, $SiMe_3$), 9.11 (CH_3), 41.4 (CH_3, NMe_2), 63.9 (d, CH-N, $^{3}J_{C-P}$= 3.1 Hz), 78.7 (CH-O), 122.0-152.8 (aromatic carbons). TOF-MS (ESI+): m/z = 638.2665, calcd. for $C_{37}H_{44}NO_3PSi_2$ $[M+H]^+$: 638.2670.

L18g: Yield: 666 mg (95%). ^{31}P NMR (C_6D_6): δ = 151. (s). ^{1}H NMR (C_6D_6): δ = 0.4 (s, 9H, CH_3, $SiMe_3$), 0.47 (s, 9H, CH_3, $SiMe_3$), 0.55 (d, 3H, CH_3, $^{3}J_{H-H}$ = 6.8 Hz), 1.85 (s, 6H, CH_3, NMe_2), 2.57 (m, 1H, CH-N), 5.2 (m, 1H, CH-O), 6.79-7.16 (m, 9H, CH=), 7.19 (d, 1H, CH=, $^{4}J_{H-H}$ = 8 Hz), 7.32 (d, 1H, CH=, $^{4}J_{H-H}$ = 8 Hz), 7.66 (d, 1H, CH=, $^{4}J_{H-H}$ = 8.8 Hz), 7.73 (d, 1H, CH=, $^{4}J_{H-H}$ = 8.4 Hz), 8.0 (s, 2H, CH=). ^{13}C NMR (C_6D_6): δ = -0.3 (d, 9H, CH_3, $SiMe_3$, J_{C-P} = 4.6 Hz), -0.1 ($SiMe_3$), 9.1 (CH_3), 41.2 (CH_3, NMe_2), 64.2 (CH-N), 78.4 (d, CH-O, $^{2}J_{C-P}$ = 2.3 Hz), 122.6-152.9 (aromatic carbons). TOF-MS (ESI+): m/z = 638.2669, calcd. for $C_{37}H_{44}NO_3PSi_2$ $[M+H]^+$: 638.2670.

L19d: Yield: 362 mg (64%). ^{31}P NMR (C_6D_6): δ = 143.7 (s). ^{1}H NMR (C_6D_6): δ = 1.51 (s, 9H, CH_3, ^{t}Bu), 1.76 (s, 9H, CH_3, ^{t}Bu), 1.82 (s, 3H, CH_3), 1.89 (s, 3H, CH_3), 2.17 (s, 6H, CH_3, NMe_2), 2.23 (s, 3H, CH_3), 2.24 (s, 3H, CH_3), 2.30 (dd, 1H, CH_2, $^{2}J_{H-H}$ = 12.4 Hz,$^{3}J_{H-H}$ = 5.6 Hz), 2.73 (dd, 1H, CH_2, $^{2}J_{H-H}$ = 12.4 Hz,$^{3}J_{H-H}$ = 6 Hz), 5.33 (m, 1H, CH-O), 7.13-7.4 (m, 7H, CH=). ^{13}C NMR (C_6D_6): δ = 16.1 (CH_3), 16.4 (CH_3), 20.0 (CH_3), 20.1 (CH_3), 30.9 (d, CH_3,^{t}Bu, J_{C-P}= 4.6 Hz), 31.3 (CH_3, ^{t}Bu), 34.5 (C, ^{t}Bu), 34.6 (C, ^{t}Bu), 45.5 (CH_3, NMe), 45.6 (CH_3, NMe), 67.6 (CH_2-N), 75.2 (d, CH-O, $^{2}J_{C-P}$ = 13.6 Hz), 125.3-146.3

(aromatic carbons). TOF-MS (ESI+): m/z = 548.3287, calcd. for $C_{34}H_{46}NO_3P$ $[M+H]^+$: 548.3288.

L19e: Yield: 362 mg (64%). ^{31}P NMR (C_6D_6): δ = 138.1 (s). ^1H NMR (C_6D_6): δ = 1.44 (s, 9H, CH_3, ^{t}Bu), 1.46 (s, 9H, CH_3, ^{t}Bu), 1.65 (s, 3H, CH_3), 1.72 (s, 3H, CH_3), 1.98 (s, 6H, CH_3, NMe_2), 2.07 (s, 3H, CH_3), 2.1(s, 3H, CH_3), 2.43 (dd, 1H, CH_2, $^2J_{H-H}$ = 12.4 Hz,$^3J_{H-H}$ = 5.6 Hz), 2.85 (dd, 1H, CH_2, $^2J_{H-H}$ = 12.4 Hz, $^3J_{H-H}$ = 6 Hz), 5.1 (m, 1H, CH-O), 6.95-7.19 (m, 7H, CH=). ^{13}C NMR (C_6D_6): δ = 16.1 (CH_3), 16.3 (CH_3), 20.0 (CH_3), 20.1 (CH_3), 30.9 (d, CH_3, ^{t}Bu, J_{C-P}= 5.3 Hz), 31.3 (CH_3, ^{t}Bu), 34.3 (C, ^{t}Bu), 34.6 (C, ^{t}Bu), 45.6 (CH_3, NMe_2), 66.7 (d, CH_2-N, $^2J_{C-P}$ = 3.8 Hz), 75.2 (d, CH-O, $^2J_{C-P}$ = 8.4 Hz), 125.3-145.8 (aromatic carbons). TOF-MS (ESI+): m/z = 548.3287, calcd. for $C_{34}H_{46}NO_3P$ $[M+H]^+$: 548.3288.

L20d: Yield: 362 mg (64%). ^{31}P NMR (C_6D_6): δ = 129.7 (s). ^1H NMR (C_6D_6): δ = 1.48 (s, 9H, CH_3, ^{t}Bu), 1.53 (s, 9H, CH_3, ^{t}Bu), 1.64 (s, 3H, CH_3), 1.72 (s, 3H, CH_3), 2.02 (s, 3H, CH_3), 2.02 (s, 3H, CH_3), 2.04 (s, 6H, CH_3, NMe_2), 3.4 (m, 1H, CH-N), 3.6 (m, 1H, CH_2-O), 4.3 (m, 1H, CH_2-O), 6.95-7.2 (m, 7H, CH=). ^{13}C NMR (C_6D_6): δ = 16.1 (CH_3), 16.3 (CH_3), 20.0 (CH_3), 20.1 (CH_3), 30.9 (CH_3, ^{t}Bu), 31.2 (d, CH_3, ^{t}Bu, J_{C-P}= 5.3 Hz), 34.4 (C, ^{t}Bu), 34.5 (C, ^{t}Bu), 42.9 (CH_3, NMe_2), 66.4 (CH_2-O), 70.6 (d, CH-N, $^2J_{C-P}$ = 3.0 Hz), 125.3-146.1(aromatic carbons). TOF-MS (ESI+): m/z = 548.3489, calcd. for $C_{34}H_{46}NO_3P$ $[M+H]^+$: 548.3288.

L20e: Yield: 362 mg (64%). ^{31}P NMR (C_6D_6): δ = 131.1 (s). ^1H NMR (C_6D_6): δ = 1.46 (s, 9H, CH_3, ^{t}Bu), 1.55 (s, 9H, CH_3, ^{t}Bu), 1.64 (s, 3H, CH_3), 1.71 (s, 3H, CH_3), 2.02 (s, 3H, CH_3), 2.03 (s, 3H, CH_3), 2.06 (s, 6H, CH_3, NMe_2), 3.6 (m, 1H, CH-N), 3.8 (m, 1H, CH_2-O), 4.0 (m, 1H, CH_2-O), 6.95-7.2 (m, 7H, CH=). ^{13}C NMR (C_6D_6): δ = 16.1 (CH_3), 16.3 (CH_3), 20.0 (CH_3), 20.1 (CH_3), 30.9 (CH_3, ^{t}Bu), 31.2 (d, CH_3, ^{t}Bu, J_{C-P}= 5.3 Hz), 34.5 (C, ^{t}Bu), 34.6 (C, ^{t}Bu), 42.9 (CH_3, NMe_2), 66.1 (CH_2-O), 70.6 (d, CH-N, $^2J_{C-P}$ = 2.3 Hz), 125.3-146.1 (aromatic carbons). TOF-MS (ESI+): m/z = 548.3287, calcd. for $C_{34}H_{46}NO_3P$ $[M+H]^+$: 548.3288.

3.5.4.7. General procedure for the preparation of [Pd(η^3-allyl)(P-N)]BF_4 complexes 50-54

The corresponding 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 room temperature under argon. $AgBF_4$ (9.8 mg, 0.05 mmol) was added after 30 minutes and the mixture was stirred for 30 minutes. The mixture was then filtered over celite under argon and the resulting solutions were analyzed by NMR. After the NMR analysis, the complexes were precipitated as pale yellow solids by adding hexane.

[Pd(η^3-1,3-diphenylallyl)(L18d)]BF_4 (50). Isomer *endo* (77%): ^{31}P NMR (CD_2Cl_2, 298 K), δ = 136.8 (s, 1P). ^{1}H NMR (CD_2Cl_2, 298 K), δ = 0.50 (d, 3H, CH_3, $^3J_{H-H}$= 6.8 Hz), 1.22 (s, 9H, CH_3, ^{t}Bu), 1.47 (s, 3H, CH_3-Ar), 1.66 (s, 3H, CH_3-Ar), 1.71 (s, 9H, CH_3, ^{t}Bu), 2.13 (s, 3H, CH_3-Ar), 2.29 (s, 3H, CH_3-Ar), 2.75 (s, 3H, CH_3-N), 2.76 (s, 3H, CH_3-N), 3.19 (m, 1H, CH-N), 5.35 (dd, 1H, CH allyl *trans* to N, $^3J_{H-H}$= 12.0 Hz, $^3J_{H-P}$= 4.4 Hz), 5.64 (dd, 1H, CH allyl *trans* to P, $^3J_{H-H}$= 12.0 Hz, $^3J_{H-P}$= 16.4 Hz), 5.79 (dd, 1H, CH-O, $^3J_{H-H}$= 4.8 Hz, J_{C-P}= 7.2 Hz), 6.68 (m, 1H, CH allyl central), 6.9-7.8 (m, 17H, CH=). ^{13}C NMR (CD_2Cl_2, 298 K), δ = 10.4 (CH_3), 16.7 (CH_3, Ar), 16.8 (CH_3, Ar), 20.5 (CH_3, Ar), 20.7 (CH_3, Ar), 32.0 (CH_3, ^{t}Bu), 32.3 (CH_3, ^{t}Bu), 35.0-35.8 (C, ^{t}Bu), 42.9 (CH_3-N), 48.6 (CH_3-N), 73.5 (CH-N), 79.2 (d, CH allyl *trans* to N, J_{C-P}= 8.3 Hz), 84.6 (d, CH-O, J_{C-P}= 11.5 Hz), 105.3 (d, CH allyl *trans* to P, J_{C-P}= 33.8 Hz), 114.8 (d, CH allyl central, J_{C-P}= 12.2 Hz), 123-145 (aromatic carbons). Isomer *exo* (23%): ^{31}P NMR (CD_2Cl_2, 298 K), δ = 132.9 (s, 1P). ^{1}H NMR (CD_2Cl_2, 298 K), δ = 0.50 (d, 3H, CH_3, $^3J_{H-H}$= 6.8 Hz), 0.91 (s, 9H, CH_3, ^{t}Bu), 1.59 (s, 3H, CH_3-Ar), 1.74 (s, 3H, CH_3-Ar), 1.79 (s, 9H, CH_3, ^{t}Bu), 2.17 (s, 6H, CH_3-N and CH_3-Ar), 2.21 (s, 3H, CH_3-N), 2.43 (s, 3H, CH_3-Ar), 3.10 (m, 1H, CH-N), 4.50 (m, 1H, CH allyl *trans* to N), 5.22 (m, 1H, CH-O), 5.45 (m, 1H, CH allyl *trans* to P), 6.59 (m, 1H, CH allyl central), 6.9-7.8 (m, 17H, CH=). ^{13}C NMR (CD_2Cl_2, 298 K), δ = 10.1 (CH_3), 17.1 (CH_3, Ar), 17.3 (CH_3, Ar), 20.4 (CH_3, Ar), 20.8 (CH_3, Ar), 31.9 (CH_3, ^{t}Bu), 32.8 (CH_3, ^{t}Bu), 35.0-35.8 (C, ^{t}Bu), 38.8 (CH_3-N), 50.5 (CH_3-N), 71.8 (d, CH allyl *trans* to N, J_{C-P}= 9.2 Hz), 72.1 (CH-N), 84.0 (d, CH-O, J_{C-P}= 9.1 Hz), 99.3 (d, CH allyl *trans* to P, J_{C-P}= 33.0 Hz), 113.4 (d, CH allyl central, J_{C-P}= 14.0 Hz), 123-145 (aromatic carbons). Anal. calcd (%) for $C_{50}H_{61}BF_4NO_3PPd$: C 63.33, H 6.48, N 1.48; found: C 63.12, H 6.43, N 1.45.

[Pd(η^3-1,3-diphenylallyl)(L18e)]BF_4 (51). Isomer *endo* (17%): ^{31}P NMR (CD_2Cl_2, 298 K), δ = 129.8 (s, 1P). ^{1}H NMR (CD_2Cl_2, 298 K), δ = 0.43 (d, 3H, CH_3, $^3J_{H-H}$= 6.8 Hz), 1.33 (s, 9H, CH_3, ^{t}Bu), 1.66 (s, 3H, CH_3-Ar), 1.74 (s, 9H, CH_3, ^{t}Bu), 1.84 (s, 3H, CH_3-N), 2.14 (s, 3H, CH_3-Ar), 2.23 (s, 3H, CH_3-Ar), 2.26 (s, 3H, CH_3-N), 2.40 (s, 3H, CH_3-Ar), 3.40 (m, 1H, CH-N), 3.72 (dd, 1H, CH allyl *trans* to N, $^3J_{H-H}$= 10.2 Hz, $^3J_{H-P}$= 6.8 Hz), 4.40 (m, 1H, CH allyl *trans* to P), 5.54 (m, 1H, CH-O), 6.60 (m, 1H, CH allyl central), 6.8-7.8 (m, 17H, CH=). ^{13}C NMR (CD_2Cl_2, 298 K), δ = 10.8 (CH_3), 16.7 (CH_3, Ar), 17.0 (CH_3, Ar), 20.5 (CH_3, Ar), 20.6 (CH_3, Ar), 32.2 (d, CH_3, ^{t}Bu, J_{C-P}= 6.3 Hz), 32.5 (CH_3, ^{t}Bu), 35.0-35.8 (C, ^{t}Bu), 43.0 (CH_3-N), 49.1 (CH_3-N), 67.3 (d, CH allyl *trans* to N, J_{C-P}= 12.8 Hz), 68.7 (CH-N), 84.9 (CH-O), 108.6 (d, CH allyl *trans* to P, J_{C-P}= 32.4 Hz), 114.5 (d, CH allyl central, J_{C-P}= 12.4 Hz), 127-145 (aromatic carbons). Isomer *exo* (83%): ^{31}P NMR (CD_2Cl_2, 298 K), δ = 128.7 (s, 1P). ^{1}H NMR (CD_2Cl_2, 298 K), δ = 0.54 (d, 3H, CH_3, $^3J_{H-H}$= 7.2 Hz), 1.34 (s, 9H, CH_3, ^{t}Bu), 1.62 (s, 3H, CH_3-Ar), 1.78 (s, 9H, CH_3, ^{t}Bu), 2.11 (s, 3H, CH_3-Ar), 2.19 (s, 3H, CH_3-Ar), 2.40 (s, 3H, CH_3-N), 2.42 (s, 3H, CH_3-Ar), 2.61 (s, 3H, CH_3-N), 3.16 (m, 1H, CH-N), 4.40 (m, 1H, CH allyl *trans* to N), 5.03 (m, 1H, CH-O), 5.73 (m, 1H, CH allyl *trans* to P), 6.60 (m, 1H, CH allyl central), 6.9-7.8 (m, 17H, CH=). ^{13}C NMR (CD_2Cl_2, 298 K), δ = 9.7 (CH_3), 16.9 (CH_3, Ar), 17.3 (CH_3, Ar), 20.5 (CH_3,

Ar), 20.7 (CH_3, Ar), 32.0 (CH_3, ^{t}Bu), 32.6 (CH_3, ^{t}Bu), 35.0-35.8 (C, ^{t}Bu), 42.9 (CH_3-N), 48.8 (CH_3-N), 67.5 (d, CH allyl *trans* to N, J_{C-P}= 12.6 Hz), 69.4 (CH-N), 81.4 (CH-O), 110.6 (d, CH allyl *trans* to P, J_{C-P}= 30.6 Hz), 113.5 (d, CH allyl central, J_{C-P}= 13.8 Hz), 123-145 (aromatic carbons). Anal. calcd (%) for $C_{50}H_{61}BF_4NO_3PPd$: C 63.33, H 6.48, N 1.48; found: C 63.02, H 6.43, N 1.44.

[Pd(η^3-1,3-diphenylallyl)(L19e)]BF_4 (52). Isomer *endo* (33%): ^{31}P NMR (CD_2Cl_2, 298 K), δ = 132.7 (s, 1P). ^{1}H NMR (CD_2Cl_2, 298 K), δ = 1.45 (s, 9H, CH_3, ^{t}Bu), 1.68 (s, 3H, CH_3-Ar), 1.71 (s, 3H, CH_3-Ar), 1.73 (s, 9H, CH_3, ^{t}Bu), 2.11 (s, 3H, CH_3-Ar), 2.30 (s, 3H, CH_3-Ar), 2.32 (s, 3H, CH_3-N), 2.42 (m, 1H, CH_2), 2.70 (s, 3H, CH_3-N), 3.56 (dd, 1H, CH_2, $^3J_{H-H}$= 10.0 Hz, $^3J_{H-P}$= 14.4 Hz), 4.49 (m, 1H, CH allyl *trans* to N), 4.84 (m, 1H, CH allyl *trans* to P), 5.23 (m, 1H, CH-O), 6.19 (m, 1H, CH allyl central), 6.7-7.8 (m, 17H, CH=). ^{13}C NMR (CD_2Cl_2, 298 K), δ = 16.5 (CH_3, Ar), 16.7 (CH_3, Ar), 20.0 (CH_3, Ar), 20.1 (CH_3, Ar), 31.9 (CH_3, ^{t}Bu), 32.4 (d, CH_3, ^{t}Bu, J_{C-P}= 4.6 Hz), 34.4-35.3 (C, ^{t}Bu), 48.7 (CH_3-N), 54.3 (CH_3-N), 69.8 (m, CH allyl *trans* to N), 70.9 (CH_2), 74.8 (CH-O), 93.8 (d, CH allyl *trans* to P, J_{C-P}= 39.7 Hz), 114.1 (d, CH allyl central, J_{C-P}= 12.2 Hz), 125-146 (aromatic carbons). Isomer *exo* (67%): ^{31}P NMR (CD_2Cl_2, 298 K), δ = 130.3 (s, 1P). ^{1}H NMR (CD_2Cl_2, 298 K), δ = 1.31 (s, 9H, CH_3, ^{t}Bu), 1.60 (s, 9H, CH_3, ^{t}Bu), 1.62 (s, 3H, CH_3-Ar), 1.74 (s, 3H, CH_3-Ar), 2.16 (s, 6H, CH_3-Ar and CH_3-N), 2.45 (s, 3H, CH_3-Ar), 2.52 (m, 1H, CH_2), 2.75 (s, 3H, CH_3-N), 3.19 (dd, 1H, CH_2, $^3J_{H-H}$= 9.6 Hz, $^3J_{H-P}$= 14.4 Hz), 4.52 (m, 1H, CH allyl *trans* to N), 5.30 (m, 1H, CH-O), 5.61 (m, 1H, CH allyl *trans* to P), 6.54 (m, 1H, CH allyl central), 6.7-7.8 (m, 17H, CH=). ^{13}C NMR (CD_2Cl_2, 298 K), δ = 16.2 (CH_3, Ar), 16.7 (CH_3, Ar), 20.0 (CH_3, Ar), 20.2 (CH_3, Ar), 31.6 (CH_3, ^{t}Bu), 32.1 (CH_3, ^{t}Bu), 34.4-35.3 (C, ^{t}Bu), 49.9 (CH_3-N), 51.6 (CH_3-N), 69.8 (m, CH allyl *trans* to N), 71.2 (CH_2), 75.6 (CH-O), 105.6 (d, CH allyl *trans* to P, J_{C-P}= 32.0 Hz), 112.3 (d, CH allyl central, J_{C-P}= 10.7 Hz), 125-146 (aromatic carbons). Anal. calcd (%) for $C_{49}H_{59}BF_4NO_3PPd$: C 63.00, H 6.37, N 1.50; found: C 59.61, H 6.31, N 1.46.

[Pd(η^3-1,3-cyclohexenylallyl)(L18e)]BF_4 (53). Isomer *endo* (91%): ^{31}P NMR (CD_2Cl_2, 298 K), δ = 134.4 (s, 1P). ^{1}H NMR(CD_2Cl_2, 298 K), δ = 0.74 (d, 3H, CH_3, $^3J_{H-H}$= 6.8 Hz), 1.2-1.6 (m, 4H, CH_2), 1.46 (s, 9H, CH_3, ^{t}Bu), 1.54 (s, 9H, CH_3, ^{t}Bu), 1.69 (s, 3H, CH_3-Ar), 1.80 (m, 1H, CH_2), 1.87 (s, 3H, CH_3-Ar), 2.21 (m, 1H, CH_2), 2.23 (s, 3H, CH_3-Ar), 2.34 (s, 3H, CH_3-Ar), 2.82 (s, 3H, CH_3-N), 3.24 (s, 3H, CH_3-N), 3.31 (m, 1H, CH allyl *trans* to N), 3.38 (m, 1H, CH-N), 4.97 (dd, 1H, CH-O, $^3J_{H-H}$= 7.2 Hz, $^3J_{H-P}$= 12 Hz), 5.49 (m, 1H, CH allyl central), 5.96 (m, 1H, CH allyl *trans* to P), 7.2-7.5 (m, 7H, CH=).^{13}C NMR (CD_2Cl_2, 298 K), δ = 9.9 (CH_3), 16.7 (CH_3, Ar), 20.5 (CH_3, Ar), 20.6 (CH_3, Ar), 21.4 (b, CH_2), 27.4 (b, CH_2), 21.4 (d, CH_2, J_{C-P}= 8.4 Hz), 31.7 (CH_3, ^{t}Bu), 32.0 (CH_3, ^{t}Bu), 35.2-35.4 (C, ^{t}Bu), 44.8 (CH_3-N), 53.4 (CH_3-N), 64.7 (d, CH allyl *trans* to N, J_{C-P}= 10 Hz), 69.7 (CH-N), 82.7 (d, CH-O, J_{C-P}= 6.1 Hz), 109.2 (d, CH allyl *trans* to P, J_{C-P}= 40 Hz), 113.5 (d, CH allyl central, J_{C-P}= 10.7 Hz), 127-145 (aromatic carbons). Isomer *exo* (9%): ^{31}P NMR (CD_2Cl_2, 298 K), δ = 133.0 (s, 1P). ^{1}H NMR(CD_2Cl_2, 298 K), δ = 0.72 (d,

3H, CH_3, $^3J_{H-H}$= 6.8 Hz), 1.2-1.6 (m, 4H, CH_2), 1.45 (s, 9H, CH_3, ^{t}Bu), 1.54 (s, 9H, CH_3, ^{t}Bu), 1.62 (s, 3H, CH_3-Ar), 1.80 (m, 1H, CH_2), 1.89 (s, 3H, CH_3-Ar), 2.21 (m, 1H, CH_2), 2.27 (s, 3H, CH_3-Ar), 2.29 (s, 3H, CH_3-Ar), 2.68 (s, 3H, CH_3-N), 3.20 (s, 3H, CH_3-N), 3.36 (m, 1H, CH allyl *trans* to N), 3.42 (m, 1H, CH-N), 5.21 (m, 1H, CH-O), 5.68 (m, 1H, CH allyl central), 6.08 (m, 1H, CH allyl *trans* to P), 7.2-7.5 (m, 7H, CH=).^{13}C NMR (CD_2Cl_2, 298 K), δ = 9.2 (CH_3), 16.7 (CH_3, Ar), 16.8 (CH_3, Ar), 20.4 (CH_3, Ar), 20.6 (CH_3, Ar), 21.4 (b, CH_2), 27.4 (b, CH_2), 21.4 (d, CH_2, J_{C-P}= 8.4 Hz), 31.5 (CH_3, ^{t}Bu), 31.6 (CH_3, ^{t}Bu), 35.2-35.4 (C, ^{t}Bu), 45 (CH_3-N), 52.8 (CH_3-N), 64.2 (d, CH allyl *trans* to N, J_{C-P}= 9.2 Hz), 69.7 (CH-N), 81.9 (d, CH-O, J_{C-P}= 7.3 Hz), 110.8 (d, CH allyl *trans* to P, J_{C-P}= 38.6 Hz), 113.2 (d, CH allyl central, J_{C-P}= 9.6 Hz), 127-145 (aromatic carbons). Anal. calcd (%) for $C_{41}H_{57}BF_4NO_3PPd$: C 58.90, H 6.87, N 1.68; found: C 58.21, H 6.84, N 1.65.

[Pd(η^3-1,3-cyclohexenylallyl)(L19e)]BF_4 (54).[34] Isomer *endo* (96%): ^{31}P NMR (CD_2Cl_2, 298 K), δ = 135.2 (s, 1P). ^{1}H NMR(CD_2Cl_2, 298 K), δ = 1.25 (m, 1H, CH_2), 1.43 (m, 2H, CH_2), 1.45 (s, 9H, CH_3, ^{t}Bu), 1.54 (s, 9H, CH_3, ^{t}Bu), 1.70 (m, 1H, CH_2), 1.73 (s, 3H, CH_3-Ar), 1.88 (s, 3H, CH_3-Ar), 1.90 (m, 1H, CH_2), 2.16 (m, 1H, CH_2), 2.24 (s, 3H, CH_3-Ar), 2.35 (s, 3H, CH_3-Ar), 2.71 (d, 1H, CH_2-N, $^3J_{H-H}$= 14.4 Hz), 2.90 (s, 3H, CH_3-N), 3.12 (s, 3H, CH_3-N), 3.42 (dd, 1H, CH_2-N, $^3J_{H-H}$= 14.4 Hz, $^3J_{H-P}$= 9.6 Hz), 3.49 (m, 1H, CH allyl *trans* to N), 5.23 (m, 1H, CH-O), 5.44 (m, 1H, CH allyl central), 6.03 (m, 1H, CH allyl *trans* to P), 7.2-7.5 (m, 7H, CH=).^{13}C NMR (CD_2Cl_2, 298 K), δ = 16.7 (CH_3, Ar), 16.8 (CH_3, Ar), 20.5 (CH_3, Ar), 20.6 (CH_3, Ar),), 20.9 (d, CH_2, J_{C-P}= 2.3 Hz), 27.6 (b, CH_2), 28.5 (d, CH_2, J_{C-P}= 7.6 Hz),31.8 (CH_3, ^{t}Bu), 32.0 (d, CH_3, ^{t}Bu, J_{C-P}= 1.5 Hz)), 35.2 (C, ^{t}Bu), 35.5 (C, ^{t}Bu), 51.8 (CH_3-N), 56.7 (CH_3-N), 67.6 (d, CH allyl *trans* to N, J_{C-P}= 9.1 Hz), 71.8 (CH-N), 77.9 (d, CH-O, J_{C-P}= 6.8 Hz), 105.0 (d, CH allyl *trans* to P, J_{C-P}= 40.3 Hz), 113.5 (d, CH allyl central, J_{C-P}= 10.6 Hz), 126-146 (aromatic carbons). Isomer *exo* (4%): ^{31}P NMR (CD_2Cl_2, 298 K), δ = 134.2 (s, 1P). ^{1}H NMR(CD_2Cl_2, 298 K), δ = 1.25 (m, 1H, CH_2), 1.43 (m, 2H, CH_2), 1.47 (s, 9H, CH_3, ^{t}Bu), 1.54 (s, 9H, CH_3, ^{t}Bu), 1.70 (m, 1H, CH_2), 1.74 (s, 3H, CH_3-Ar), 1.90 (bs, 4H, CH_3-Ar and CH_2), 2.16 (m, 1H, CH_2), 2.24 (s, 3H, CH_3-Ar), 2.35 (s, 3H, CH_3-Ar), 2.81 (d, 1H, CH_2-N, $^3J_{H-H}$= 14.0 Hz), 2.91 (s, 3H, CH_3-N), 3.09 (s, 3H, CH_3-N), 3.27 (dd, 1H, CH_2-N, $^3J_{H-H}$= 14.0 Hz, $^3J_{H-P}$= 8.4 Hz), 3.39 (m, 1H, CH allyl *trans* to N), 5.39 (m, 1H, CH-O), 5.54 (m, 1H, CH allyl central), 5.84 (m, 1H, CH allyl *trans* to P), 7.2-7.5 (m, 7H, CH=). Anal. calcd (%) for $C_{40}H_{55}BF_4NO_3PPd$: C 58.44, H 6.74, N 1.70; found: C 58.06, H 6.70, N 1.67.

3.5.4.8. Study of the reactivity of the [Pd(η^3-allyl)(L))]BF_4 with sodium malonate by in situ NMR[35]

A solution of *in situ* prepared [Pd(η^3-allyl)(**L**)]BF_4 (**L**= phosphite-amine, 0.05 mmol) in CD_2Cl_2 (1 mL) was cooled in the NMR at -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.

The relative reaction rates were calculated using a capillary containing a solution of triphenylphosphine in CD_2Cl_2 as external standard.

3.5.4.9. Typical procedure for the allylic alkylation of linear (S1 and S3-S5) and cyclic (S2, S6 and S7) substrates

A degassed solution of $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (0.9 mg, 0.0025 mmol) and the corresponding amino-phosphite (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 a pinch of KOAc 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 $MgSO_4$. For compounds **12**, **14**-**21**, **27**-**29**, **32**, **34**-**36** and **42**, the solvent was removed, conversions were measured by ^{1}H-NMR and enantiomeric excesses were determined by HPLC (See Section 3.2). For compounds **13**, **30**-**31**, **37**-**38** and **40**-**41**, conversion and enantiomeric excesses were determined by GC (See Section 3.2). For compounds **33** and **39**, conversions were measured by ^{1}H-NMR and ees were determined by ^{1}H-NMR using $[Eu(hfc)_3]$ (See Section 3.2).

3.5.4.10. Typical procedure for the allylic amination of substrate S1

A degassed solution of $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (0.9 mg, 0.0025 mmol) and the corresponding amino-phosphite 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) 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 $MgSO_4$. Conversion was measured by ^{1}H-NMR and enantiomeric excess was determined by HPLC.

3.5.4.11. Typical procedure for the allylic etherification of substrate S1

A degassed solution of $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (0.9 mg, 0.0025 mmol) and the corresponding amino-phosphite ligand (0.0055 mmol) in dichloromethane (0.5 mL) was stirred for 30 min. Subsequently, a solution of the corresponding substrate (31.5 mg, 0.125 mmol) in dichloromethane (1.5 mL) was added. After 10 minutes, Cs_2CO_3 (122 mg, 0.375 mmol) and alkyl alcohol (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 $MgSO_4$. Conversion was measured by ^1H-NMR. HPLC was used to determine enantiomeric excesses.

3.5.4.12. Procedure for the preparation of carbocyclic compounds 46-51

A solution of Grubbs II catalyst (5 mg, 0.006 mmol) and the corresponding alkylated product (0.12 mmol) in CH_2Cl_2 (3 mL) was stirred for 16 h. The solution was directly purified by flash chromatography (95:5; Hex: EtOAc) to obtained the desired carbocycle compounds.

Dimethyl 2-phenylcyclopent-3-ene-1,1-dicarboxylate (46). Enantiomeric excess determined by HPLC using Chiralpak IC column (87% 2-propanol/hexane, flow 0.5 mL/min, λ= 226 nm). tR 15.3 min (S); tR 17.0 min (R). ^1H NMR ($CDCl_3$), δ: 2.76 (d, 1H, CH2, J= 17.4 Hz), 3.06 (s, 3 H, CH3), 3.45 (d, 1H, CH2, J= 17.4 Hz), 3.74 (s, 3H, CH3), 4.86 (s, 1H, CH), 5.68 (m, 1H, CH=), 5.85 (m, 1H, CH=), 7.1-7.3 (m, 5H, CH=).

Dimethyl 2-(p-tolyl)cyclopent-3-ene-1,1-dicarboxylate (47). Enantiomeric excess determined by HPLC using Chiralpak IA column (98% 2-propanol/hexane, flow 0.5 mL/min, λ= 226 nm). tR 12.1 min (-); tR 12.8 min (+). ^1H NMR ($CDCl_3$), δ: 2.30 (s, 3H, CH3), 2.81 (bd, 1H, CH2, J= 12.6 Hz), 3.22 (s, 3 H, CH3), 3.49 (m, 1H, CH2), 3.76 (s, 3H, CH3), 4.86 (s, 1H, CH), 5.71 (m, 1H, CH=), 5.87 (m, 1H, CH=), 7.1-7.3 (m, 4H, CH=).

Dimethyl 2-methylcyclopent-3-ene-1,1-dicarboxylate (48). Enantiomeric excess determined by HPLC using Chiralpak OJ-H column (98% 2-propanol/hexane, flow 0.5 mL/min, λ= 226 nm). tR 15.6 min (-); tR 16.7 min (+). ^1H NMR ($CDCl_3$), δ: 0.96 (d, 3H, CH3, J= 7.6 Hz), 2.72 (d, 1H, CH2, J= 16.8 Hz), 3.26 (d, 1H, CH2, J= 16.8 Hz), 3.62 (q, 1H, CH, J= 7.6 Hz), 3.73 (s, 6 H, CH3), 5.57 (m, 2H, CH=).

Diethyl 2-phenylcyclohex-3-ene-1,1-dicarboxylate (49). Enantiomeric excess determined by HPLC using Chiralpak OJ-H column (98% 2-propanol/hexane, flow 0.5 mL/min, λ= 220 nm). tR 12.5 min (-); tR 17.5 min (+). ^1H NMR ($CDCl_3$), δ: 1.25 (t, 6H, CH3, J= 7.2 Hz), 1.9-2.3 (m, 4H, CH2), 3.91 (m, 1H, CH), 4.19 (m, 4H, CH2), 5.76 (m, 1H, CH=), 5.90 (m, 1H, CH=), 7.1-7.4 (m, 5H, CH=).

Diethyl 2-(p-tolyl)cyclohex-3-ene-1,1-dicarboxylate (50). Enantiomeric excess determined by HPLC using Chiralpak OJ-H column (98% 2-propanol/hexane, flow 0.5 mL/min, λ= 220 nm). tR 12.5 min (-); tR 18.7 min (+). ^1H NMR ($CDCl_3$), δ: 1.26 (t, 6H, SI-10 CH3, J= 7.2 Hz), 1.9-2.2 (m, 4H, CH2), 2.26 (s, 3H, CH3), 3.97 (m, 1H, CH), 4.20 (m, 4H, CH2), 5.73 (m, 1H, CH=), 5.85 (m, 1H, CH=), 7.1-7.4 (m, 4H, CH=).

Diethyl 2-phenylcyclohept-3-ene-1,1-dicarboxylate (51). Enantiomeric excess determined by HPLC using Chiralpak OJ-H column (98% 2-propanol/hexane, flow 0.5 mL/min, λ= 220 nm). tR 11.2 min (-); tR 13.8 min (+). ^1H NMR ($CDCl_3$), δ: 1.26 (t, 6H,

CH3, J= 7.2 Hz), 1.9-2.3 (m, 6H, CH2), 4.10 (m, 1H, CH), 4.17 (m, 4H, CH2), 4.98 (m, 1H, CH=), 5.72 (m, 1H, CH=), 7.0-7.3 (m, 4H, CH=).

3.5.5. References

1 For reviews, see: a) *Palladium Reagents and Catalysis, Innovations in Organic Synthesis*; Tsuji, J., Ed.; Wiley: New York, 1995. b) Trost, B. M.; van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395. c) Johannsen, M.; Jorgensen, K. A. *Chem. Rev.* **1998**, *98*, 1689. d) Pfaltz, A.; Lautens, M. in *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, 1999; Vol. 2, Chapter 24. e) Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000**, *33*, 336. f) Masdeu-Bultó, A. M.; Diéguez, M.; Martín, E.; Gómez, M. *Coord. Chem. Rev.* **2003**, *242*, 159. g) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921. h) Martín, E.; Diéguez, M. *C. R. Chemie* **2007**, *10*, 188. i) Lu, Z.; Ma, S. *Angew. Chem. Int. Ed.* **2008**, *47*, 258. j) Trost, B. M.; Zhang, T.; Sieber, J. D. *Chem. Sci.* **2010**, *1*, 427. k) Trost, B. M. *Org. ProcessRes. Dev.* **2012**, *16*, 185.

2 a) Hayashi, T.; Yamamoto, A.; Hagihara, T.; Ito, Y. *Tetrahedron Lett.* **1986**, *27*, 191. b) Recently this concept has also been use to explain the chiral induction by the Trost ligand, see: Butts, C. P.; Filali, E.; Lloyd-Jones, G. C.; Norrby, P. O.; Sale, D. A.; Schramm, Y. *J. Am. Chem. Soc.* **2009**, *131*, 9945.

3 See, for instance: a) Dawson, G. J.; Frost, C. G.; Williams, J. M. J. *Tetrahedron Lett.* **1993**, *34*, 3149. b) von Matt, P.; Pfaltz, A. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 566. c) Sennhenn, P.; Gabler, B.; Helmchen, G. *Tetrahedron Lett.* **1994**, *35*, 8595.

4 See, for instance: a) Pàmies, O.; Diéguez, M. *Acc. Chem. Res.* **2010**, *43*, 212. b) van Leeuwen, P. W. N. M.; Kamer, P. C. J.; Claver, C.; Pàmies, O.; Diéguez, M. *Chem. Rev.* **2011**, *111*, 2077. c) Raluy, E.; Claver, C.; Pàmies, O.; Diéguez, M. *Org. Lett.* **2007**, *9*, 49. d) Pàmies, O.; Diéguez, M., Claver, C. *Adv. Synth. Catal.* **2007**, *349*, 836. e) Pàmies, O.; Diéguez, M. *Chem. Eur. J.* **2008**, *14*, 944. f) Raluy, E.; Pàmies, O.; Diéguez, M. *Adv. Synth. Catal.* **2009**, *351*, 1648.

5 a) Pàmies, O.; Diéguez, M.; Claver, C. *J. Am. Chem. Soc.* **2005**, *127*, 3646. b) Mata, Y.; Diéguez, M.; Pàmies, O.; Claver, C. *Adv. Synth. Catal.* **2005**, *347*, 1943. c) Diéguez, M.; Pàmies, O. *Chem. Eur. J.* **2008**, *14*, 3653. d) Mata, Y.; Pàmies, O.; Diéguez, M. *Adv. Synth. Catal.* **2009**, *351*, 3217.

6 Only two ligand series (Trost-diphosphine and PHOX-type ligands) have been successfully applied in a very broad range of nucleophiles. However, while the use of Trost diphosphines has been mainly limited to unhindered substrates, the PHOX-type ligands have been mainly limited to hindered substrates.[1]

7 a) Mazuela, J.; Pàmies, O.; Diéguez, M. *Chem. Eur. J.* **2013**, *19*, 2416. b) Coll, M.; Pàmies, O.; Diéguez, M. *Org. Lett.* **2014**, *16*, 1892.

8 See, for instance: a) Kubota, H.; Koga, K. *Heterocycles*, **1996**, *42*, 543 (up to >95% ee for **S1**). b) Jin, M.-J.; Jung, J.-A.; Kim, S.-H. *Tetrahedron Lett*. **1999**, *40*, 5197 (up to 98% ee at 0 °C for **S1**). c) Okuyama, Y.;Nakano, H.; Hongo, H. *Tetrahderon: Asymmetry* **2000**, *11*, 1193 (up to 96% ee for **S1**). d) Widhalm, M.; Nettekoven, U.; Kalchhauser, H.;

Mereiter, K.; Calhorda, M. J.; Félix, V. *Organometallics* **2002**, *21*, 315 (up to 97% ee for **S1** and 49% ee for **S2**). e) Vasse, J.-L.; Stranne, R.; Zalubovskis, R.; Gayet, C.; Moberg, C. *J. Org. Chem.* **2003**, *68*, 3258 (up to 98% ee for **S1** and 27% ee for **S2**). f) Chen, G.; Li, X.; Zhang, H.; Gong, L.; Mi, A.; Cui, X.; Jiang, Y.; Choi, M. C. K.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2002**, *13*, 809 (up to 95% ee at -20 °C for **S1**). g) Jin, M.-J.; Kim, S.-H.; Lee, S.-J.; Kim, Y.-M. *Tetrahedron Lett.* **2002**, *43*, 7409 (up to 99% ee at 10 °C for **S1**). h) Mino, T.; Hata, S.; Ohtaka, K.; Sakamoto, M.; Fujita, T. *Tetrahedron Lett.* **2001**, *42*, 4837 (up to 95% ee at -20 °C for **S1**). i) Lee, E.-K.; Kim, S.-H.; Jung, B.-H.; Ahn, W.-S.; Kim, G.-J. *Tetrahedron Lett.* **2003**, *44*, 1971 (up to 98% ee at 0 °C for **S1**). j) Tanaka, Y.; Mino, T.; Akita, K.; Sakamoto, M.; Fujita, T. *J. Org. Chem.* **2004**, *69*, 6679 (up to 98% ee at -20 °C for **S1**). k) Sun, X.-M.; Koizumi, M.; Manabe, K.; Kobayashi, S. *Adv. Synth. Catal.* **2005**, *347*, 1893 (up to 96% ee at -20 °C for **S1**).

[9] See for example: a) Jang, H.-Y.; Seo, H.; Han, J. W.; Chung, Y. K. *Tetrahedron Lett* **2000**, *41*, 5083 (up to 98% ee for **S1**). b) Lee, J. H.; Son, S. U.; Chung, Y. K. *Tetrahedron: Asymmetry* **2003**, *14*, 2109 (up to 98% ee for **S1**). c) Hu, X.; Dai, H.; Hu, X.; Chen, H.; Wang, J.; Bai, C.; Zheng, Z. *Tetrahedron: Asymmetry* **2002**, *13*, 1687 (up to 96% ee at 0 °C for **S1**). d) Hu, X.; Dai, H.; Chen, H.; Wang, J.; Bai, C.; Zheng, Z. *Tetrahedron: Asymmetry* **2004**, *15*, 1065 (up to 99% ee at 0 °C for **S1** and 73% ee for **S2**). e) Thiesen, K. E.; Maitra, K.; Olmstead, M. M.; Attar, S. *Organometallics* **2010**, *29*, 6334 (up to 94% ee for **S1**). f) Tsarev, V. N.; Lyubimov, S. E.; Bondarev, O. G.; Korlyukov, A.; Antipin, M. Y.; Pretovskii, P. V.; Davankov, V. A.; Shiryaev, A. A.; Benetsky, E. B.; Vologzhanin, P. A.; Gavrilov, K. N. *Eur. J. Org. Chem.* **2005**, 2097 (up to 97% ee for **S1**).

[10] See for instance: a) Bunlaksananusorn, T.; Luna, A. P.; Bonin, M.; Micouin, L.; Knochel, P. *Synlett* **2003**, 2240 (up to 96% ee for **S1**). b) Ito, K.; Kashiwagi, R.; Iwsaki, K.; Katsuki, T. *Synlett* **1999**, 1563 (up to 96% ee for **S1**). c) Goldfuss, B.; Löschmann, T.; Rominger, F. *Chem. Eur. J.* **2004**, *10*, 5422 (up to 83% ee for **S1**). d) Liu, Q.-B.; Zhou, Y.-G. *Tetrahedron Lett.* **2007**, *48*, 2101 (up to 95% ee for **S1**). e) Meng, X.; Gao, Y.; Li, X.; Xu, D. *Cat. Commun.* **2009**, *10*, 950 (up to 97% ee for **S1** and 80% ee for **S2**). f) Leca, F.; Fernández, F.; Muller, G.; Lescop, C.; Réau, R.; Gómez, M. *Eur. J. Inorg. Chem.* **2009**, 5583 (up to 12% ee and 31% ee for **S1** and **S2**, respectively). g) Lega, M.; Margalef, J.; Ruffo, F.; Pàmies, O.; Diéguez, M. *Tetrahedron: Asymmetry* **2013**, *24*, 995 (up to 50% ee for **S1** and 86% ee at 0 °C for **S2**).

[11] See: a) Evans, D. A.; Campos, K. R.; Tedrow, J. S.; Michael, F. E.; Gagné, M. R. *J. Am. Chem. Soc.* **2000**, *122*, 7905 (up to 98%, 90%, and 65% ee at -20 °C for **S1**, **S2** and **S4**, respectively). b) Nakano, H.; Okuyama, Y.; Hongo, H. *Tetrahedron Lett.* **2000**, *41*, 4615 (up to 94% ee at -30 °C for **S1**). c) García Mancheño, O.; Priego, J.; Cabrera, S.; Gómez Arrayás, R.; Llamas, T.; Carretero, J. C. *J. Org. Chem.* **2003**, *68*, 3679 (up to 97% ee at -20 °C for **S1**). d) Enders, D.; Peters, R.; Runsink, J.; Bats, J. W. *Org. Lett.* **1999**, *1*, 1863 (up to 97% ee at -20 °C for **S1**). e) Guimet, E.; Diéguez, M.; Ruiz, A.; Claver, C. *Tetrahedron: Asymmetry* **2005**, *16*, 959 (up to 93% ee at 0 °C for **S1**). f) Caldentey, X.; Pericàs, M. A. *J. Org. Chem.* **2010**, *75*, 2628 (up to 96% ee at rt for **S1**).

[12] Bernardi, L.; Bonini, B. F.; Comes-Franchini, M.; Fochi, M.; Mazzanti, G.; Ricci, A.; Varchi, G. *Eur. J. Org. Chem.* **2002**, 2776.

[13] Khruscheva, N. S.; Loim, N. M.; Sokolov, V. I.; Makhaev, V. D. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2425.

[14] Page, P. C. P.; Heaney, H.; Reignier, S.; Rassias, G. A. *Synlett* **2003**, 22.

[15] Pàmies, O.; Diéguez, M.; Net, G.; Ruiz, A.; Claver, C. *Organometallics* **2000,** *19,* 1488.

[16] a) Oslob, J. D.; Åkermark, B.; Helquist, P.; Norrby, P.-O. *Organometallics* **1997**, *16,* 3015. b) Hagelin, H.; Åkermark, B.; Norrby, P.-O. *Organometallics* **1999**, *18,* 2884.

[17] a) Hagelin, H.; Svensson, M.; Åkermark, B.; Norrby, P.-O. *Organometallics* **1999**, *18,* 4574. b) Moberg, C.; Bremberg, U.; Hallman, K.; Svensson, M.; Norrby, P.-O.; Hallberg, A.; Larhed, M.; Csöregh, I. *Pure Appl. Chem.* **1999**, *71,* 1477.

[18] Peña-Cabrera, E.; Norrby, P.-O.; Sjögren, M. P. T.; Vitagliano, A.; deFelice, V.; Oslob, J. D.; Ishii, S.; Åkermark, B.; Helquist, P. *J. Am. Chem. Soc.* **1996**, *118,* 4299.

[19] a) Katcher, M. H.; Norrby, P.-O.; Doyle, A.G. *Organometallics* **2014**, *33*, 2121. b) Hagelin, H.; Åkermark, B.; Norrby, P.-O. *Chem. Eur. J.* **1999**, *5,* 902.

[20] Fristrup, P.; Ahlquist, M.; Tanner, D.; Norrby, P.-O. *J. Phys. Chem.* **2008**, *112,* 12862.

[21] a) Fristrup, P.; Jensen, T.; Hoppe, J.; Norrby, P.-O. *Chem. Eur. J.* **2006**, *12,* 5352. b) Johansson, C.; Lloyd-Jones, G. C.; Norrby, P.-O. *Tetrahedron: Asymmetry.* **2010**, *21,* 1585.

[22] a) *Dictionary of Natural Products*; Buckingham, J., Ed.; Cambridge University Press.: Cambridge, 1994. b) Lumbroso, A.; Cooke, M. L.; Breit, B. *Angew. Chem. Int. Ed.* **2013**, *52*, 1890.

[23] For successful examples of Pd-catalysts, see: a) Trost, B. M.; Shen, H. C.; Dong, L.; Surivet, J.-P. *J. Am. Chem. Soc.* **2003**, *125*, 9276. b) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1998**, *120*, 815; c) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1999**, *121*, 4545; d) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **2000**, *122*, 11262; e) Uozumi, Y.; Kimura, M. *Tetrahedron: Asymmetry* **2006**, *17*, 161; f) Tietze, L. F.; Lohmann, J. K.; Stadler, C. *Synlett* **2004**, 1113. For successful applications of Ir-catalysts with phenols, see: g) Shu, C.; Hartwig, J. F. *Angew. Chem. Int. Ed.* **2004**, *43*, 4794. h) Fischer, C.; Defieber, C.; Suzuki, T.; Carreira, E. M. *J. Am. Chem. Soc.* **2004**, *126*, 1628; i) Lopez, F.; Ohmura, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 3426. j) Lyothier, I.; Defieber, C.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2006**, *45*, 6204. k) Welter, C.; Dahnz, A.; Brunner, B.; Streiff, S.; Dubon, P.; Helmchen, G. *Org. Lett.* **2005**, *7*, 1239. l) Kimura, M.; Uozumi, Y. *J. Org. Chem.* **2007**, *72*, 707.

[24] a) Iourtchenko, A.; Sinou, D. *J. Mol. Catal. A* **1997**, *122*, 91. b) Haight, A. R.; Stoner, E. J.; Peterson, M. J.; Grover, V. K. *J. Org. Chem.* **2003**, *68*, 8092; c) Lam, F. L.; Au Yeung, T. T.-L.; Kwong, F. Y.; Zhou, Z.; Wong, K. Y.; Chan, A. S. C. *Angew. Chem. Int. Ed.* **2008**, *47*, 1280. d) Ye, F.; Zheng, Z.-J.; Li, L.; Yang, K.-F. ; Xia, C. G.; Xu, L.-W. *Chem. Eur. J.* **2013**, *19*, 15452. e) Liu, Z.; Du, H. *Org. Lett.* **2010**, *12*, 3054. f), Kato, M.; Nakamura, T.; Ogata, K.; Fukuzawa, S. *Eur. J. Org. Chem.* **2009**, 5232. g) Feng, B.; Cheng, H.-G.; Chen, J.-R.; Deng, Q.-H.; Lu, L.-Q.; Xiao, W.-J. *Chem. Commun.* **2014**, *50*, 9550. For a report based on Ir-catalysts, see: h) Ueno, S.; Hartwig, J. F. *Angew. Chem. Int. Ed.* **2008**, *47*, 1928.

[25] For a review on Hammett studies, see: Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165.

[26] There are therefore fewer successful catalyst systems for the Pd-catalyzed allylic substitution of this substrate than for the allylic substitution of substrate **S1**. If enantiomeric excesses are to be high, the ligand must create a small chiral pocket around the metal center, mainly because of the presence of less sterically demanding methyl *syn* substituents.

[27] a) Deerenberg, S.; Schrekker, H. S.; van Strijdonck, G. P. F.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Fraanje, J.; Goubitz, K. *J. Org. Chem.* **2000**, *65*, 4810. b) Fernández, F.; Gómez, M.; Jansat, S.; Muller, G.; Martín, E.; Flores Santos, L.; García, P. X.; Acosta, A.; Aghmiz, A.; Jiménez-Pedrós, M.; Masdeu-Bultó, A. M.; Diéguez, M.; Claver, C.; Maestro, M. A. *Organometallics* **2005**, *24*, 3946.

[28] The equilibrium between the two diastereoisomers takes place via the so-called apparent ɳ-allyl rotation. This has been shown to occur via dissociation of one of the coordinated atoms of the bidentate ligand, which allows the ligand to rotate. See: Gogoll, A.; Örnebro, J.; Grennberg, H.; Bäckvall, J. E. *J. Am. Chem. Soc.* **1994**, *116*, 3631.

[29] Buisman, G. J. H.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Tetrahedron: Asymmetry* **1993**, *4*, 1625.

[30] a) Auburn, P. R.; Mackenzie, P. B.; Bosnich, B. *J. Am. Chem. Soc.* **1985**, *107*, 2033. b) Jia, C.; Müller, P.; Mimoun, H. *J. Mol. Cat. A: Chem.* **1995**, *101*, 127. c) Lehman, J.; Lloyd-Jones, G. C. *Tetrahedron* **1995**, *51*, 8863. d) Hayashi, T.; Yamamoto, A.; Ito, Y.; Nishioka, E.; Miura, H.; Yanagi, K. *J. Am. Chem. Soc.* **1989**, *111*, 6301.

[31] von Matt, P.; Lloyd-Jones, G. C.; Minidis, A. B. E.; Pfaltz, A.; Macko, L.; Neuburger, M.; Zehnder, M.; Ruegger, H.; Pregosin, P. S. *Helv. Chim. Acta* **1995**, *78*, 265.

[32] Trost, B. M.; Strege, P. E.; Weber, L. *J. Am. Chem. Soc.* **1978**, *11*, 3407.

[33] Nakai, Y.; Uozumi, Y. *Org. Lett.* **2005**, *7*, 291.

[34] The chemical shifts of allylic terminal carbons of the minor isomer of complex **54** were obtained from the HSQC experiment (the signals at the ^{13}C NMR spectra were not detected).

[35] van Haaren, R. J.; Keeven, P. H.; van der Veen, L. A.; Goubitz, K.; van Strijdonck, G. P. F.; Oevering, H.; Reek, J. N. H.; Kamer, P. C. J.; van Leeuwen, P. W: N. M. *Inorg. Chim. Acta* **2002**, *327*, 108.

3.6. Furanoside phosphite-phosphoramidite and diphosphoramidite ligands applied to Cu-catalyzed allylic substitution reaction

Magre, M.; Mazuela, J.; Pàmies, O.; Diéguez, M.; Alexakis, A. *Tetrahedron Asymmetry* **2012**, *23*, 67.

Abstract: *A phosphite-phosphoramidite and diphosphoramidite ligand library **L21**-**L25a**-**f** was applied in the Cu-catalyzed allylic substitution of a range of cinnamyl-type substrates using several organometallic nucleophiles. Results indicated that selectivity depended strongly on the ligand parameters (position of the phosphoramidite group at either C-5 or C-3 of the furanoside backbone, as well as the configuration of C-3, the introduction of a second phosphoramidite moiety, the substituents and configurations in the biaryl phosphite/phosphoramidite moieties), the nature of the leaving group of the substrate and the alkylating reagent. Good enantioselectivities (up to 76%) and activity combined with high regioselectivities were obtained.*

3.6.1. Introduction

Developing methods for enantioselective carbon-carbon bond formation is one of the key issues in organic synthesis. A versatile method for doing so is transition metal-catalyzed asymmetric allylic substitution with carbon nucleophiles.[1] Great effort has been put into controlling the chemo-, regio-, and enantioselectivity outcome of the reaction. Most asymmetric allylic substitutions have been reported with soft nucleophiles (*i.e.* malonates and related stabilized anions) and Pd as the metal source, although Mo, W, Ru, Rh and Ir catalysts have also proved to be effective for these nucleophiles.[1] In contrast, copper allows the use of hard, non-stabilized nucleophiles, such as small alkyl groups in the form of organometallic species.[2] Among the broad range of reagents available, the use of Grignard reagents in the catalyzed asymmetric allylic substitution reaction was first reported by Bäckvall and van Koten, with chiral copper thiolate **1** (Figure 3.6.1), yielding moderate ee values.[3] This pioneering work was soon followed by a paper from Dübner and Knochel, who reported a highly enantioselective version using a different system based on diorganozinc reagents with ligand **2** (Figure 3.6.1).[4]

Since then, most efforts have been directed towards developing new efficient Cu catalysts for these organozinc reagents.[5] An important breakthrough in the use of Grignard reagents was made by Alexakis *et al.* They reported highly regio- and enantioselective Cu-phosphoramidite catalyzed allylic substitution of di- and tri-substituted cinnamyl chloride substrates (Figure 3.6.1, ligands type **3**).[6]

Other successful ligands have been introduced for stereoselective allylic addition of organomagnesium reagents, such as chiral N-heterocyclic carbenes (Figure 3.6.1, ligands type **4**) by Okamoto et al.[7] and more recently ferrocenic bidentate phosphines (Figure 3.6.1, ligand type **5**) by Feringa *et al.*[8]

Apart from these latter bidentate phosphines, the most successful ligands developed for this transformation are monodentate. However, Alexakis *et al.* found that successfully used OMe-substituted phosphoramidite monodentate-based ligands **3** can act as bidentate P,O-ligands.[6b]

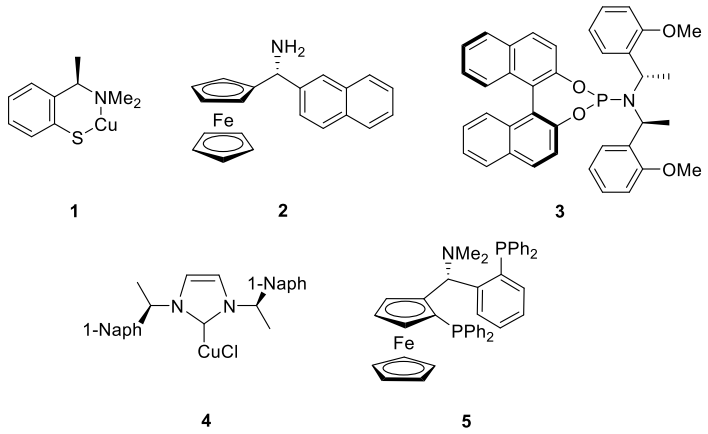


Figure 3.6.1. Previous ligands applied in Cu-catalyzed allylic substitution reactions.

On the basis of this finding, we decided to study a library of bidentated furanoside phosphite-phosphoramidite and diphosphoramidite ligands **L21**-**L25a**-**f** in the Cu-catalyzed allylic substitution reaction (Figure 3.6.2).

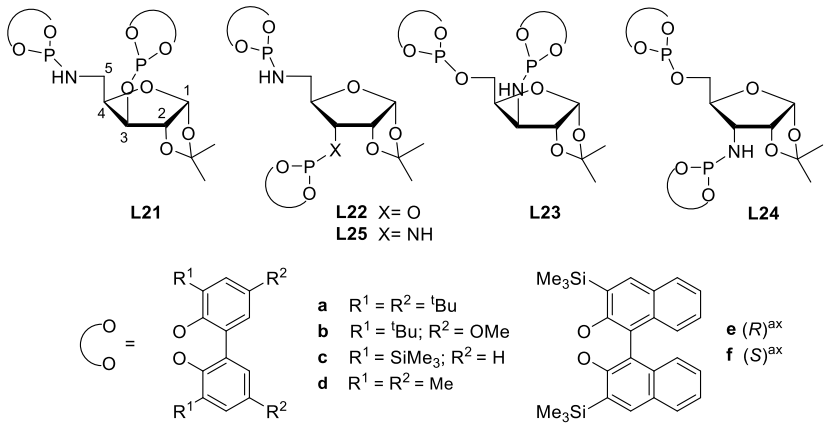


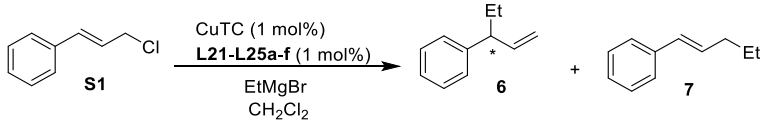
Figure 3.6.2. Furanoside phosphite-phosphoramidite and diphosphoramidite ligand library **L21**-**L25a**-**f**.

These ligands have the same advantages as carbohydrate and phosphite/phosphoramidite ligands: that is, they are cheaply available, they have high resistance to oxidation and they have facile modular constructions.[9]

Therefore, with this library we fully investigated the effects of systematically varying the position of the phosphoramidite group at both C-5 (ligands **L21** and **L22**) and C-3 (ligands **L23** and **L24**) of the furanoside backbone, as well as the effects of the configuration at C-3 of the furanoside backbone, the introduction of second phosphoramidite moiety (ligands **L25**) and the substituents/configurations in the biaryl phosphite/phosphoramidite moieties (**a**-**f**). By carefully selecting these elements and using a range of Grignard reagents, we achieved good regio- and enantioselectivities, and activities in different substrate types.

3.6.2. Results and discussion

Initially, we evaluated phosphite-phosphoramidite and diphosphoramidite ligand library **L21**-**L25a**-**f** (Figure 3.6.2) in the copper-catalyzed asymmetric allylic alkylation of cinnamyl chloride **S1** using EtMgBr as nucleophile (Scheme 3.6.1). The catalytic system was generated *in situ* by adding the corresponding ligand to a suspension of the catalyst precursor CuTC (copper thiophene 2-carboxylate).



Scheme 3.6.1. Cu-catalyzed asymmetric allylic alkylation using **L21**-**L25a**-**f**.

The results are shown in Table 3.6.1. They indicate that regio- and enantioselectivity are affected by the position of the phosphoramidite group at either C-5 or C-3 of the furanoside backbone, and by the configuration of C-3, the introduction of a second phosphoramidite moiety, and the substituents and configurations in the biaryl phosphite/phosphoramidite moieties (**a**-**f**).

We first studied the effect of the position of the phosphoramidite group at either C-5 (ligands **L21** and **L22**) or C-3 (ligands **L23** and **L24**) of the furanoside backbone and the configuration of C-3 (Table 3.6.1, entries 1-4). We observed a cooperative effect between the position of the phosphoramidite group and the configuration of carbon atom C-3 of the furanoside backbone. The results indicate that the matched combination is achieved with ligands **L2**, whose phosphoramidite moiety is attached to C-5 and which have an *R* configuration of carbon atom C-3 on the tetrahydrofuran ring (Table 3.6.1, entries 1-4).

We then used ligands **L5** to study how catalytic performance was affected by replacing the phosphite moiety with a phosphoramidite group in preferred ligands **L22**. The results

indicated that the presence of a second phosphoramidite moiety in the ligands had a negative effect on enantioselectivity (Table 3.6.1, entries 5 vs 2).

We next studied the effects of the biaryl phosphite/phosphoramidite moieties using ligands **L22a-f** (Table 3.6.1). We found that these moieties mainly affected enantioselectivity, while their effect on regioselectivity was less important. Results indicated that bulky substituents at both *ortho* and *para* positions of the biphenyl phosphite/phosphoramidite moieties need to be present if enantioselectivities are to be high (Table 3.6.1, entries 2 vs 6-8). This indicates that bulky substituents are necessary to control the tropoisomerization of the biaryl phosphite/phosphoramidite moieties in the catalytic active species. Similar behavior has been observed for other phosphite/phosphoramidite based ligands in other metal-catalyzed asymmetric transformations.[10] Moreover, the presence of bulky enantiopure binaphthyl moieties (**e**-**f**) did not further improve enantioselectivity (Table 3.6.1, entries 2 vs 9-10). This suggests that in ligand **L22a**, the biphenyl moiety attached to the phosphoramidite adopts a configuration that is different from that of the configuration of the biphenyl phosphite moiety.

Table 3.6.1. Selected results for the Cu-allylic substitution of cinnamyl chloride with EtMgBr using ligands **L21**-**L25a**-f.[a]

Entry	Ligand	% Conv[b]	**6**/**7**[c]	% ee[d]
1	**L21a**	100	94/6	39 (*S*)
2	**L22a**	99	97/3	60 (*S*)
3	**L23a**	100	88/12	3 (*S*)
4	**L24a**	100	92/8	38 (*S*)
5	**L25a**	100	96/4	12 (*S*)
6	**L22b**	100	95/5	48 (*S*)
7	**L22c**	100	96/4	32 (*S*)
8	**L22d**	100	97/3	6 (*S*)
9	**L22e**	96	96/4	16 (*R*)
10	**L22f**	90	95/5	43 (*S*)
11[e]	**L22a**	99	98/2	70 (*S*)

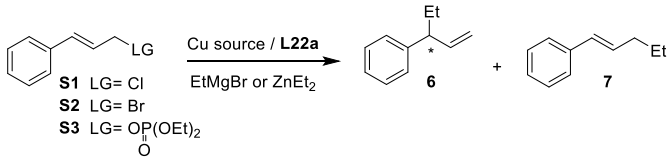
[a] Reaction conditions: CuTC (1 mol%), ligand (1 mol%), EtMgBr (1.2 eq, 1.2 mmol), **S1** (1 mmol), CH_2Cl_2 (2 mL), T= -50 °C. [b] Conversion determined by ^{1}H NMR after 1 h. [c] Regioselectivity determined by ^{1}H NMR. [d] Enantiomeric excess determined by GC on a Supelco β-DEX 120 column. [e] Reaction carried out at -78 °C.

To sum up, the best result was obtained with ligand **L22a**, which contains the optimal combination of ligand parameters. These results clearly show the efficiency of highly modular scaffolds in ligand design. Regio- and enantioselectivity can be improved by controlling not only the structural but also the reaction parameters. In this case, both regio- and enantioselectivity were further improved (98% regioselectivity with 70% ee) with ligand **L22a** by lowering the reaction temperature to -78 ºC (Table 3.6.1, entry 11).

It has been shown that the catalytic performance for this transformation is highly dependent on a subtle balance between the nature of the leaving group, the type of organometallic reagent and the copper source among other reaction parameters.[2] So we next investigated whether the performance of our CuTC/**L22a** catalytic system can be improved by using other leaving groups in the substrate and by using dialkylzincs instead of Grignard reagents. The results are summarized in Table 3.6.2.

Using EtMgBr, we found that the replacement of the chloride leaving group by a bromide (**S2**) or phosphonate group (**S3**) leads to lower regio- and enantioselectivities (Table 3.6.2, entries 2 and 3 vs 1).

Table 3.6.2. Selected results for Cu-catalyzed allylic alkylation of several cinnamyl halides (**S1**-**S2**) and phosphonate (**S3**) using EtMgBr and $ZnEt_2$.[a]



Entry	Cu salt	Substrate	Organometallic reagent	% Conv	**6**/**7**	% ee
1	CuTC	**S1**	EtMgBr	99	97/3	60 (S)
2	CuTC	**S2**	EtMgBr	100	92/8	53 (S)
3	CuTC	**S3**	EtMgBr	85	70/30	42 (*S*)
4	CuTC	**S1**	$ZnEt_2$	100	84/16	39 (*S*)
5	CuTC	**S2**	$ZnEt_2$	100	78/22	44 (*S*)
6	CuTC	**S3**	$ZnEt_2$	40	75/25	55 (*S*)
7	$CuOTf_2$	**S1**	$ZnEt_2$	92	82/18	36 (*S*)
8	$CuOTf_2$	**S2**	$ZnEt_2$	85	70/30	46 (*S*)

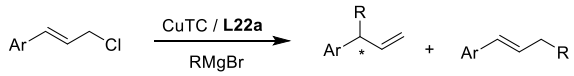
[a] Reaction conditions: Cu source (1 mol%), ligand (1 mol%), nucleophile (1.2 eq, 1.2 mmol), **S1** (1 mmol), CH_2Cl_2 (2 mL), T= -50 °C. [b] Conversion determined by ^1H NMR after 1 hour. [c] Regioselectivity determined by ^1H NMR. [d] Enantiomeric excess determined by GC on a Supelco β-DEX 120 column.

On the other hand, the use of dialkylzincs instead of Grignard reagents for the allylic substitution of cinnamyl halides (**S1** and **S2**) leads to significantly lower regio- and enantioselectivities (Table 3.6.2, entries 4 and 5 vs 1 and 2, respectively). However, for phosphonate **S3,** enantioselectivity and to a lesser extent regioselectivity increased when $ZnEt_2$ was used, but at the cost of activity (Table 3.6.2, entry 6 vs 3). Finally, and on the basis of our previous results on Cu-catalyzed conjugated addition which show that for some substrates the combination of dialkylzincs with $CuOTf_2$ leads to higher enantioselectivities, we decided to assess the use of $CuOTf_2$ as a source of copper. Disappointingly, no improvement in the catalytic performance was observed (Table 3.6.2, entries 7 and 8 vs 4 and 5, respectively).

Finally, we investigated the allylic substitution of a range of cinnamyl type chlorides with various Grignard reagents. Cinnamyl chloride **S1** reacts with methyl and *n*-propyl Grignard reagents as EtMgBr does (Table 3.6.3, entries 2 and 3 vs 1). However, the use of a secondary Grignard reagent, ^{i}PrMgBr, decreases both regio- and enantioselectivities (Table 3.6.3, entry 4 vs 1).

Regarding the substrate scope, Table 3.6.3 shows that soft electron-donating groups at the *para* positions of the phenyl group (substrate **S4**) slightly decrease both regio- and enantioselectivities (Table 3.6.3, entries 5 and 6 *vs* 1 and 4, respectively), while strongly electron-donating groups (substrate **S5**) slightly increase enantioselectivities (Table 3.6.3, entries 7 and 8 *vs* 1 and 4, respectively). Interestingly, the allylic substitution of 2-(3-chloro-propenyl)-naphthalene **S6** provided the highest enantioselectivities (ee's up to 76%, Table 3.6.3, entries 9-14) while maintaining the excellent regioselectivity.

Table 3.6.3. Selected results for the Cu-catalyzed asymmetric allylic substitution of a range of cinnamyl-type chlorides with various Grignard reagents [a]



S1 Ar= Ph
S4 Ar= 4-Me-C_6H_4
S5 Ar= 4-MeO-C_6H_4
S6 Ar= 2-Naph

Entry	Substrate	R	% Conv[b]	γ/α[c]	% ee[d]
1	**S1**	Et	99 (95)	97/3	60 (S)
2	**S1**	Me	98 (94)	98/2	59 (S)
3	**S1**	^{n}Pr	99 (96)	97/3	59 (*S*)
4	**S1**	^{i}Pr	98 (92)	92/8	35 (*S*)
5	**S4**	Et	100 (93)	93/7	54 (*S*)
6	**S4**	^{i}Pr	100 (91)	88/12	32 (*S*)
7	**S5**	Et	99 (94)	97/3	62 (*S*)
8	**S5**	^{i}Pr	100 (90)	92/8	40 (*S*)
9	**S6**	Et	100 (92)	96/4	68 (*S*)
10	**S6**	Me	100 (94)	96/4	67 (*S*)
11	**S6**	^{n}Pr	100 (96)	95/5	67 (*S*)
12	**S6**	^{i}Pr	100 (92)	90/10	41 (*S*)
13[e]	**S6**	Et	100 (91)	96/4	76 (*S*)
14[e]	**S6**	Me	100 (95)	97/3	73 (*S*)

[a] Reaction conditions: CuTC (1 mol%), **L22a** (1 mol%), RMgBr (1.2 eq, 1.2 mmol), substrate (1 mmol), CH_2Cl_2 (2 mL), T= -50 °C. [b] Conversion determined by ^{1}H NMR after 1 hour. In parentheses the isolated yield of the mixture of regioisomers. [c] Regioselectivity determined by ^{1}H NMR. [d] Enantiomeric excess determined by GC on a Supelco β-DEX 120 column. [e] Reaction performed at -78 °C .

3.6.3. Conclusions

A library of furanoside phosphite-phosphoramidite and diphosphoramidite **L21**-**L25a**-**f** was applied in the Cu-catalyzed allylic substitution of a range of cinnamyl-type substrates using several organometallic nucleophiles. Good enantioselectivities (up to 76%) and activity combined with high regioselectivities were obtained. Systematically varying the position of the phosphoramidite group, at either C-5 or C-3 of the furanoside backbone, as well as the configuration of C-3 and several substituents and configurations in the biaryl phosphite/phosphoramidite moieties had a strong effect on rate and selectivity. Enantioselectivity was best with the catalyst precursor containing ligand **L22a**, which has the optimal combination of ligand parameters.
Our results also showed that the nature of the leaving group of the substrate and the alkylating reagent also play an important role in determining activity and the regio- and enantioselectivity.

3.6.4. Experimental Section

3.6.4.1. General considerations

All syntheses were performed using standard Schlenk techniques under argon atmosphere. Solvents were purified by standard procedures. Ligands **L21**-**L25a**-**f**[11] and substrates **S3**-**S6**[12] were prepared by previously described methods. All other reagents were used as commercially available.

3.6.4.2. General procedure for the Cu-catalyzed enantioselective allylic substitution

A dried Schlenk tube was charged with copper salt (1 mol%) and the chiral ligand (1 mol%). Dichloromethane (2 mL) was added and the mixture was stirred at room temperature for 30 min. The allylic chloride (1 mmol) was introduced dropwise and the reaction mixture was stirred at room temperature for a further 5 min before being cooled to −50°C. Grignard reagent (2-3 M in diethyl ether, 1.2 eq) in dichloromethane (0.5 mL) was added for 40 min via syringe pump. Once the addition was complete the reaction mixture was left at −50°C for one hour. The reaction was then quenched by addition of aqueous hydrochloric acid (1N, 2 mL). Diethyl ether (10 mL) was added and the aqueous phase was separated and extracted further with diethyl ether (3 x 3 mL). The combined organic fractions were washed with brine (5 mL), dried over anhydrous sodium sulfate, filtered and reduced *in vacuo*. Conversion and regioselectivity were determined by ^{1}H-NMR, and enantiomeric excess was determined by GC.[6a] The absolute configuration of the alkylation products has been assigned by comparing the retention time with those

obtained with enantioenriched samples prepared according to reference 6a. The oily residue was purified by flash column chromatography (eluent = pentane) to yield the product as a mixture of SN_2' and SN_2 regioisomers.[6a]

3.6.5. References

1 For reviews, see: a) Trost, B. M.; Lee C. in *Catalytic Asymmetric Synthesis* (Ed.: I. Ojima), 2nd ed., Wiley, New York, 2000, p. 593; b) Pfaltz, A.; Lautens, M. in *Comprehensive Asymmetric Catalysis I–III* (Ed.: E. N. Jacobsen, E. N.; Pfaltz, A.; Yamamoto H.), Springer, Berlin, 1999, p. 833. c) Trost, B. M.; van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395. d) Johannsen, M.; Jorgensen, K. A. *Chem. Rev.* **1998**, *98*, 1689. e) Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000**, *33*, 336. f) Takeuchi, R. *Synlett* **2002**, 1954. g) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921. h) Miyabe, H.; Takemoto, Y. *Synlett* **2005**, 1641. i) Martín, E.; Diéguez, M. *C. R. Chemie* **2007**, *10*, 188. j) Lu, Z.; Ma, S. *Angew. Chem. Int. Ed.* **2008**, *47*, 258. k) Diéguez, M.; Pàmies, O. *Acc. Chem. Res.* **2010**, *43*, 312.

2 For specific reviews on Cu-catalyzed allylic alkylation ractions, see: a) Yorimitsu, H.; Oshima, K. *Angew. Chem. Int. Ed.* **2005**, *44*, 4435. b) Kar, A.; Argade, N. P. *Synthesis* **2005**, 2995. c) Alexakis, A.; Malan, C.; Lea, L.; Tissot-Croset, K.; Polet, D.; Falciola, C. *Chimia* **2006**, *60*, 124. d) Alexakis, A.; Bäckvall, B.; Krause, N.; Pàmies, O.; Diéguez, M. *Chem. Rev.* **2008**, *108*, 2796. e) Falciola, C. A.; Alexakis, A. *Eur. J. Org. Chem.* **2008**, 3765. f) Harutyunyan, S. R.; den Hartog, T.; Geurts, K.; Minnaard, A. J.; Feringa, B. L. *Chem. Rev.* **2008**, *108*, 2824.

3 a) van Klaveren, M.; Persson, E. S. M.; del Villar, A.; Grove, D. M.; Bäckvall, J. E.; van Koten, G. *Tetrahedron Lett.* **1995**, *36*, 3059. b) Karlstrom, A. S. E.; Huerta, F. F.; Meuzelaar, G. J.; Bäckvall, J. E. *Synlett* **2001**, 923.

4 Dübner, F.; Knochel, P. *Angew. Chem. Int. Ed.* **1999**, *38*, 379. b) Dübner, F.; Knochel, P. *Tetrahedron Lett.* **2000**, *41*, 9233.

5 More recently, triorganomaluminum reagents and organoboronates have also been successfully applied to this process. See, for instance: a) Bournaud, C.; Falciola, C.; Lecourt, T.; Rosset, S.; Alexakis, A.; Micouin, L. *Org. Lett.* **2006**, 8, 3581. b) Lee, Y.; Akiyama, K.; Gillingham, D. G.; Brown, K.; Hoveyda, A. H. *J. Am. Chem. Soc*. **2008**, *130*, 446. c) Pineschi, M.; Del Moro, F.; Crotti, P.; Macchia, F. *Org. Lett*. ***2005***, *7*, 3605. e) Ito, H.; Ito, S.; Sasaki, Y.; Matsuura, K.; Sawamura, M. *J. Am. Chem. Soc.* **2007**, *129*, 14856.

6 a) Alexakis, A.; Croset, K. *Org. Lett.* **2002**, *4*, 4147. b) Tissot-Croset, K.; Polet, D.; Alexakis, A. *Angew. Chem. Int. Ed.* **2004**, *43*, 2426. c) Falciola, C. A.; Tissot-Croset, K.; Alexakis, A. *Angew. Chem. Int. Ed.* **2006**, *45*, 5995. d) Falciola, C. A.; Alexakis, A. *Angew. Chem. Int. Ed.* **2007**, *46*, 2619.

7 a) Tominaga, S.; Oi, Y.; Kato, T.; An, D. K.; Okamoto, S. *Tetrahedron Lett.* **2004**, *45*, 5585. b) Okamoto, S.; Tominaga, S.; Saimo, N.; Kase, K.; Shomoda, K. *J. Organomet. Chem.* **2005**, *690*, 6001.

[8] Lopez, F.; van Zijl, A. W.; Minaard, A. J.; Feringa, B. L. *Chem. Commun.* **2006**, 409.

[9] See for instance: a) Feringa, B. L. *Acc. Chem. Res*. **2000**, *33*, 346. b) Diéguez, M.; Pàmies, O.; Claver, C. *Chem. Rev.* **2004**, *104*, 3189. c) Woodward, S.; Diéguez, M.; Pàmies, O. *Coord. Chem. Rev.* **2010**, *254*, 2007. d) Diéguez, M.; Ruiz, A.; Claver, C. *Dalton Trans.* **2003**, 2957. e) Diéguez, M.; Pàmies, O.; Ruiz, A.; Claver, C. in *Methodologies in Asymmetric Catalysis* (Ed. Malhotra, S. V.); American Chemical Society, Washington DC, 2004. f) Diéguez, M.; Pàmies, O.; Claver, C. *Tetrahedron: Asymmetry* **2004**, *15*, 2113. g) Minnaard, A. J.; Feringa, B. L.; Lefort, L.; de Vries, J. G. *Acc. Chem.. Res.* **2007**, *40*, 1267. h) Börner, A. *Phosphorous Ligands in Asymmetric Catalysis* **2008**, Wiley-VCH, Weinheim. i) van Leeuwen, P. W. N. M.; Kamer, P. C. J.; Claver, C.; Pàmies, O.; Diéguez, M. *Chem. Rev.* **2011**, *111*, 2077.

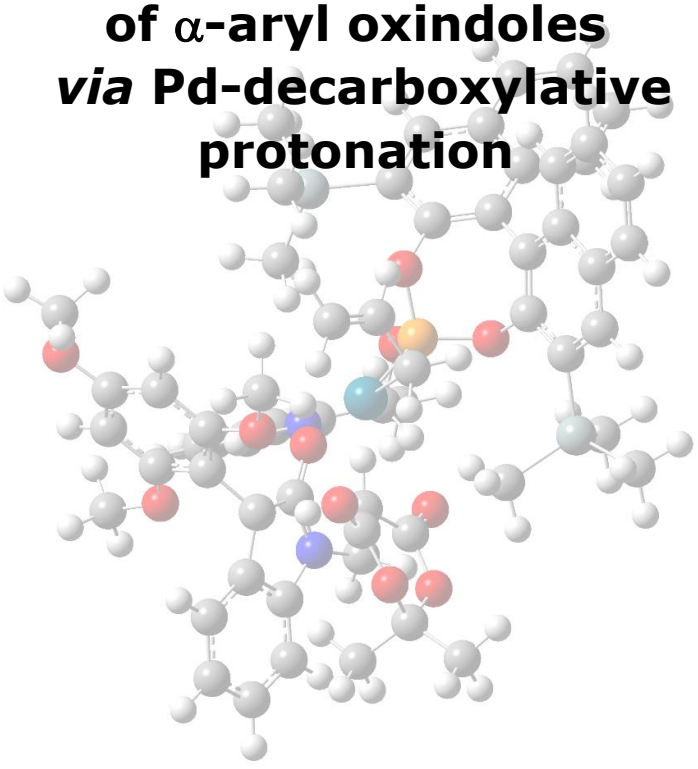
[10] The rapid ring inversions (tropoisomerization) in the biaryl phosphite/ phosphoramidite moieties are usually stopped upon coordination to the metal center when bulky substituents are present. See for example: a) Buisman, G. J. H.; van der Veen, L. A.; Klootwijk, A.; de Lange, W. G. J.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Vogt, D. *Organometallics* **1997**, *16*, 2929. b) Diéguez, M.; Pàmies, O.; Ruiz, A.; Claver, C.; Castillón, S. *Chem. Eur. J.* **2001**, *7*, 3086. c) Pàmies, O.; Diéguez, M.; Net, G.; Ruiz, A.; Claver, C. *Organometallics* **2000**, *19*, 1488. d) Pàmies, O.; Diéguez, M.; Net, G.; Ruiz, A.; Claver, C. *J. Org. Chem.* **2001**, *66*, 8364. e) Pàmies, O.; Diéguez, M. *Chem. Eur. J.* **2008**, *14*, 944.

[11] a) Diéguez, M. ; Ruiz, A. ; Claver, C. *Chem. Commun.* **2001**, 2702. b) Diéguez, M.; Ruiz, A.; Claver, C. *Tetrahedron: Asymmetry* **2001**, *12*, 2827. c) Raluy, E.; Claver, C.; Pàmies, O.; Diéguez, M. *Org. Lett.* **2007**, *9*, 49. d) Raluy, E.; Pàmies, O.; Diéguez, M. *Adv. Synth. Catal.* **2009**, *351*, 1648. e) Raluy, E.; Diéguez, M.; Pàmies, O. *J. Org. Chem.* **2007**, *72*, 2842

[12] Tissot-Croset, K. PhD Thesis, University of Geneva, **2005**.

Chapter 4

Enantioselective synthesis of α-aryl oxindoles *via* Pd-decarboxylative protonation



UNIVERSITAT ROVIRA I VIRGILI
DESIGN OF TAILOR-MADE CHIRAL LIGAND LIBRARIES FOR C-X BOND FORMING REACTIONS. STUDY OF THE KEY INTERMEDIATES BY NMR AND DFT
Marc Magre Rosich

4. Enantioselective synthesis of α-aryl oxindoles *via* Pd-decarboxylative protonation

4.1. Background

One of the most challenging problems in organic chemistry which needs to be overcame is the formation of stereoselective C-C bond between an aromatic carbon and a carbon α to a carbonyl group. Transition metal-catalyzed α-arylation has attracted considerable attention due to its versatility and utility of many medicinal targets.

Oxindoles skeleton is present in some natural products which present a wide range of properties and are reported to exhibit an extensive range of biological effects such as antiviral, antibacterial and anticancer activities. As C-3 substituted oxindoles present biological activity, many efforts have been made to prepare enantioselective α-substituted oxindoles. Among α-substituted oxindoles, α-aryl oxindoles has been less developed and many efforts have to be made for their preparation.

Palladium catalyzed asymmetric intramolecular cyclization for preparation of 3,3-disubstituted oxindoles has been widely developed to achieve enantioselective α-substituted oxindoles, but this protocol is not useful is the oxindole core is already existing in the molecule. For that reason, metal-catalyzed direct α-arylation of oxindoles has appeared as an alternative to intramolecular cyclization.

The α-arylation of amide enolates represents one of the most challenging chemical transformation due to the high pKa of the substrates, necessitating the use of strong bases which can limit the substrate scope, due to the easy racemization of the new created stereocentre. To the best of our knowledge, no asymmetric α-aryl oxindoles are present in the literature.

Guiry *et al.* have developed an alternative to the catalytic asymmetric α-arylation of carbonyls, which is having the aryl group already introduced in the α-position of carbonyl compound and, by Pd-catalyzed asymmetric decarboxylative protonation, generating the chiral stereocentre at α-position of the carbonyl compound. These authors have reported the application of electron-deficient PHOX-type ligands for the Pd-catalyzed enantioselective decarboxylative protonation of isoflavanones and cyclic ketones with a great success. They could determine that replacing PHOX ligand by electron-deficient CF_3-PHOX-type ligands, enantioselectivities of the reaction were further improved.

With the precedents in the literature about Pd-decarboxylative protonation and the fact that there is no reported example of enantioselective α-aryl oxindole (if the oxindole core is already present in the molecule), we thought that the use of the large number of π-acceptor phosphite-containing ligands developed previously in our laboratories could be a good choice of ligands for the Pd-catalyzed enantioselective decarboxylative protonation reactions.

The group of Prof. Patrick Gury at UCD in Dublin, was working on the synthesis of chiral α-aryl oxindoles. They successfully developed a methodology for their synthesis through Pd-decarboxylative protonation of α-aryl-β-amido allyl esters.

In Section 4.2 we present a collaboration of the Guiry's group in the screening of three main ligand phosphite-N libraries **L1**-**L4** and **L26**-**L37a**-**e** for this reactions. Different α-aryl oxindoles, with different electronic and steric properties, have been enantioselectively synthesized.

4.2. First catalytic asymmetric synthesis of sterically hindered tertiary α-aryl oxindoles via Pd-catalyzed decarboxylative protonation

Magre, M.[+]; Jackson, M.[+]; Biosca, M.; Pàmies, O.; Norrby, P.-O.; Diéguez, M.; Guiry, P. J. *Manuscript in preparation.* [+] Both authors contributed equally to this work.

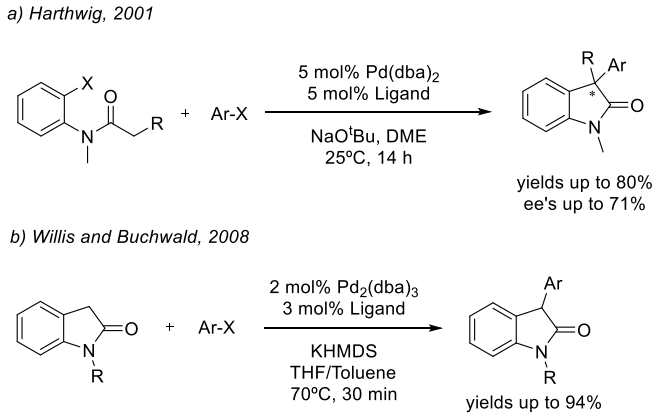
Abstract: *In collaboration with Prof. Guiry we have been able to develop the first catalytic asymmetric preparation of tertiary sterically hindered α-aryl oxindoles via enantioselective Pd-catalyzed decarboxylative protonation of the corresponding α-aryl-β-amido allyl esters. The reaction occurs under very mild conditions and in short reaction times, providing excellent yields and promising enantioselectivities (ee's up to 78%).*

4.2.1. Introduction

One of the most challenging problems in organic chemistry is the formation of stereoselective C-C bond between an aromatic carbon and an α–carbon to a carbonyl group.[1] The asymmetric synthesis of α-aryl carbonyl-containing molecules has attracted much attention over the last decade, due to the presence of this structural motif in biologically active products such as isoflavanones and oxindoles among others.[2]

Oxindoles are endogenous aromatic organic compounds that are found in the tissues and body fluids of mammals. The oxindole skeleton is also present in many natural products with antiviral, antibacterial and anticarcinogenic effects.[2f]

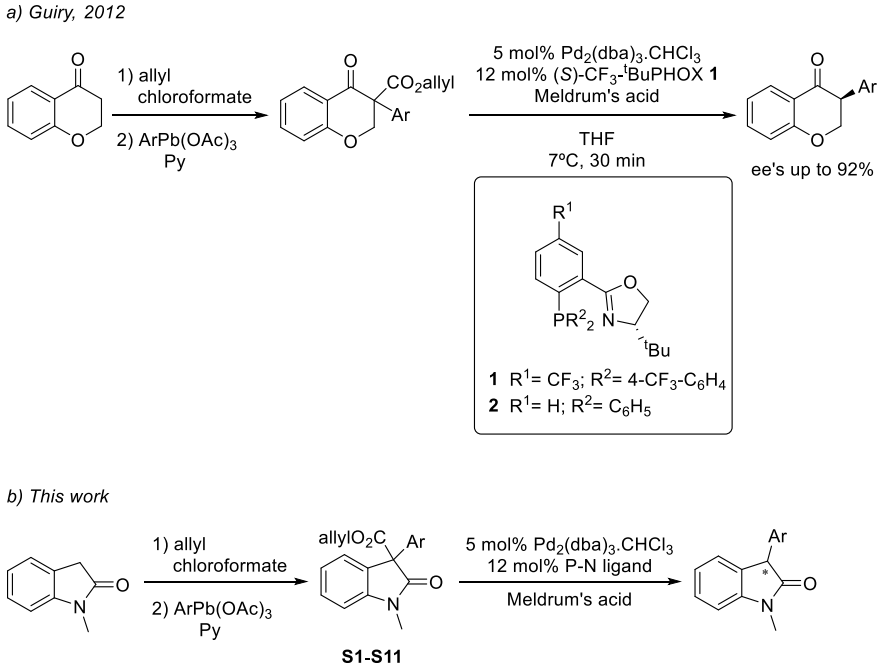
The first approach to the asymmetric synthesis of oxindoles was reported by Hartwig *et al.* (Scheme 4.2.1a) in 2001. They reported the preparation of 3,3-disubstituted oxindoles using a Pd-catalyzed intramolecular cyclization with excellent conversions and promising enantioselectivities (ee's up to 71%).[3] However, such an approach was not suitable when the substrate had an oxindole core and only quaternary α-aryl oxindoles were achieved. In contrast to the catalytic asymmetric synthesis of quaternary α-aryl carbonyl stereocenters, the synthesis of the corresponding tertiary α-aryl carbonyl containing compounds remains a challenge due to the ease at which such compounds racemize. As an alternative to the cyclization method, direct metal-catalyzed α-arylation of carbonyl compounds emerged for a wide range of nucleophiles such as enolates of ketones, esters, nitriles and amides.[4] The first metal-catalyzed α-arylation of oxindoles was reported by Willis'[5] and Buchwald's[6] groups independently in 2008 (Scheme 4.2.1b). They applied Pd-phosphine complexes to catalyze the α-arylation of oxindoles with several aryl halides with good to excellent yields. The application of strong bases (such as NaO^{t}Bu or KHMDS) is necessary in all α-arylation of oxindoles to deprotonate the amidic α-proton. Due to such strong basic media, the asymmetric α-arylation of oxindoles has not been reported yet because of the easy racemization of that tertiary stereocentre in α-position to the amide group.



Scheme 4.2.1. Previous methodologies for the preparation of α-aryl oxindoles.

An alternative path to catalytic asymmetric α-arylation of carbonyls using strong bases is to use α-aryl-β-keto allyl esters that already have an aryl group in the α-position of the carbonyl (Scheme 4.2.2). With this idea, Guiry *et al.* have reported the preparation of chiral α-aryl carbonyl-containing compounds via Pd-decarboxylative protonation of α-aryl-β-keto esters using phosphine-oxazoline PHOX-based ligands (Scheme 4.2.2a). With this protocol they synthesized several chiral isoflavanones and chiral α-aryl cyclic ketones in excellent yields and enantioselectivities, with the (*S*)-CF_3-^{t}BuPHOX ligand **1** (Scheme 4.2.2a).[7,8] A relevant finding was that the electron deficient phosphine-oxazoline ligand (*S*)-CF_3-^{t}BuPHOX **1** provided much higher enantioselectivity than usual phosphine-oxazoline ^{t}BuPHOX ligand **2**. We now wish to go further and achieve, for the first time, the catalytic asymmetric synthesis of chiral tertiary α-aryl oxindoles by a lead mediated arylation of β-amido esters followed by a Pd-catalyzed decarboxylative protonation (Scheme 4.2.2b). We studied several α-aryl-β-amido esters **S1**-**S11**[9] containing aryl substituents with different electronic and steric properties.

Because the use of electron-deficient ligands was seen to facilitate the asymmetric Pd-decarboxylative protonation of α-aryl-β-keto allyl esters (Scheme 4.2.2a), we focused in electron deficient P,N ligands and applied several π-acceptor phosphite-N ligand families (Figure 4.2.1) that our group had developed previously.



Scheme 4.2.2. Synthesis of chiral α-aryl isoflavanones (Scheme 4.2.2a) and oxindoles (Scheme 4.2.2b) by a lead mediated arylation followed by an enantioselective Pd-catalyzed decarboxylative protonation.

We know that in some asymmetric catalytic transformations the biaryl π-acceptor phosphite groups in the ligands have a positive effect on activity and widen substrate versatility.[10] The higher flexibility of a biaryl phosphite compared with a phosphine moiety help the P-N ligands to accommodate a wider range of substrates, thereby yielding excellent enantioselectivities for a broad range of substrates and catalytic reactions.[10] In the present study we applied, using the methodology developed by Guiry's group, three of our phosphite-N ligand families in the Pd-decarboxylative protonation of α-aryl-β-amido esters (Figure 4.2.1).[11] These phosphite-oxazoline ligands are based on three main ligand structures. The first one is based on the phosphine-oxazoline PHOX ligands **2**, in which the phosphine moiety has been replaced by biaryl phosphite groups (ligands **L1**-**L4**).[11a-c] In the second one the flat *ortho*-phenylene tether in **L1**-**L4** has been replaced by an alkyl chain bonded to carbon 4 of the oxazoline moiety, which shifts the chirality from the oxazoline to the alkyl chain (ligands **L26**-**L29**).[11d-g] In the third one the oxazoline group has been replaced by a more robust pyridine group (ligands **L30**-**L37**).[11h-i] Several configuration/substituents on the biaryl phosphite moiety will be also studied (**a**-**e**). Finally, in this work we also perform theoretical studies in order to explain the origin of enantioselectivity.

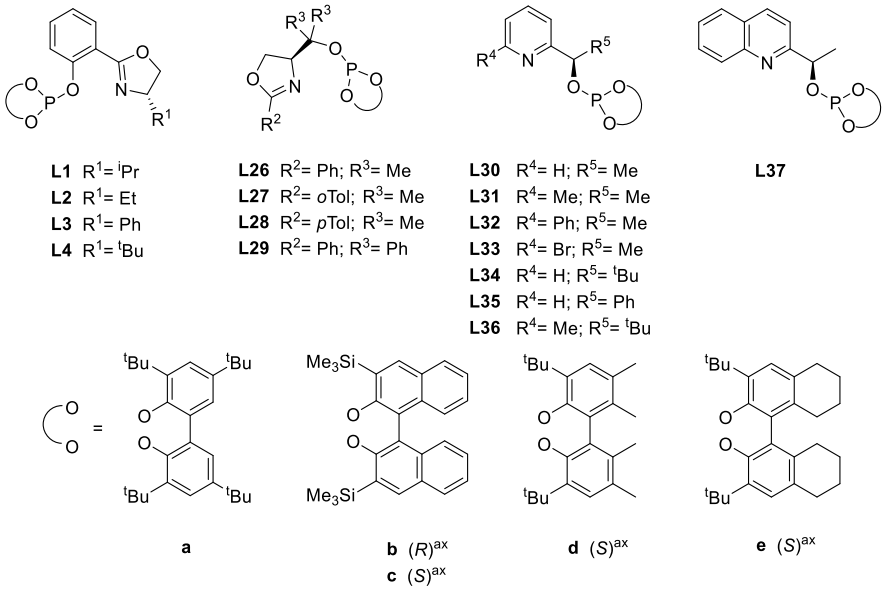
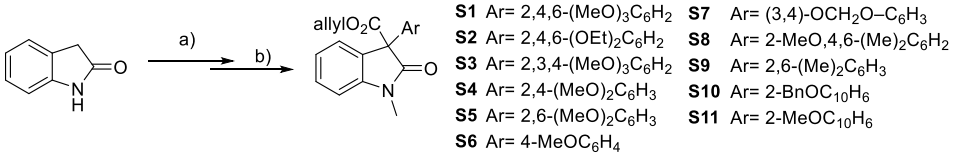


Figure 4.2.1. Phosphite-nitrogen ligand families.

4.2.2. Results and discussion

4.2.2.1. Synthesis of S1-S11

The synthesis of compounds **S1**-**S11** was straightforward in only two steps synthesis from the already available 2-oxindole (Scheme 4.2.3). The first step of the synthesis is the methylation of 2-oxindole with Me_2SO_4 as strongly methylating agent. Then, using LDA and allylchloroformate the corresponding allyl 1-methyl-2-oxoindoline-3-carboxylate intermediate is obtained and without further purification, $ArPb(OAc)_3$ in pyridine were added to the reaction mixture to afford the corresponding α-aryl-β-amido ester **S1**-**S11** in moderate-to-good yields (41-75% yield).[9]



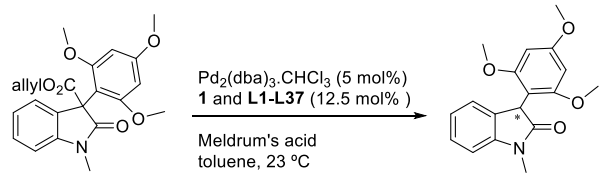
Scheme 4.2.3. Synthetic route to substrates **S1-S11:** a) NaH, Me_2SO_4, Toluene, reflux, 3 h. b) LDA, allylchloroformate, -65ºC, then Py, $ArPb(OAc)_3$, $CHCl_3$ 40ºC, 18 h.

4.2.2.2. Catalytic reactions

In a first set of experiments we used as a model allyl 1-methyl-2-oxo-3-(2',4',6'-trimethoxyphenyl)indoline-3-carboxylate **S1**. We tested the ligands in the optimal reaction conditions found by Guiry *et al*. in the Pd-decarboxylative protonation of α-aryl-β-keto allyl esters.[7] Reactions were therefore performed at room temperature, using 5 mol% of *in situ* generated catalyst $Pd_2(dba)_3.CHCl_3$ and the corresponding ligand in the presence of Meldrum's acid. In this protocol pre-activation of the catalyst was needed. The results are collected in Table 4.2.1. All catalytic systems were very active, achieving full conversion in less than 2 hours. Disappointingly, the use of the electron deficient phosphine-oxazoline ligand **1**, which has been the best ligand for the Pd-decarboxylative protonation of α-aryl-β-keto esters, provided low enantioselectivities (37% ee, Table 4.2.1, entry 1).[7,12] The use of related phosphite-oxazoline ligands **L1**-**L4a**, in which the phosphine moiety in ligand **1** has been replaced by a biaryl phosphite group, provided even lower enantioselectivities (ee's up to 3%, Table 4.2.1, entries 2-5). The use of ligands **L26**-**L29a** in which the flat *ortho*-phenylene tether in **L1**-**L4** has been replaced by an alkyl chain bonded to carbon 4 of the oxazoline moiety, provided also lower enantioselectivities than those achieved with ligand **1**. In this case we found that enantioselectivity is affected by the substituent at the alkyl backbone chain. Thus, the best enantioselectivity (18% ee, entry 9) was achieved with ligand **L29a** which contains a Ph substituents on the alkyl backbone. Similar values of enantioselectivity than previous ligand **L29a** were achieved using more robust phosphite-pyridine ligands **L30**-**L37a** (entry 12, 20% ee). By varying the substituent of the ligand backbone (R^4 and R^5) with ligands **L30**-**L37a** we found that the best enantioselectivity was obtained with **L30a**, which contain a hydrogen in R^4 and a Me in R^5.

To improve the enantioselectivities further we used ligands **L29**-**L30a**-**e** to study the effect of the biaryl phosphite moiety. The results indicated that enantioselectivity could be increased with the adequate configuration and substituent at the biaryl phosphite moiety (ligand **L30c**, up to 49% ee, entry 14). Thus, ligands **L29**-**L30c** (entries 11 and 14) with an *S*-biaryl phosphite group provided higher enantioselectivities than ligands **L29**-**L30b** containing an *R*-biaryl group (entries 10 and 13). On the other hand, enantioselectivities are very sensitive to variations in the substituents of the biaryl and therefore sensitive to the dihedral angle of the biaryl phosphite group. Accordingly, the use of ligands **L30d**-**e** (entries 15 and 16), which also contains *S*-biaryl phosphite groups, provided lower enantioselectivities than ligand **L30c**.

Table 4.2.1. Initial ligand screening of Pd-catalyzed decarboxylative protonation of **S1.**



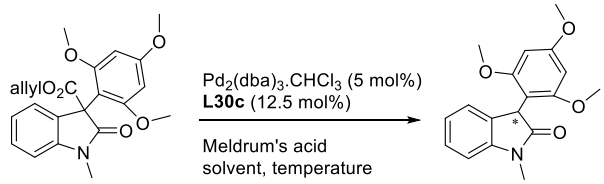
S1 **3**

Entry [a]	Ligand	Time (min)	Conversion (%) [b]	ee (%) [c]
1	**1**	60	100	37 (+)
2	**L1a**	60	100	1 (+)
3	**L2a**	60	100	2 (+)
4	**L3a**	60	100	1 (+)
5	**L4a**	60	100	3 (+)
6	**L26a**	60	100	4 (+)
7	**L27a**	60	100	3 (+)
8	**L28a**	60	100	10 (+)
9	**L29a**	60	100	18 (+)
10	**L29b**	60	100	11 (+)
11	**L29c**	60	100	38 (+)
12	**L30a**	60	100	20 (+)
13	**L30b**	60	100	9 (+)
14	**L30c**	120	100	49 (+)
15	**L30d**	60	100	5 (+)
16	**L30e**	60	100	4 (+)
17	**L31a**	120	100	3 (+)
18	**L32a**	120	100	1 (-)
19	**L33a**	120	100	1 (-)
20	**L34a**	120	100	8 (-)
21	**L35a**	120	100	17 (-)
22	**L36a**	120	100	2 (-)
23	**L37a**	120	100	2 (-)

[a] Reaction conditions: 50 mg substrate (0.125 mmol), 5 mol% $Pd_2(dba)_3.CHCl_3$, 12.5 mol% Ligand, 2.5 eq. Meldrum's acid. [b] Determined by ^1H NMR. [c] Determined by SFC

Optimization of the reaction conditions. We next optimized the reaction conditions for ligand **L30c**, that had provided the best results (Table 4.2.2). The screening of seven solvents (toluene, chloroform, dichloromethane, 1,4-dioxane, tetrahydrofuran, diethyl ether and methyl *tert*-butyl ether (MTBE)) showed that enantioselectivities were higher when coordinating solvents were used (Table 4.2.2, entries 1, 4-7 vs 2-3).

Table 4.2.2. Reaction optimization: solvent and temperature with ligand **L30c.**



S1 **3**

Entry [a]	Solvent	Temp (ºC)	Time (h)	Conversion (%) [b]	ee (%) [c]
1	toluene	23	2	100 (94)	49 (+)
2	$CHCl_3$	23	1	<5 (nd)	5 (+)
3	CH_2Cl_2	23	1	100 (93)	17 (+)
4	1,4-dioxane	23	1	100 (93)	54 (+)
5	THF	23	1	100 (94)	46 (+)
6	Et_2O	23	1	100 (64)	63 (+)
7	MTBE	23	1	100 (60)	70 (+)
8	MTBE:dioxane (2:1)	23	1	100 (92)	50 (+)
9	MTBE:dioxane (4:1)	23	1	100 (93)	33 (+)
10	MTBE:toluene (1:1)	23	1	100 (91)	36 (+)
11[d]	MTBE	23	1	100 (92)	66 (+)
12[e]	MTBE	23	3	100 (93)	70 (+)
13[e]	MTBE	5	3	100 (92)	78 (+)
14[e]	MTBE	-20	3	43 (nd)	63 (+)
15[e]	1,4-dioxane	40	1	97 (nd)	17 (+)

[a] Reaction conditions: 50 mg substrate (0.125 mmol), 5 mol% $Pd_2(dba)_3.CHCl_3$, 12.5 mol% **L30c**, 2.5 eq. Meldrum's acid. [b] Determined by ^1H NMR. [c] Determined by SFC. [d] Substrate and Meldrum's acid added as solids. [e] Catalyst precursor, ligand, Meldrum's acid and substrate all together in the Schlenk without catalyst preactivation.

Of them, MTBE had the highest positive effect on enantioselectivity (ee's increased to 70%; Table 4.2.2, entry 7), albeit with isolated yields up to 64%. This lower yield with MTBE were attributed to the difficulty of a quantitative transfer of the substrate solution to the catalyst mixture due to the low solubility of the substrate in MTBE. To improve the yields, we added both Meldrum's acid and substrate as solids to the preactivated solution of the catalyst precursor and ligand. This increased the isolated yields while maintaining the enantioselectivity up to 70% (entry 11). Another tested strategy, namely using mixtures of solvents (entries 8-10), was not successful and enantioselectivity decreased although yields were higher than when using MTBE alone. We also found that catalyst did not need to be preactivated to achieve high yields and enantioselectivities, albeit the reaction time required to achieve full conversions, increased (entry 12).

Finally, we studied the effect of the temperature. By decreasing the temperature to 5ºC, enantioselectivity increased up to 78% while maintaining the excellent yield (Table 4.2.2, entry 13 vs entry 12). Further decreasing the temperature to -20 ºC did not improve neither conversion nor enantioselectivity and these were even worse (Table 4.2.2, entry 14). We also tested the reaction at 40ºC, since the literature indicated that higher temperatures could provide better enantioselectivities[7c] but enantioselectivity did not improve further. (Table 4.2.2, entry 15).

Substrate scope. After optimizing the reaction, we tested a wide substrate scope. Substrates **S1-S11** with different electronic and steric aryl substituents on the oxindole core were studied. The results (Figure 4.2.2) underline the importance of bulkiness and of the presence of electron donating substituents in the selectivity. The best enantioselectivities (ee's up to 78%) were therefore obtained with the bulkiest and electronically rich substrates **S1** and **S2**. When other substrates that had less bulky aryl substituents (**S3** and **S4**) were tested, enantioselectivity decreased due to the removal of one *ortho* substituent. Comparing the results for **S3** with those of **S4** we can also determine that substituents at *meta*-position have almost no effect on the catalytic performance. When the electron-donating methoxy group in *para*-position was removed (**S5**), enantioselectivity decreased but it was higher than those without two substituents in *ortho*-position (**S3** and **S4**). These results indicate that the substituent in the *para* position also plays a small but crucial role. As expected, when non-*ortho* substituted aryl groups were studied (**S6** and **S7**) almost racemic compounds (**8** and **9**) were attained.

The importance of an ortho-ethereal substituent was corroborated by its sequential replacement by methyl groups. Products **10** and **11** were obtained with lower enantioselectivities than **3** and **7**, respectively. Accordingly, substrates with *ortho*-substituted naphthyl groups (**S10** and **S11**) provided moderate levels of enantioselectivities, comparable to those found when using **S3** and **S4** (ee's up to 28% and 15% respectively). As a summary, for enantioselectivities to be high, the aryl group of the substrate must contain substituents in *ortho* and *para* positions, that are, at the same time, strongly electron donators.

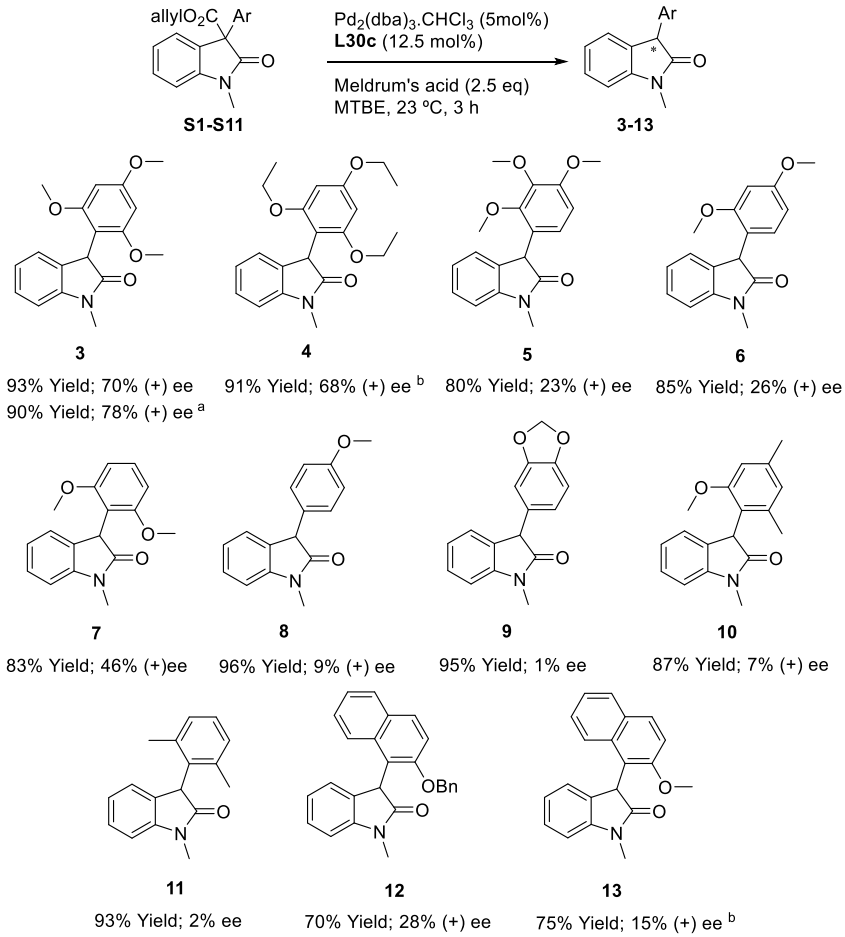


Figure 4.2.2. Pd-decarboxylative protonation of **S1**-**S11**. Reaction conditions: substrate (0.125 mmol), 5 mol% $Pd_2(dba)_3.CHCl_3$, 12.5 mol% **L30c**, 2.5 eq. Meldrum's acid. [a]Reaction carried out at 5ºC [b] Reaction carried out in Et_2O due to insolubility of **S2** and **S11** in MTBE.

4.2.2.3. Study of the key intermediate. Theoretical studies

Although the mechanism for the asymmetric decarboxylative allylation of allyl β-ketoesters by Pd catalysts has been investigated both experimentally and computationally, the mechanism for decarboxylative protonation is still not understood. The current mechanistic proposal for decarboxylative protonation mainly relies on some preliminary kinetic experiments developed by Stoltz.[8b] On the other hand, based on experimental results, Guiry et al. have proposed that in the key Pd-enolate intermediate using ligand **1**, the preferentially attack of the proton electrophile through one of the enolate faces is controlled by both the oxazoline substituent and the presence of the *ortho* substituents in the aryl group.[7a] However, this type of interaction cannot explain

our experimental results that show that for enantioselectivities to be high, the aryl group of the substrate must contain substituents at both *ortho* and *para* positions. So, further studies are required to elucidate the mechanism and the origin of enantioselectivity.

Recent DFT studies by Stoltz et al.[13] have demonstrated that for the Pd-decarboxylative allylation of allyl β-ketoesters the enantioselective step is the nucleophilic attack of the enolate to the allyl system via an inner-sphere mechanism. Similarly, they have also postulated that in the Pd-decarboxylative protonation, the enantioselective step is the outer-sphere protonation of the prochiral enolate formed by the decarboxylation of the α,β–keto ester[8b] (in our case, α,β–amido ester). Based on these previous studies and in attempt to explain the enantioselectivity achieved in the Pd-decarboxylative protonation of **S1** using Pd-**L30c** catalyst, we performed a computational study of the transition states arising from the outer-sphere protonation to the enolate-intermediates involved in the enantiocontrol. In accordance to what has already been described in the literature,[12] only the two Pd-enolates *trans* to the phosphite moiety (named Pd-enolate **A** and Pd-enolate **B**; Figure 4.2.3) were taken into account.

Calculations have been carried out using the Gaussian 09 program[14], employing B3LYP-D3 density functional[15], the 6-31G*/LAN2DZ basis set[16], and the PCM solvent model with the parameters[17] for Et_2O, as implemented by Gaussian 09. We chose diethyl ether conditions because experimental results are the closest to those obtained with MTBE. The energies were further refined by performing single-point calculations at 6-311+G**/SDD level.

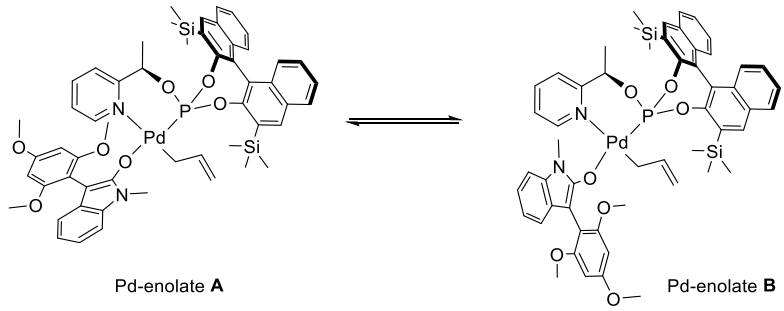
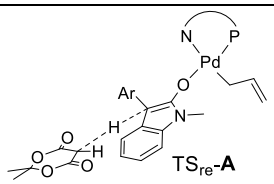
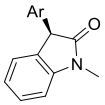
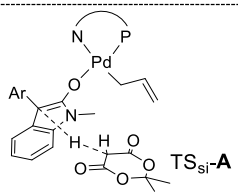
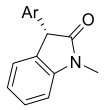
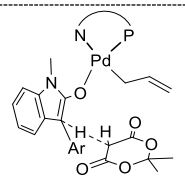
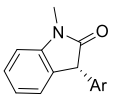
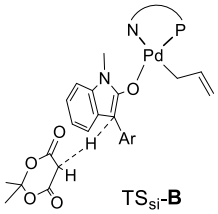
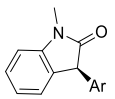


Figure 4.2.3. Two possible Pd-enolate intermediates for the decarboxylative protonation of **S1** (**A** and **B**).

Table 4.2.3 shows the calculated energies of the most stable isomers of the transitions states (TS_{re} and TS_{si}). These transition states are the result of considering the protonation attack from both Pd-enolate intermediates through the re face and the si face, respectively. The results show that the most stable transition state is TS_{re}-**B**, which provides the *S*-product. We also found that the difference in energy between the most stable transition state for the major (TS_{re}-**B**) and the minor (TS_{si}-**B**) product is 9.3 kJ/mol (Table 4.2.3), which agrees with the enantioselectivities achieved experimentally (70%

ee) using the Pd/**L30c**. Both enantiomers therefore arise from the protonation attack through the different enantiotopic faces of Pd-enolate **B**, being the protonation through Pd-enolate **A** significantly higher in energy.

Table 4.2.3. Calculated energies for the 4 possible TS of Pd-decarboxylative protonation of **S1.**

Transition state	Energy (kJ/mol)	Product
 TS_{re}-**A**	18.5	
 TS_{si}-**A**	14	
 TS_{re}-**B**	0	
 TS_{si}-**B**	9.3	

Ar=2,4,6-$(OMe)_3$-C_6H_2

4.2.3. Conclusions

In collaboration with Prof. Guiry, we have been able to develop the first catalytic asymmetric preparation of tertiary sterically hindered α-aryl oxindoles via enantioselective Pd-catalyzed decarboxylative protonation of the corresponding α-aryl-β-amido allyl esters. The method utilizes readily accessible α-aryl-β-amido allyl esters and commercially available Meldrum's acid as the proton donor. The reaction occurs under very mild conditions and in short reaction times, providing excellent yields and promising enantioselectivities (ee's up to 78%). In contrast to the Pd-decarboxylative

protonation for synthesizing chiral isoflavanones and α-aryl cyclic ketones, phosphine-oxazoline PHOX-based ligands have provided low selectivity. After the screening of three large series of phosphite-N (N=oxazoline and pyridine) ligand families we found that the best results were obtained with a readily accessible phosphite-pyridine ligand library. The introduction of an enantiopure biaryl phosphite moiety played an essential role in increasing the enantioselectivity of the Pd-catalytic systems. An important advantage over PHOX based-ligands is that these phosphite-pyridine ligands are stable to air and therefore easier to handle, manipulate and store. As far as the substrates is concerning, for enantioselectivities to be high, the aryl group of the substrate must contain substituents in *ortho* and *para*-positions, that are, at the same time, strongly electron-donators. In this study we have been therefore able to identify a readily accessible phosphite-pyridine palladium catalytic system (Pd–**L30c**) that can be used in the preparation of hindered and electronrich α-aryl oxindoles with excellent yields (up to 96%) and promising enantioselectivities (ee's up to 78%).
Using DFT calculations, we have been able to see that the most stable transition state is that in which the protonation occurs from the *re*-face of the prochiral Pd-enolate (TS_{re}-**B**), providing the *S*-product.

4.2.4. Experimental Part

4.2.4.1. General Considerations

All reactions were performed under an inert atmosphere of nitrogen in flame-dried glassware with magnetic stirring. All reagents were obtained from commercial sources and used without further purification unless otherwise stated. Anhydrous methyl *tert*-butyl ether (MTBE) was dried refluxing it over sodium and benzophenone. All other solvents were obtained from dry solvent dispenser. Aryl lead triacetates ($ArPb(OAc)_3$) were synthesized according to literature procedures.[7a] α-aryl-β-amido allyl esters **S1** and **S3**-**S11** have been synthesized and characterized following a reported procedure.[9] $Pd_2dba_3.CHCl_3$ was freshly synthesized following reported method.[18] Meldrum's acid was recrystallized from ethyl acetate before its use. Ligands **1**,[7a] **L1**-**L4**,[11a] **L26**-**L29**[11d] and **L30**-**L37**[11h] were prepared as previously described. Hydroxyl-pyridine intermediate for the preparation of ligands **L30e** was prepared following the reported procedure.[11h] Phosphorochloridite was easily prepared in one step from the corresponding binaphthol.[19] In *vacuo* refers to the evaporation of solvent under reduced pressure on a rotatory evaporator. Thin layer chromatography (TLC) was performed on aluminum plates precoated with silica gel F254. They were visualized with UV-light (254 nm) fluorescence quenching, or by charring with acidic vanillin solution (vanillin, H_2SO_4 in ethanol). $[\alpha]_D^{20}$ values have been determined using PE MC240 apparatus with a sodium (Na) lamp at 589 nm. ^1H, $^{13}C\{^1H\}$, and $^{31}P\{^1H\}$ NMR spectra were recorded using a 400

MHz spectrometer. Chemical shifts are relative to that of $SiMe_4$ (^1H and ^{13}C) as internal standard or H_3PO_4 (^{31}P) as external standard. ^1H, ^{13}C and ^{31}P assignments were made on the basis of ^1H-^1H gCOSY, ^1H-^{13}C gHSQC and ^1H-^{31}P gHMBC experiments.

4.2.4.2. General procedure for phosphite-pyridine ligands L30e

The corresponding phosphorochloridite (1.1 mmol) produced *in situ* was dissolved in toluene (5 mL) and pyridine (0.19 mL, 2.3 mmol) was added. The corresponding hydroxyl-pyridine compound (1 mmol) was dried azeotropically with toluene (3 x 2 mL) and then dissolved in toluene (5 mL) to which pyridine (0.19 mL, 2.3 mmol) was added. The phosphorochloridite solution was transferred slowly at room temperature to the solution of hydroxyl-pyridine. Reaction was left at 80ºC for 90 min. Pyridine salts were removed through filtration. Evaporation of the solvent gave white foam, which was purified by flash chromatography under argon in dry alumina (toluene:hexane: NEt_3, 5:5:0,1) to produce the corresponding ligand as a white solid.

L30e: Yield: 345.9 mg (56%); ^{31}P NMR (C_6D_6): $\delta =$ 136.8 ppm (s); ^1H NMR (C_6D_6): δ = 1.1-1.3 (m, 6H, CH_2), 1.38 (s, 9H, CH_3, ^{t}Bu), 1,45 (d, 3H, CH_3, $^3J_{H-H}$ = 6.7 Hz), 1.57 (s, 9H, CH_3, ^{t}Bu), 2.1-2.6 (m, 10H, CH_2), 5.35 (m, 1H, CH-O), 6.54 (m, 1H, CH=), 6,9-7.21 (m, 4H, CH=), 8.3 (m, 1H, CH=). ^{13}C NMR (C_6D_6): $\delta =$ 22.7 (CH_2), 22.9 (CH_2), 23.1 (CH_2), 23.2 (CH_2), 23.6 (CH_3), 27.2 (CH_2), 27.5 (CH_2), 29.5 (CH_2), 29.6 (CH_2), 30.8 (CH_3, ^{t}Bu), 31.0 (CH_3, ^{t}Bu), 34.3 (C, ^{t}Bu), 34.6 (C, ^{t}Bu), 75.7 (d, CH-O, $^2J_{C-P}$ = 9.3 Hz), 119.7 (CH=), 121.7 (CH=), 125.3 (C), 128.9 (CH=), 130.1 (C), 130.9 (C), 132.3 (C), 132.9 (C), 134.8 (C), 135.1 (C), 135.8 (CH=), 137.8 (C), 138.3 (C), 145.0 (C), 145.4 (C), 148.6 (CH=), 162.9 (C). MS HR-ESI [found 557.3062, $C_{35}H_{44}NO_3P$ $(M)^+$ requires 557.3059].

4.2.4.3. Characterization details for (2,4,6-triethoxyphenyl)lead triacetate and allyl 1-methyl-2-oxo-3-(2',4',6'-triethoxyphenyl)indoline-3-carboxylate S2

(2,4,6-triethoxyphenyl)lead triacetate: Yield: 3.56 g (50%) as bright yellow crystalline solid. ^1H NMR ($CDCl_3$): δ= 1.39 (m, 9H, CH_3, OEt), 2.05 (s, 9H, CH_3, OAc), 3.99 (q, 2H, CH_2, OEt, $^3J_{H-H}$= 5.6 Hz), 4.02 (q, 4H, CH_2, OEt, $^3J_{H-H}$= 6.8 Hz), 6.18 (s, 2H, CH=, $^4J_{H-Pb}$= 84.8 Hz), ^{13}C NMR ($CDCl_3$): δ= 14.3 (CH_3, OEt), 14.6 (CH_3, OEt), 20.4 (CH_3, OAc), 64.0 (CH_2, OEt), 64.8 (CH_2, OEt), 92.9 (CH=, $^3J_{C-Pb}$= 43.2 Hz), 159.5 (C), 163.9 (C), 179.0 (C-Pb). TOF-HRMS (ESI+): m/z = 595.1421, calcd. for $C_{18}H_{26}O_9Pb$ $[M+H]^+$: 595.1418.

allyl 1-methyl-2-oxo-3-(2',4',6'-triethoxyphenyl)indoline-3-carboxylate S2: Yield: 850.6 mg (80%) as yellowish solid. ^1H NMR (DMSO d^6, 100ºC): $\delta =$ 1.14 (b, 6H, CH_3, OEt), 1.30 (t, 3H, CH_3, OEt, $^3J_{H-H}$= 8.0 Hz), 3.16 (s, 3H, NCH_3), 3.90 (b, 4H, CH_2, OEt), 4.04 (q, 1H, CH_2, OEt, $^3J_{H-H}$= 8.0 Hz), 4.53 (m, 2H, CH_2allyl), 5.11 (m, 2H,

CH_2allyl), 5.80 (m, 1H, CHallyl), 6.18 (s, 2H, CH=), 6.93 (m, 2H, CH=), 7.21 (m, 2H, CH=). ^{13}C NMR (DMSO d^6, 100ºC): δ= 14.7 (CH_3, OEt), 14.9 (CH_3, OEt), 26.9 (CH_3, NCH_3), 60.0 (C), 63.9 (CH_2, OEt), 64.5 (CH_2, OEt), 65.5 (CH_2, OEt), 93.9 (CH=), 94.0 (CH=), 108.0 (CH=), 108.5 (C), 117.3 (CH=), 122.3 (CH=), 124.9 (CH=), 128.4 (CH=), 130.4 (CH=), 132.8 (CH=), 144.2 (C), 158.3 (C), 160.127 (C), 168.3 (C=O), 172.3 (C=O). TOF-HRMS (ESI+): m/z = 440.2073, calcd. for $C_{25}H_{30}NO_6$ $[M+H]^+$: 440.2069.

4.2.4.4. General procedure for racemic protonated compounds (3-13)

$Pd(OAc)_2$ (0.0063 mmol) and 1,2-bis(diphenylphosphino)ethane (dppe) (0.0078 mmol) were added to a flame dried Schlenk flask and dry 1,4-dioxane (1.5 ml) were added. The suspension was stirred at 40ºC for 90 min and formic acid (0.37 mmol) was added followed immediately by a solution of the corresponding substrate (0.063 mmol) in 1,4-dioxane (1.5 ml). The reaction mixture was stirred at 40ºC for 10h, cooled to room temperature and solvent was removed under vacuum and the resulting residue was purified by silica gel column chromatography (pentane:EtOAc) to afford the corresponding α-aryl oxindole.

4.2.4.5. General procedure for enantioenriched protonated compounds (3-13)

$Pd_2(dba)_3.CHCl_3$ (0.0125 mmol, 6.6 mg) , phosphite-pyridine **L30c** (0.016 mmol, 9 mg), substrate (0.125 mmol), meldrum's acid (2.5 eq, 0.31 mmol, 42.4 mg) were added to a flame dried Schlenk flask and dry methyl *tert*-buthyl ether (MTBE) (for **S1, S3**-**S10**) or diethyl ether (for **S2** and **S11**) (5 ml) were added. The suspension was stirred at room temperature for 3 hours. The solvent was removed under vacuum and the resulting residue was purified by silica gel column chromatography (pentane: EtOAc), to achieve the corresponding product.

1-methyl-3-(2',4',6'-trimethoxyphenyl)indolin-2-one 3: Yield: 36.4 mg (93%) as yellowish solid. $[\alpha]_D^{20}$: +24.4º (*c* 0.82 in CH_2Cl_2) for 70% *ee*); ^{1}H NMR ($CDCl_3$): δ= 3.32 (s, 3H, NCH_3), 3.41 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 5.08 (s, 1H, CH), 6.03 (d, $^4J_{H-H}$= 2.6 Hz, 1H, CH=), 6.21 (d, $^4J_{H-H}$= 2.6 Hz, 1H, CH=), 6.8 (d, $^3J_{H-H}$= 10.5 Hz, 1H, CH=), 6.95 (m, 2H, CH=), 7.2 (t, $^3J_{H-H}$= 10.6 Hz, 1H, CH=). ^{13}C NMR ($CDCl_3$): δ= 26.1 (CH_3, NCH_3), 42.0 (CH), 55.2 (CH_3, OCH_3), 56.1 (CH_3, OCH3), 91.1 (CH=), 92.0 (CH=), 106.8 (C), 107.1 (CH=), 122.0 (CH=), 123.1 (CH=), 127.1 (CH=), 130.2 (C), 144.2 (C), 158.3 (C), 159.1 (C), 160.3 (C), 178.0 (C=O). TOF-HRMS (ESI+): m/z = 314.1389, calcd. for $C_{18}H_{20}NO_4$ $[M+H]^+$: 314.1392. ee determined by SFC using Chiralcel IC-3 column (flow: 3 ml/min, 70:30 $scCO_2$:MeOH; λ= 254.0 nm). Tr (+): 1.71 min (major), Tr (-): 2.29 min (minor).

1-methyl-3-(2',4',6'-triethoxyphenyl)indolin-2-one 4: Yield: 40.4 mg (91%) as white solid ($[\alpha]_D^{20}$: +30.0º (*c* 0.98 in CH_2Cl_2) for 68% *ee*); ^{1}H NMR ($CDCl_3$): δ= 0.89 (t, 3H, CH_3, OEt, $^3J_{H-H}$= 6.8 Hz), 1.38 (t, 3H, $_{CH3}$, OEt, $^3J_{H-H}$= 7.2 Hz), 1.41 (t, 3H, CH_3, OEt, $^3J_{H-H}$= 7.2 Hz), 3.26 (s, 3H, NCH_3), 3.56 (m, 1H, CH_2, OEt), 3.78 (m, 1H, CH_2, OEt), 4.05 (m, 2H, CH_2, OEt), 4.11 (m, 2H, CH_2, OEt), 5.12 (s, 1H, CH), 5.97 (d, 1H, CH=, $^4J_{H-H}$= 2.0 Hz), 6.18 (d, 1H, CH=, $^4J_{H-H}$= 2.4 Hz), 6.80 (d, 1H, CH=, $^3J_{H-H}$= 7.2 Hz), 6.95 (m, 2H, CH=), 7.22 (m, 1H, CH=). ^{13}C NMR ($CDCl_3$): δ= 14.2 (CH_3, OEt), 14.8 (CH_3, OEt), 14.9 (CH_3, OEt), 26.2 (CH_3, NCH_3), 42.1 (CH), 63.4 (CH_2, OEt), 64.2 (CH_2, OEt), 92.0 (CH=), 92.2 (CH=), 107.0 (CH=), 121.8 (C), 123.2 (CH=), 127.0 (CH=), 130.5 (C), 144.6 (C), 158.0 (C), 158.7 (C), 159.9 (C), 178.0 (C=O). TOF-HRMS (ESI+): m/z = 356.1862, calcd. for $C_{21}H_{26}NO_4$ $[M+H]^+$: 356.1860. ee determined by SFC using Chiralpack IA column (flow: 3 ml/min, 90:10 $scCO_2$:MeOH; λ= 254.0 nm). Tr (-): 1.55 min (minor), Tr (+): 2.42 min (major).

1-methyl-3-(2',3',4'-trimethoxyphenyl)indolin-2-one 5: Yield: 31.3 mg (80%) as white solid ($[\alpha]_D^{20}$: +3.5º (*c* 0.77 in CH_2Cl_2) for 23% *ee*); ^{1}H NMR ($CDCl_3$): δ= 3.28 (s, 3H, NCH_3), 3.62 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 4.62 (s, 1H, CH), 6.6 (d, $^3J_{H-H}$= 6.4 Hz, 1H, CH=), 6.8 (d, $^3J_{H-H}$= 6.8 Hz, 1H, CH=), 6.88 (d, $^3J_{H-H}$= 6.5 Hz, 1H, CH=), 7.0 (m, 2H, CH=), 7.24 (m, 1H, CH=). ^{13}C NMR ($CDCl_3$): δ= 26.1 (CH_3, NCH_3), 48.0 (CH), 56.1 (CH_3, OCH_3), 60.2 (CH_3, OCH_3), 107.4 (CH=), 107.9 (CH=), 122.4 (CH=), 124.0 (C), 124.2 (CH=), 124.4 (CH=), 128.0 (CH=), 130.1 (C), 142.1 (C), 144.2 (C), 152.3 (C), 153.9 (C), 176.2 (C=O). TOF-HRMS (ESI+): m/z = 314.1387, calcd. for $C_{18}H_{20}NO_4$ $[M+H]^+$: 314.1392. ee determined by SFC using Chiralcel IC-3 column (flow: 3 ml/min, 70:30 $scCO_2$:MeOH; λ= 254.0 nm). Tr (+): 2.77 min (major), Tr (-): 5.85 min (minor).

3-(2',4'-dimethoxyphenyl)-1-methylindolin-2-one 6: Yield: 33.3 mg (85%) as yellowish solid ($[\alpha]_D^{20}$: +2.40º (*c* 0.75 in CH_2Cl_2) for 26% *ee*); ^{1}H NMR ($CDCl_3$): δ= 3.27 (s, 3H, NCH_3), 3.68 (s. CH_3, OCH_3), 3.80 (s, 3H, OCH_3), 4.80 (s, 1H, CH), 6.48 (m, 2H, CH=), 6.83 (d, $^3J_{H-H}$= 6.8 Hz, 1H, CH=), 6.94 (m, 2H, CH=), 7.02 (m, 1H, CH=), 7.25 (m, 1H, CH=). ^{13}C NMR ($CDCl_3$): δ= 26.1 (CH_3, NCH_3), 47.1 (CH), 55.5 (CH_3, OCH_3), 55.8 (CH_3, OCH_3), 99.1 (CH=), 104.3 (CH=), 107.8 (CH=), 118.1 (C), 122.0 (CH=), 124.1 (CH=), 127.9 (CH=), 129.9 (C), 130.1 (CH=), 144.1 (C), 158.3 (C), 160.2 (C), 176.8 (C=O). TOF-HRMS (ESI+): m/z = 284.1282, calcd. for $C_{17}H_{18}NO_3$ $[M+H]^+$: 284.1287. ee determined by SFC using Chiralcel IC-3 column (flow: 3 ml/min, 90:10 $scCO_2$:MeOH; λ= 254.0 nm). Tr (+): 7.43 min (major), Tr (-): 8.19 min (minor).

3-(2',6'-dimethoxyphenyl)-1-methylindolin-2-one 7: Yield: 29.4 mg (83%) as white solid ($[\alpha]_D^{20}$: +14.6º (*c*= 0. 28 in CH_2Cl_2) for 46% *ee*); ^{1}H NMR ($CDCl_3$): δ= 3.28 (s, 3H, NCH_3), 3.44 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 5.16 (s, 1H, CH), 6.44 (d, $^3J_{H-H}$= 6.5 Hz, 1H, CH=), 6.64 (d, $^3J_{H-H}$= 6.6 Hz, 1H, CH=), 6.82 (d, $^3J_{H-H}$ = 6.8 Hz, 1H, CH=), 6.92 (m, 2H, CH=), 7.1 (m, 2H, CH=). ^{13}C NMR ($CDCl_3$): δ= 26.0 (CH_3, NCH_3), 42.0

(CH), 56.1 (CH_3, OCH_3), 104.1 (CH=), 105.2 (CH=), 107.5 (CH=), 114.2 (C), 122.0 (CH=), 123.7 (CH=), 127.7 (CH=), 129.1 (CH=), 130.0 (C), 144.2 (C), 158.1 (C), 159.0 (C), 176.7 (C=O). TOF-HRMS (ESI+): m/z = 284.1280, calcd. for $C_{17}H_{18}NO_3$ $[M+H]^+$: 284.1287. ee determined by SFC using Chiralcel IC-3 column (flow: 3 ml/min, 90:10 $scCO_2$:MeOH; λ= 254.0 nm). Tr (+): 6.75 min (major), Tr (-): 7.52 min (minor).

3-(4'-methoxyphenyl)-1-methylindolin-2-one 8: Yield: 30.4 mg (96%) as white solid (9% ee); ^{1}H NMR ($CDCl_3$): δ= 3.24 (s, 3H, NCH_3), 3.78 (s, 3H, OCH_3), 4.57 (s, 1H, CH), 6.87 (m, 3H, CH=), 7.06 (m, 1H, CH=), 7.15 (m, 3H, CH=), 7.33 (m, 1H, CH=). ^{13}C NMR ($CDCl_3$): δ= 26.1 (CH_3, NCH_3), 51.1 (CH), 55.2 (CH_3, OCH_3), 108.0 (CH=), 114.2 (CH=), 122.5 (CH=), 124.8 (CH=), 128.0 (CH=), 128.2 (C), 129.0 (C), 129.5 (CH=), 144.2 (C), 159.0 (C), 176.0 (C=O). TOF-HRMS (ESI+): m/z = 254.1181, calcd. for $C_{16}H_{17}NO_2$ $[M+H]^+$: 254.1173. ee determined by SFC using Chiralcel IC-3 column (flow: 3 ml/min, 70:30 $scCO_2$:MeOH; λ= 254.0 nm). Tr (+): 1.79 min (major), Tr (-): 2.04 min (minor).

3-(benzo[*d*][1,3]dioxol-5-yl)-1-methylindolin-2-one 9: Yield: 31.7 mg (95%) as yellowish solid (1% ee); ^{1}H NMR ($CDCl_3$): δ= 3.26 (s, 3H, NCH_3), 4.51 (s, 1H, CH), 5.91 (s, 2H, CH_2), 6.60 (s, 1H, CH=), 6.69 (m, 1H, CH=), 6.76 (m, 1H, CH=), 6.87 (d, $^3J_{H-H}$ = 6.4 Hz, 1H, CH=), 7.08 (t, $^3J_{H-H}$ = 6.5 Hz, 1H, CH=), 7.18 (d, $^3J_{H-H}$ = 6.6 Hz, 1H, CH=), 7.35 (t, $^3J_{H-H}$ = 6.7 Hz, 1H, CH=). ^{13}C NMR ($CDCl_3$): δ= 26.1 (CH_3, NCH_3), 51.5 (CH), 101.2 (CH_2), 108.0 (CH=), 108.2 (CH=), 122.0 (CH=), 122.8 (CH=), 124.8 (CH=), 128.3 (CH=), 128.5 (C), 130.0 (C), 144.2 (C), 147.1 (C), 148.0 (C), 176.0 (C=O). TOF-HRMS (ESI+): m/z = 268.0967, calcd. for $C_{16}H_{14}NO_3$ $[M+H]^+$: 268.0974. ee determined by SFC using Chiralcel IC-3 column (flow: 3 ml/min, 70:30 $scCO_2$:MeOH; λ= 254.0 nm). Tr (+): 1.88 min (major), Tr (-): 2.07 min (minor).

3-(2'-methoxy-4',6'-dimethylphenyl)-1-methylindolin-2-one 10: Yield: 30.6 mg (87%) as white solid (7% ee); ^{1}H NMR ($CDCl_3$): δ= 1.62 (s, 3H, CH_3), 2.49 (s, 3H, CH_3), 3.31 (s, 3H, NCH_3), 3.68 (s, 3H, OCH_3), 4.67 (s, 1H, CH), 6.41 (s, 1H, CH=), 6.72 (s, 1H, CH=), 6.83 (m, 2H, CH=), 6.93 (m, 2H, CH=). 13C NMR (CDCl3): δ= 20.3 (CH_3), 21.6 (CH_3), 26.1 (CH_3, NCH_3), 46.2 (CH), 56.0 (CH_3, OCH_3), 107.6 (CH=), 109.7 (C), 111.1 (CH=), 122.0 (CH=), 122.2 (C), 122.8 (CH=), 123.6 (CH=), 124.2 (C), 127.5 (CH=), 138.1 (CH=), 144.1 (C), 157.3 (C), 177.8 (C=O). TOF-HRMS (ESI+): m/z = 284.1280, calcd. for $C_{17}H_{18}NO_3$ $[M+H]^+$: 284.1287. ee determined by SFC using Chiralcel IC-3 column (flow: 3 ml/min, 85:15 $scCO_2$:MeOH; λ= 210.0 nm). Tr (+): 2.78 min (major), Tr (-): 3.17 min (minor).

3-(2',6'-dimethylphenyl)-1-methylindolin-2-one 11: Yield: 29.2 mg (93%) as white solid (2% ee); ^{1}H NMR ($CDCl_3$): δ= 1.64 (s, 3H, CH_3), 2.58 (s, 3H, CH_3), 3.32 (s, 3H, NCH_3), 5.05 (s, 1H, CH), 6.9 (m, 3H, CH=), 6.97 (m, 1H, CH=), 7.12 (m, 2H, CH=), 7.30 (m, 1H, CH=). ^{13}C NMR ($CDCl_3$): δ= 18.6 (CH_3), 21.8 (CH_3), 26.2 (CH_3, NCH_3), 48.1

(CH), 107.9 (CH=), 122.5 (CH=), 122.8 (CH=), 127.8 (CH=), 127.9 (CH=), 128.1 (CH=), 128.2 (CH=), 128.3 (C), 129.5 (CH=), 133.5 (C), 137.2 (C), 138.0 (C), 142.0 (C), 176.1 (C=O). TOF-HRMS (ESI+): m/z = 252.1385, calcd. for $C_{17}H_{19}NO$ $[M+H]^+$: 252.1388. ee determined by SFC using Chiralcel IC-3 column (flow: 3 ml/min, 90:10 $scCO_2$:MeOH; λ= 254.0 nm). Tr (+): 3.02 min (major), Tr (-): 4.31 min (minor).

1-methyl-3-(2'-phenoxynaphthalen-1-yl)indolin-2-one 12: Yield: 33.2 mg (70%) as yellowish solid ($[\alpha]_D^{20}$: +47.5º (*c*= 0.61 in CH_2Cl_2) for 28% *ee*); ^{1}H NMR ($CDCl_3$): δ= 2.68 (s, 3H, NCH_3), 4.80 (d, $^2J_{H-H}$ = 11.4Hz, 1H, CH_2) 4.85 (d, $^2J_{H-H}$ = 11.4 Hz, 1H, CH_2), 5.29 (s, 1H, CH), 6.61 (d, $^3J_{H-H}$ = 6.4 Hz, 1H, CH=), 6.92 (m, 4H, CH=), 7.27 (m, 6H, CH=), 7.43 (m, 1H, CH=), 7.61 (m, 1H, CH=), 7.85 (m, 1H, CH=), 8.15 (d, $^3J_{H-H}$ = 6.8 Hz, 1H, CH=). ^{13}C NMR ($CDCl_3$): δ= 25.6 (CH_3, NCH_3), 44.6 (CH), 70.7 (CH_2), 107.8 (CH=), 114.1 (CH=), 118.9 (C), 121.9 (CH=), 122.3 (CH=), 123.2 (CH=), 123.6 (CH=), 127.3 (CH=), 127.9 (C), 128.3 (CH=), 128.5 (C), 128.6 (CH=), 128.8 (CH=), 129.4 (CH=), 129.5 (CH=), 129.6 (CH=). 134.1 (C), 136.2 (C), 144.6 (C), 153.8 (C), 177.1 (C=O). TOF-HRMS (ESI+): m/z = 380.1651, calcd. for $C_{26}H_{22}NO_2$ $[M+H]^+$: 380.1638. ee determined by SFC using Chiralcel IC-3 column (flow: 3 ml/min, 70:30 $scCO_2$:MeOH; λ= 254.0 nm). Tr (+): 2.9 min (major), Tr (-): 3.23 min (minor).

3-(2'-methoxynaphthalen-1-yl)-1-methylindolin-2-one 13: Yield: 30.3 mg (80%) as white solid ($[\alpha]_D^{20}$: +25.2º (*c*= 0.61 in CH_2Cl_2) for 15% *ee*); ^{1}H NMR ($CDCl_3$): δ= 3.37 (s, 3H, NCH_3), 3.61 (s, 3H, OCH_3), 5.28 (s, 1H, CH), 6.90 (m, 3H, CH=), 7.21 (m, 2H, CH=), 7.42 (m, 1H, CH=), 7.58 (m, 1H, CH=), 7.85 (m, 2H, CH=), 8.15 (d, $^3J_{H-H}$ = 7.0 Hz, 1H, CH=). ^{13}C NMR ($CDCl_3$): δ= 26.6 (CH_3, NCH_3), 44.5 (CH), 57.2 (CH_3), 107.5 (CH=), 114.6 (CH=), 122.1 (CH=), 122.4 (CH=), 122.6 (C), 122.8 (C), 123.4 (CH=), 122.3 (CH=), 123.7 (CH=), 126.9 (C), 127.7 (CH=), 128.6 (C), 129.6 (CH=), 130.1 (CH=). 133.9 (C), 154.7 (C), 177.0 (C=O). TOF-HRMS (ESI+): m/z = 303.1259, calcd. for $C_{20}H_{18}NO_2$ $[M+H]^+$: 303.1265. ee determined by SFC using Chiralcel IC-3 column (flow: 3 ml/min, 90:10 $scCO_2$:MeOH; λ= 254.0 nm). Tr (+): 9.63 min (major), Tr (-): 11.36 min (minor).

4.2.5. References

[1] a) Hartwig, J. F. *Synlett* **2006**, *9*, 1283. b) Culkin, D. A.; Hartwig, J. F. *Acc. Chem. Res.* **2003**, *36*, 234. c) Hartwig, J. F. *Pure Appl. Chem*. **2009**, *71*, 1417. d) Johansson, C. C. C.; Colacot, T. J. *Angew. Chem. Int. Ed.* **2010**, *49*, 676. e) Sivanandan, S. T.; Shaji, A.; Ibnusaun, I.; Johansson, C. C. C.; Colacot, T. J. *Eur. J. Org. Chem.* **2015**, *1*, 38.

[2] a) Shou, Q.-Y.; Fu, R.-Z.; Tan, Q.; Shen, Z.-W. *J. Agric. Food Chem.* **2009**, *57*, 6712. b) McKee, T. C.; Bokesch, H. R.; McCormick, J. L.; Rashid, M. A.; Spielvogel, D.; Gustafson, K. R.; Alavanja, M. M.; Cardellina, J. H.; Boyd, M. R. *J. Nat. Prod*. **1997**, *60*, 431. c) Carril, M.;

SanMartin, R.; Churruca, F.; Tellitu, L.; Dominguez, E. *Org. Lett.* **2005**, *7*, 4787. d) Honda, T.; Namiki, H.; Satoh, F. *Org. Lett.* **2001**, *3*, 631. e) Honda, T.; Sakamaki, Y. *Tetrahedron Lett.* **2005**, *46*, 6823. f) Rudrangi, S. R. S.; Bontha, V. K.; Manda, V. R.; Bethi, S. *Asian J. Research Chem.* **2011**, *4*, 335.

[3] a) Lee, S.; Hartwig, J. F. *J. Org. Chem.* **2001**, *66*, 3402. Other examples for synthesis of chiral oxindoles *via* Pd-intramolecular cyclization reactions, see: b) Jia, Y.-X.; Hillgre, J. M.; Watson, E. L.; Mardsen, S. P.; Kündig, E. P. *Chem. Commun.* **2008**, 4040 (ee's up to 90%). c) Luan, X.; Xu, L.; Drinkel, E.; Mariz, R.; Gatti, F.; Dorta, R. *Org. Lett.* **2010**, *12*, 1912 (ee's up to 94%). For Pd-intramolecular Heck reaction, see: d) Dounay, A. B.; Hatanaka, K.; Kodanko, J. K.; Ostereich, M.; Overman, L. E.; Pfeifer, L. A.; Weiss, M. W. *J. Am. Chem. Soc.* **2003**, *125*, 6261 (ee's up to 98%).

[4] For α-arylation of ketones, see: a) Culkin, D. A.; Hartwig, J. F. *Acc. Chem. Res.* **2003**, *36*, 234. b) Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 11108. c) Hamada, T.; Chieffi, A.; Ahman, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 1261. d) Muratake, H.; Natsume, M. *Tetrahedron Lett.* **1997**, *38*, 7581. For α-arylation of esters, see: e) Lee, S.; Beare, N. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 8410. f) Moradi, W. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7996. g) Bentz, E.; Moloney, M. G.; Westaway, S. M. *Tetrahedron Lett.* **2004**, *45*, 7395. For α-arylation of nitriles, see: h) You, J.; Verkade, J. G. *Angew. Chem., Int. Ed.* **2003**, *42*, 5051. i) Wu, L.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 15824. For α-arylation of amides, see: j) Shaughnessy, K. H.; Hamann, B. C.; Hartwig, J. F. *J. Org. Chem.* **1998**, *63*, 6546. k) Hennessy, E. J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 12084.

[5] Durbin, M. J.; Willis, M. C. *Org. Lett.* **2008**, *10*, 1413.

[6] a) Altman, R. A.; Hyde, A. M.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2008**, *130*, 9613. b) Li, P.; Buchwald, S. L. *Angew. Chem. Int. Ed*. **2011**, *50*, 6396.

[7] a) Carroll, M. P.; Mueller-Bunz, H.; Guiry, P. J. *Chem. Commun.* **2012**, *48*, 11142. b) Doran, R.; Carroll, M. P.; Akula, R.; Hogan, B. F.; Martins, M.; Fanning, S.; Guiry, P. J. *Chem. Eur. J.* **2014**, *20*, 15354. c) Doran, R.; Guiry, P. J. *J. Org. Chem.* **2014**, *79*, 9112.

[8] See also the pioneering work of Stoltz *et al.* on the use of the asymmetric Pd-catalyzed decaboxylative protonation of allyl β-ketoesters to prepare α-alkyl cyclic ketones with the phosphine-oxazoline ^{t}BuPHOX ligand **2**. See: a) Mohr, J. T.; Nishimata, T.; Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc*., **2006**, *128*, 11348. b) Marinescu, S. C.; Nishimata, T.; Mohr, J. T.; Stoltz, B. M. *Org. Lett.* **2008***, 10,* 1039.

[9] These compounds have been synthesized following Guiry *et al.*'s procedure. See: Mark Jackson's PhD Thesis, Univeristy College Dublin, Ireland.

[10] a) Pàmies, O.; Diéguez, M. *Acc. Chem. Res.* **2010**, 43, 212. b) van Leeuwen, P. W. N. M.; Kamer, P. C. J.; Claver, C.; Pàmies, O.; Diéguez, M. *Chem. Rev.* **2011**, 111, 2077. c) Pàmies, O.; Andersson, P. G.; Diéguez, M. *Chem. Eur. J.* **2010**, *16*, 14232. d) Diéguez, M.; Pàmies, O. *Isr. J. Chem.* **2012**, *52*, 572. e) Pàmies, O.; Magre, M.; Diéguez, M. *Chem. Rec.* DOI: 10.1002/tcr.201600024.

[11] These ligands have been successfully applied to other metal-catalyzed asymmetric transformations. See: a) Pàmies, O.; Diéguez, M.; Claver, C. *J. Am. Chem. Soc.* **2005**, *127*, 3646. b) Magre, M.; Biosca, M.; Pàmies, O.; Diéguez, M. *ChemCatChem* **2015**, *7*, 114. c) Bellini, R.; Magre, M.; Biosca, M.; Norrby, P.-O.; Pàmies, O.; Diéguez, M.; Moberg, C. *ACS Catalysis* **2016**, *6*, 1701. d) Diéguez, M.; Pàmies, O. *Chem. Eur. J.* **2008**, *14*, 3653. e) Diéguez, M.; Mazuela, J.; Pàmies, O.; Verendel, J. J.; Andersson, P. G. *Chem. Commun.* **2008**, 3888. f) Mazuela, J.; Verendel, J. J.; Coll, M.; Schäffner, B.; Börner, A.; Andersson, P. G.; Pàmies, O.; Diéguez, M. *J. Am. Chem. Soc.* **2009**, *131*, 12344. g) Mazuela, J.; Pàmies, O.; Diéguez, M. *Chem. Eur. J.* **2010**, *16*, 3434. h) Mazuela, J.; Pàmies, O.; Diéguez, M. *Chem. Eur. J.* **2013**, *19*, 2416. i) Mazuela, J.; Pàmies, O.; Diéguez, M. *Adv. Synth. Catal.* **2013**, *355*, 2569.

[12] Disappointingly, the application of other successful ligands for Pd-allylic substitution reactions, such as the (*R*,*R*)-ANDEN-phenyl Trost and (*R*,*R*)-DACH-phenyl Trost ligands, provide the desired product in racemic form.

[13] Keith, J. A.; Behenna, D. C.; Sherden, N.; Mohr, J. T.; Ma, S. C. Marinescu, R J. Nielsen, J. Oxgaard, B. M. Stoltz, W. A. Goddard, *J. Am. Chem. Soc.,* **2012**, *134*, 19050.

[14] Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A.; Peralta, J. E., Jr.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, O.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. Revision A.02 ed; Gaussian: Wallingford, CT, 2009.

[15] a) Lee, C.; Yang,W.; Parr, R. G. *Phys. Rev*. B **1988**, 37, 785. b) Becke, A. D. *J. Chem. Phys*. **1993**, 98, 5648.

[16] Hay, P. J.; Wadt, W. R. *J. Chem. Phys.* **1985**, 82, 299–310. a) Hehre, W. J.; Ditchfield, R.; Pople, J. A. *J. Chem. Phys.* **1972**, 56, 2257. b) Hariharan, P. C.; Pople, J. A. *Theor*. *Chim. Acta* **1973**, 28, 213. c) Francl, M. M.; Pietro,W. J.; Hehre,W. J.; Binkley, J. S.; Gordon, M. S.; Defrees, D. J.; Pople, J. A. *J. Chem. Phys*. **1982**, 77, 3654.

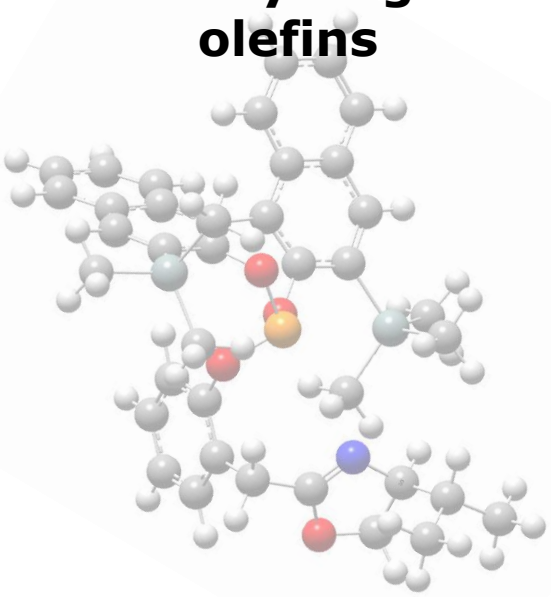
[17] a) Miertus, S.; Tomasi, *J. Chem. Phys.* **1982**, *65*, 239. b) Mennucci, B.; Tomasi, J. *J. Chem. Phys.* **1997**, 106, 5151. c) Cossi, M.; Barone, V.; Menucci, B.; Tomasi, J. *Chem. Phys. Lett*. **1998**, 286, 253.

[18] Zalesskiy, S. S.; Ananikov, V. P. *Organometallics*, **2012**, *31*, 2302.

[19] Buisman, G. J. H.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Tetrahedron: Asymmetry* **1993**, *4*, 1625.

Chapter 5

Asymmetric hydrogenation of olefins



UNIVERSITAT ROVIRA I VIRGILI
DESIGN OF TAILOR-MADE CHIRAL LIGAND LIBRARIES FOR C-X BOND FORMING REACTIONS. STUDY OF THE KEY INTERMEDIATES BY NMR AND DFT
Marc Magre Rosich

5. Asymmetric hydrogenation of olefins

5.1. Background

The enantioselective hydrogenation of olefins is one of the most powerful and sustainable transformation in asymmetric catalysis for preparing optically pure compounds due to its high efficiency, atom economy and operational simplicity.

As we presented in the introduction (Chapter 3), whereas the reduction of olefins containing an adjacent polar group catalyzed by Rh and Ru has been widely studied, the hydrogenation of minimally functionalized olefins catalyzed by Ir catalysts is less developed.

In this field, most of the efficient Ir-complexes are based on P,N ligands, more specifically phosphine-oxazoline ligands since the first breakthrough presented by Pfaltz *et al*. in 1998 with the phosphine-oxazoline PHOX ligands. Since then, most of the studies have been based on replacing the phosphine moiety by phosphinite, phosphite and even carbene moieties, whereas oxazoline unit has been replaced by thiazoline, thiazole, oxazole and pyridine. Although high enantioselectivities have been achieved using P,N ligands, these Ir-catalysts are still highly substrate dependent.

In our group, we have contributed in this field with the successful application of phosphite-containing ligands. In our laboratories, we have prepared and applied large families of phosphite-oxazolines/thiazolines, oxazoles/thiazoles and pyridines as nitrogen donor group. Moreover, recently, we have also demonstrated that N-donor group can be replaced by thioether moieties, achieving excellent enantioselectivities with a wide range of di- and trisubstituted olefins.

For that reason, in this chapter we present the application of first and second generation of PHOX-type phosphite oxazoline ligands.

In Section 5.2. we present the application of PHOX-type phosphite-oxazoline **L1**-**L7a**-**g** to Ir-catalyzed hydrogenation of minimally functionalized olefins. A wide range of (*E*)- and (*Z*)-trisubstituted alkenes including examples with neighboring polar groups and 1,1-disubstituted olefins have been successfully hydrogenated. Moreover, we present the first application of PHOX-type phosphite-oxazoline to the hydrogenation of cyclic β-enamides. We found that the introduction of a biaryl phosphite moiety was beneficial in terms of substrate scope, achieving excellent enantioselectivities for a wide range of substituted olefins.

In Section 5.3 we present the application of a second generation of phosphite-oxazoline ligands **L8**-**L14a**-**i** to Ir-catalyzed hydrogenation of minimally functionalized olefins. As in Section 5.2., we have applied these Ir-(P,N) complexes for the hydrogenation of several di- and trisubstituted substrates, including examples with neighboring polar groups (such as allylic alcohols, acetates, α,β-unsaturated esters and ketones, allylic

silanes, vinylboronates and cyclic β-enamides). Our purpose is to study if the introduction of a second stereogenic center on the ligand backbone is beneficial in terms of substrate scope.

5.2. Ir-Catalyzed asymmetric hydrogenation of olefins using PHOX-based phosphite-oxazoline ligands

Magre, M.; Coll, M.; Pàmies, O.; Diéguez, M. *Manuscript to be submitted.*

Abstract: *We have successfully applied new Ir(I)-catalyst precursors ([Ir(cod)(**L1**-**L7a**-**g**)]BAr$_F$), modified with easily accessible PHOX-based phosphite-oxazoline ligands, for the asymmetric hydrogenation of demanding minimally functionalized alkenes and cyclic β-enamides. The catalytic results indicated that enantioselectivity is highly affected by the ligand parameters as well as the substrate. The new Ir-PHOX-based phosphite-oxazoline catalysts have been able to efficiently hydrogenate not only minimally functionalized model olefins, but also a wide range of challenging olefins that have recently received a great deal of attention because the resulting hydrogenated compounds can be easily stereoselectively transformed into high-value organic compounds. The results are among the best reported so far.*

5.2.1. Introduction

The asymmetric hydrogenation of prochiral olefins have turned out to be one of the most reliable catalytic methods for the synthesis of optically active compounds, mainly because of its perfect atom economy, operational simplicity and high efficiency.[1] This field has been dominated by the Rh/Ru-catalyzed asymmetric reduction of substrates with a good coordinating group close to the C=C bond, which its chelating ability is key in transferring the chiral information from the catalysts to the product. Today, a remarkable range of ligands are being applied to transform a broad range of functionalized substrates.[2] Although, the hydrogenation of cyclic β-aryl-N-acetyl enamides is still a challenge. In contrast to Rh/Ru-hydrogenation, the asymmetric reduction of olefins that do not have an adjacent coordinative polar group - minimally functionalized olefins - is still challenging and requires more sophisticated ligand design.[3] In 1977, Crabtree described the first metal-catalyst ([Ir(cod)(Py)(PCy$_3$)]PF$_6$ (cod = 1,5-cyclooctadiene)) able to hydrogenate a wide range of minimally functionalized olefins.[4] On the basis of this pioneering work, Pfaltz and coworkers used phosphine-oxazoline PHOX ligands to design [Ir(PHOX)(cod)]BAr$_F$, that successfully reduced a broad range of chiral minimally functionalized olefins.[5] Since then, most of the research in this field have been dedicated to develop new Ir-catalysts modified with chiral heterodonor P,N-ligands. The first successful P,N ligands contained a phosphine or phosphinite moiety as P-donor group and either an oxazoline,[6] oxazole,[7] thiazole[8] or pyridine[9] as N-donor group. However, these iridium-phosphine/phosphinite,N catalysts were still highly substrate-dependent and the development of efficient chiral ligands that tolerate a broader range of substrates remained a challenge.

The discovery of efficient ligands prepared in a few steps, from simple starting materials, easy to handle (solid, robust and air stable) and modular for the M-catalyzed asymmetric hydrogenation of minimally functionalized olefins and cyclic β-enamides is still therefore a relevant topic. Over the last decades, we among others have shown the advantages of introducing a biaryl phosphite moiety in the ligand for several metal-catalyzed asymmetric transformations.[10] In general, the use of biaryl-based phosphite ligands improves both the ligand's efficiency and the substrate scope. The main reason for this behavior is that the biaryl phosphite group is flexible enough to accommodate the chiral pocket of the catalysts to the steric demands of the substrate (see previous Section 3.2). It is not surprising therefore that we have recently disclosed that phosphite-based PHOX ligands **L1**-**L4** (Figure 5.2.1) can be included in the family of privileged ligands not only because of their ability to control the stereochemistry in a variety of catalytic processes (*i.e.* asymmetric Pd-catalyzed Heck [11] and allylic substitution[12] reactions, asymmetric Ir-catalyzed hydroboration,[13] …) but also to their exceptionally broad substrate scope. Moreover, phosphite ligands are attractive for catalysis because they are less sensitive than phosphines to air and other oxidizing agents, they are easy to prepare from commercial alcohols and they are amenable to parallel synthesis. All these features make it easier to prepare large series of ligands in the quest to maximize catalytic performance for each particular reaction and substrate. In this context, we have shown the benefits of using heterodonor phosphite-N ligands for the Ir-catalyzed hydrogenation of minimally functionalized olefins,[14] which in the last decades have become the-state-of-art for the asymmetric hydrogenation of these challenging substrates. Thus, the presence of biaryl-phosphite moieties in these P,N-ligands provided greater substrate versatility than previous Ir-phosphine/phosphinite,N catalyst systems. In addition, the potential of Ir-P,N as catalyst for the asymmetric hydrogenation of functionalized olefins has been overlooked.[15]

In this chapter, we report the successful application of phosphite-based PHOX ligands **L1**-**L7a**-**g** (Figure 5.2.1) in the Ir-catalyzed asymmetric hydrogenation of minimally functionalized olefins and cyclic β-enamides. Ligands **L5**-**L7** differ from ligands **L1**-**L4** by a methylene spacer between the oxazoline and the phenyl ring of the ligand backbone, and allow studying the effect of the size of the chelate ring than has been found to influence the catalytic performance in the hydrogenation of several olefins.

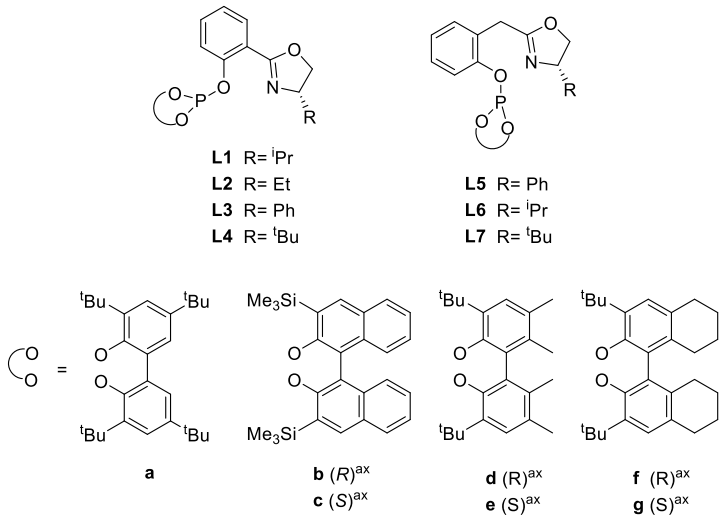
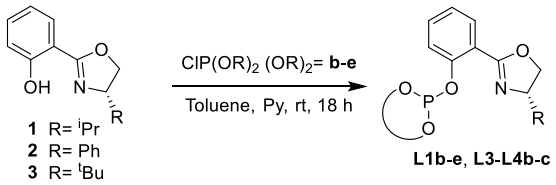


Figure 5.2.1. Phosphite-oxazoline ligands **L1**-**L7a**-**g**.

5.2.2 Results and discussion

5.2.2.1. Preparation of Ligands

The synthesis of the new phosphite-oxazoline ligands **L1b**-**e** and **L3**-**L4b**-**c** is shown in Scheme 5.2.1. As previously described in Sections 3.2 and 3.3, phosphite-oxazoline ligands were prepared by coupling the corresponding hydroxyl-oxazoline intermediates **1**-**3** with the desired phosphorochloridites ($ClP(OR)_2$; $(OR)_2$ = **b**-**e**).

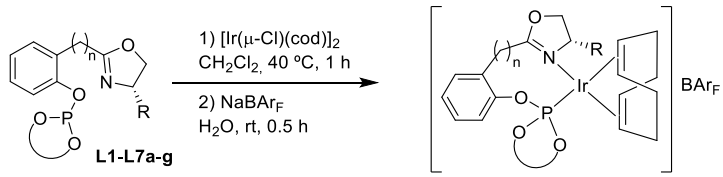


Scheme 5.2.1. Synthesis of new phosphite-oxazoline ligands **L1b**-**e** and **L3**-**L4b**-**c.**

All ligands were stable during purification on neutral alumina under an atmosphere of argon and they were isolated as white solids. They were stable at room temperature and very stable to hydrolysis. HRMS-ESI spectra were in agreement with the assigned structures. The ^{1}H and ^{13}C NMR spectra were as expected for these C_1 ligands. One singlet for each compound was observed in the ^{31}P NMR spectrum.

5.2.2.2. Synthesis of Ir(I) catalyst precursors

The Ir-catalyst precursors were prepared in a two-step, one-pot procedure (Scheme 5.2.2). First, $[Ir(\mu\text{-}Cl)(cod)]_2$ reacts with one equivalent of the appropriate ligand. Then, Cl^-/BAr_F^- counterion exchange was achieved by reaction with $NaBAr_F$ in the presence of water. The iridium catalyst precursors were isolated in pure form as air-stable orange/red solids in excellent yields (90-96%) after simple extraction workup. No further purification was needed. The HRMS-ESI spectra were in agreement with the assigned structures, displaying the heaviest ions at m/z which correspond to the loss of the BAr_F anion from the molecular species. The ^1H, ^{13}C, and ^{31}P NMR spectra show the expected pattern for these C_1-complexes. The VT-NMR in CD_2Cl_2 (+35 to -85 °C) spectra show that only one isomer is present in solution. In all cases, one singlet in the $^{31}P\text{-}\{^1H\}$ NMR spectra was observed.



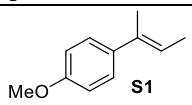
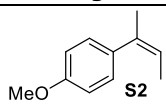
Scheme 5.2.2. Synthesis of Ir-catalyst precursors containing phosphite-oxazoline ligands **L1**-**L7a**-**g.**

5.2.2.3 Asymmetric hydrogenation of trisubstituted olefins

The asymmetric hydrogenation of minimally functionalized trisubstituted olefins is highly dependent on the olefin geometry.[4h] In this respect, *Z*-trisubstituted olefins are commonly hydrogenated less enantioselectively than the related *E*-isomers. In order to evaluate the efficiency of ligands **L1**-**L7** in the hydrogenation of olefins with different geometry, we initially tested them in the asymmetric reduction of the model (*E*)-substrate **S1** and the hydrogenation of (*Z*)-substrate **S2** (Table 5.2.1). In general, the enantioselectivities were found to be highly dependent on ligand parameters but also in the substrate type. While for substrate **S1** the best enantioselectivities (ee's up to 95%) were obtained with the ligands that contain a methylene spacer between the oxazoline and the phenyl ring of the ligand backbone (ligands **L5b** and **L5c**, Table 5.2.1 entries 16 and 17); for substrate **S2**, the best enantioselectivity (ee's up to 90%) were obtained with ligand **L1g**. Regarding the ligand parameters the enantioselectivity is dependent on the oxazoline substituents and the substituent/configuration of the biaryl phosphite group. With ligands **L1**-**L4** the best enantioselectivities were obtained with **L3g** with a Ph oxazoline substituent and the *S* binaphthyl group (**g**). Finally, with ligands **L5**-**L7**, the best enantioselectivities were

therefore obtained with **L5b**-**c**, that contain a Ph oxazoline group and the chiral binaphthyl groups (**b**) and (**c**). From these latter results we can also found that for substrate **S1**, both enantiomers of the hydrogenated product could be therefore achieved in high enantioselectivities by simple changing the configuration of the biaryl group in ligands **L5**.

Table 5.2.1. Ir-catalyzed hydrogenation of **S1** and **S2** using ligands **L1**-**L7a**-**g**[a]

		 **S1**		 **S2**	
Entry	Ligand	% Conv[b]	% ee[c]	% Conv[b]	% ee[c]
1	**L1a**	100	72 (*R*)	100	86 (*S*)
2	**L1b**	100	78 (*R*)	100	30 (*S*)
3	**L1c**	100	61 (*R*)	100	85 (*S*)
4	**L1d**	100	25 (*R*)	100	15 (*S*)
5	**L1e**	100	55 (*R*)	100	72 (*S*)
6	**L1f**	100	29 (*R*)	100	0
7	**L1g**	100	58 (*R*)	100	90 (*S*)
8	**L2a**	100	9 (*R*)	100	47 (*S*)
9	**L3a**	100	0	100	60 (*S*)
10	**L3b**	100	40 (*R*)	100	78 (*R*)
11	**L3c**	100	15 (*S*)	100	86 (*S*)
12	**L4a**	100	72 (*R*)	100	88 (*S*)
13	**L4b**	100	19 (*R*)	100	17 (*S*)
14	**L4c**	100	44 (*R*)	100	84 (*S*)
15	**L5a**	100	15 (*R*)	100	5 (*S*)
16	**L5b**	100	94 (*R*)	100	17 (*R*)
17	**L5c**	100	95 (*S*)	100	3 (*S*)
18	**L6a**	100	81 (*R*)	100	56 (*S*)
19	**L6b**	100	92 (*R*)	100	3 (*R*)
20	**L6c**	100	65 (*S*)	100	45 (*S*)
21	**L7a**	100	76 (*R*)	65	56 (*S*)
22	**L7b**	95	23 (*R*)	75	24 (*S*)
23	**L7c**	97	0	75	51 (*S*)

[a] Reactions carried out at room temperature by using 0.5 mmol of substrate and 1 mol% of Ir-catalyst precursor at 50 bar of H_2 using dichloromethane (2 mL) as solvent. [b] Conversion measured by ^1H NMR after 2 h. [c] Enantiomeric excesses measured by chiral GC

To further establish the extent of the new ligands **L1**-**L7** we first selected a representative family of minimally functionalized substrates, some of which contained poorly coordinative groups. The results are shown in Figure 5.2.2. We again found that

the ligand components must be selected correctly if the enantioselectivity is to be highest for each substrate.

We first considered the reduction of substrates **S3**-**S4**, which differ from **S1** in the substituent in the aryl ring and the substituents *trans* to the aryl group. Advantageously, Ir/**L5b-c** catalyst precursors are very tolerant to variations in the substituents of the aryl ring or to the introduction of a second aryl moiety. Again both enantiomers of the hydrogenated products could be obtained in enantioselectivities (ee's up to 97%). For the *Z*-substrates **S5** and **S6** enantioselectivities were as high as 79% and 88%, respectively. In addition, comparing the results obtained with **S5** and **S6** we found that the bulkiness of alkyl substituent of the substrate has an important effect on enantioselectivity, being the bulkier olefin the one attained in higher enantioselectivity.

We then looked into the hydrogenation of a broad range of key trisubstituted olefins with neighbouring polar groups. Hydrogenation of these olefins is of particular interest because they can be further functionalized and become important intermediates for more complex chiral molecules. Interestingly, the hydrogenation of a very large series of α,β-unsaturated esters **S7**-**S13** proceeded with excellent enantioselectivities (ee's up to 99%), comparable to the best reported to date. Again, unlike previous **S1**-**S6** substrates, the effect of the ligand parameters on enantioselectivity is different. The best enantioselectivities were obtained using the Ir/**L3a** catalytic system. Advantageously, the ee's were independent of the electronic nature of the substrate phenyl ring (**S7**-**S9**) and the steric nature of the alkyl substituent (**S7**, **S10**-**S12**). Also noteworthy were the high enantioselectivities obtained using more demanding *Z*-isomer **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.[16] As in *E*-alkenes, Ir/**L5c** catalytic system can also successfully hydrogenate a broad range of α,β-unsaturated enones **S14**-**S19** (ee's up to 98%). The hydrogenation of **S14**-**S19** yields products with opposite configuration than those achieved with the other *E*-trisubstituted olefins studied. This behaviour has been observed previously and it is attributed to the strong polarization of the double bond. It should be noted that ee's are highly independent of the nature of the alkyl substituent and the electronic nature of the substrate phenyl ring. This represents an important entry point to the synthesis of ketones with stereogenic centres in the α-position to the carbonyl group. Despite this, they have been less studied than other trisubstituted olefins with neighbouring polar groups.[17] Also, excellent enantioselectivities have been achieved in the reduction of α,β-unsaturated lactone **S20** (ee's up to >99%). α,β-Unsaturated amides **S21-S22** represent other challenging substrates that has been overlooked, despite amides with stereogenic centres in the α-position are present in several natural products and that

the amide group can be easily transformed into other useful compounds (*i.e.* amines)[18]. Interestingly both substrates proceeded with excellent enantioselectivities (ee's up >99%).

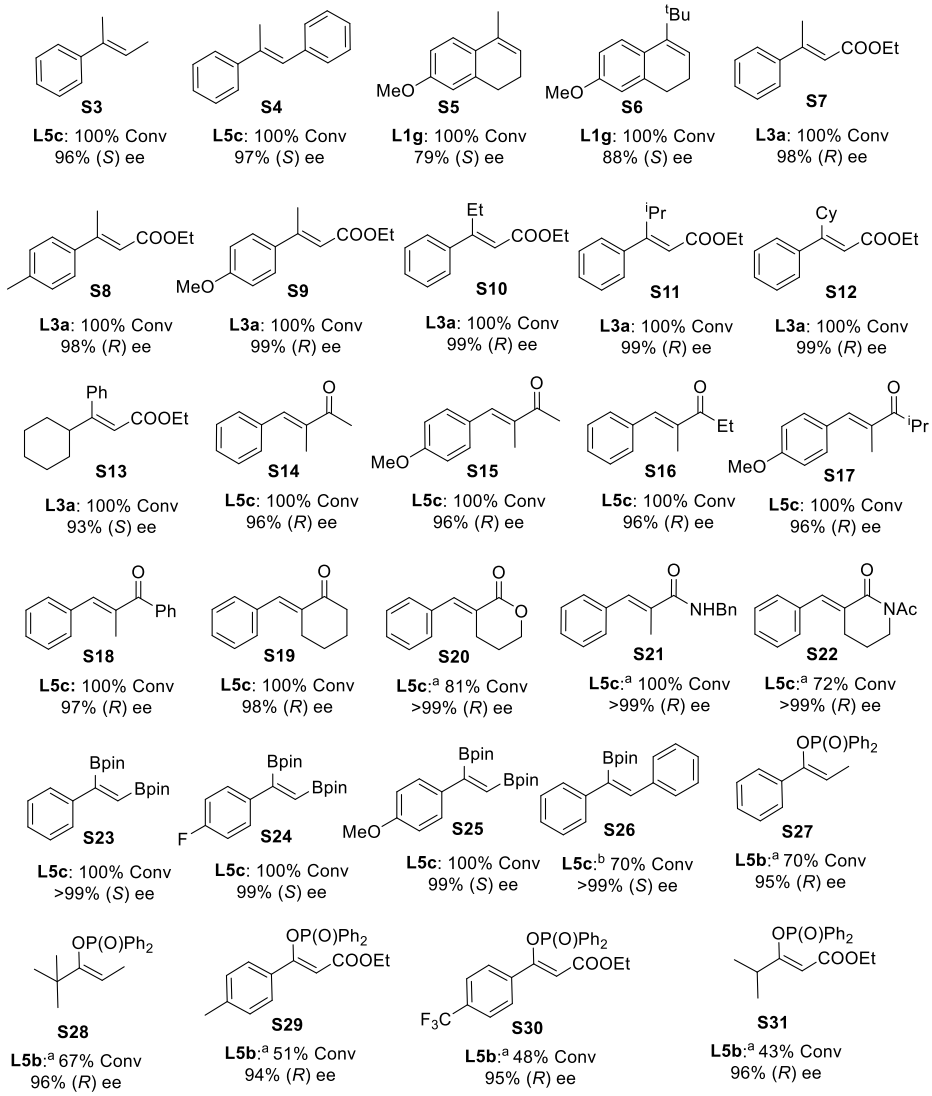


Figure 5.2.2. Selected results for the hydrogenation of trisubstituted olefins **S3**-**S31** using [Ir(cod)(**L1**-**L7a**-**g**)]BAr_F catalyst precursors. Reaction conditions: 2 mol % catalyst precursor, CH_2Cl_2 as solvent, 50 bar H_2, 4 h. [a] Reactions carried out during 24 h.

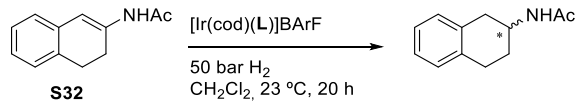
These last results encouraged us to move on to the hydrogenation of other difficult olefins, such as alkenylboronic esters **S23**-**S26** and enol phosphinates **S27**-**S31**. Few catalysts can afford high enantioselectivities for these alkenes, so it was noteworthy that we could reach high enantioselectivities in all of them by carefully modification of

the ligand parameters. In the reduction of alkenylboronic ester, the highest enantioselectivities (up to >99%) were therefore achieved using [Ir(cod)(**L5c**)]BAr_F,[19] while for enol phosphinates the best enantioselectivities (ee's up to 96%) were obtained with [Ir(cod)(**L5b**)]BAr_F[20]. Among the existing methods for preparing chiral organoboron compounds, the hydrogenation is one of the most sustainable and most straightforward. The synthesis of chiral organoboron compounds has recently received considerable attention because they are valuable organic intermediates since the C-B bond can be readily transformed into chiral C-N, C-O and C-C bonds. On the other hand, the effective hydrogenation of enol phosphinates opens up an appealing route for obtaining chiral organophosphinates, which can be easily transformed into high-value compounds such as alcohols and phosphines.

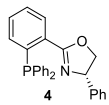
We finally also turned our attention to the Ir-catalyzed asymmetric reduction of challenging β-enamides. In contrast to the α-enamides, most of the catalysts for β-enamides provide low enantiomeric excesses[21] although some successful protocols using Ru- and Rh-based catalysts are available[22]. Among the most successful examples we can cite the Ru-diphosphine catalysts by Ratovelomanana-Vidal *et al.* that reached enantioselectivities up to 96% ee in the reduction of enamides derived from 3-chromanones.[22d] More recently, Tang *et al*. presented the nine-step synthesis of WingPhos, a P-stereogenic diphosphine ligand, that has been applied to a broader number of substrates obtaining high enantioselectivities both for enamides derived from 2-tetralines (ee's up to 96%) and also for enamides derived from 3-chromanones (ee's in the range 94-98%).[22f] We first explored the hydrogenation of N-(3,4-dihydronaphthalen-2-yl)acetamide **S32** to study the efficiency of the [Ir(cod)(**L1**-**L7a**-**g**)]BAr_F catalyst precursors (Table 5.2.2). The hydrogenations were performed under 50 bar of H_2 in dichloromethane at room temperature using 1 mol% of catalyst loading. The effect of the biaryl phosphite group on catalytic performance was studied with ligands **L1a**-**c**. We found that the presence of a chiral *R*-biaryl phosphite moiety is necessary to maximize enantioselectivities and activities (entry 2 vs 1 and 3). These results also indicated that the PHOX-ligand backbone is not able to control the tropoisomerism of the biphenyl phosphite moiety (**a**). Comparing the results of ligands **L1**-**L3b** it can be seen that the nature of the oxazoline substituent has a deep impact on catalytic performance. The presence of a *tert*-butyl oxazoline group led to low activity and enantioselectivity (entry 7). The best activity and enantioselectivity were obtained with ligand **L3b** (entry 5) which contains a phenyl oxazoline moiety. This turned to be economically advantageous because (*S*)-phenylglycinol is the less expensive of the three amino alcohols used (eight times cheaper than *tert*-leucinol used in ligand **L4**). Interestingly, the introduction of a methylene spacer between the oxazoline and the phenyl ring (with phosphite-oxazoline ligands **L5** and **L6**) had a positive effect on enantioselectivity. Both ligands **L5b** and **L6b** provided the hydrogenated product in full conversion and in 98% ee (entries 8 and 9). Finally, the

hydrogenation of **S32** by using the related phosphine-oxazoline PHOX-Ph ligand **2** provided lower conversion and enantioselectivities under the same reaction conditions (Table 5.2.2, entry 10 vs 6 and 8). This result confirms the positive effect of introducing a binaphthyl phosphite moiety into the ligand design. Interestingly, the catalytic performance is maintained regardless the hydrogen pressure. So, full conversion and excellent enantioselectivities were also achieved at 10 bar of H_2 (entry 11).

Table 5.2.2. Selected results for the asymmetric hydrogenation of **S32**[a]



S32

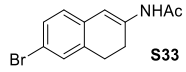
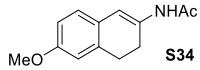
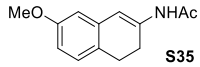
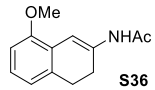
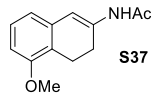
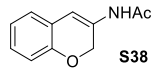
Entry	Ligand	% Conv[b]	% ee[c]
1	**L1a**	75	30 (*S*)
2	**L1b**	80	92 (*S*)
3	**L1c**	56	50 (*R*)
4	**L3a**	80	34 (*S*)
5	**L3b**	95	96 (*S*)
6	**L3c**	65	54 (*R*)
7	**L4b**	30	30 (*S*)
8	**L5b**	100	98 (*S*)
9	**L6b**	100	98 (*S*)
10	 **4**	58	72 (S)
11[d]	**L5b**	100	98 (*S*)

[a] Reactions were run at 23 °C with [[Ir(cod)(**L**)]BAr_F (1 mol%), **S32** (0.5 mmol), CH_2Cl_2 (2 mL) for 20 h. [b] Conversions were measured by ^1H NMR spectroscopy. [c] Enantiomeric excess determined by chiral HPLC. [d] Reaction carried out at 10 bar of H_2.

To further study the behavior of [Ir(cod)(**L5b**)]BArF and [Ir(cod)(**L6b**)]BArF catalyst precursors, we extended our work to the hydrogenation of other cyclic β-enamides. Table 5.2.3 shows the results using catalysts Ir/**L5b** that had provided, together with Ir/**L6b**, the best results in the asymmetric hydrogenation of **S32**. We were pleased to discover that [Ir(cod)(**L5b**)]BAr_F catalytic system is very tolerant to variations in the substitution pattern of the fused benzene ring. Thus, a range substituted cyclic β-enamides derived from β-tetralones were hydrogenated in high yields and with excellent enantioselectivities (ee's ranging from 97% to 99%; Table 5.2.3. entries 1-5) comparable to those achieved with substrate **S32**. Among them, it should be denoted the excellent result with (5-methoxy-3,4-dihydronaphthalen-2-yl)acetamide **S37**

(entry 5), whose hydrogenated product is a key intermediate for the synthesis of *Rotigotine*. Also interesting is the almost perfect enantioselectivity (99% ee, entry 6) and high yield achieved in the hydrogenation of N-(2H-chromen-3-yl)acetamide **S38**, which provides the crucial intermediate for the synthesis of *Alnespirone*.

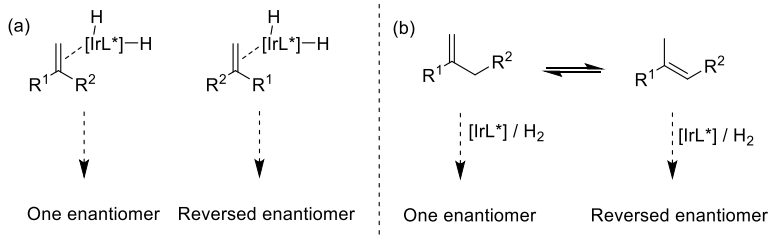
Table 5.2.3. Asymmetric hydrogenation of cyclic β-enamides using [Ir(cod)(**L5b**)]BAr_F[a]

Entry	Substrate	% Conv (% Yield)[b]	% ee[c]
1	 **S33**	100 (79)	98 (*S*)
2	 **S34**	100 (89)	98 (*S*)
3	 **S35**	100 (88)	99 (*S*)
4	 **S36**	100 (91)	99 (*S*)
5	 **S37**	100 (90)	97 (*S*)
6	 **S38**	75 (62)	99 (*R*)

[a] Reactions were run at 23 °C with [Ir(cod)(**L5b**)]BArF (1 mol%), substrate (0.5 mmol), H_2 (50 bar), CH_2Cl_2 (2 mL) for 20 h. [b] Conversions were measured by ^{1}H NMR spectroscopy. [c] Enantiomeric excess determined by chiral HPLC.

5.2.2.4. Asymmetric hydrogenation of disubstituted olefins

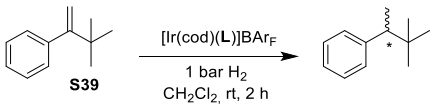
To further study the potential of the **L1**-**L7a-g** ligands, we also screened it in the Ir-catalyzed hydrogenation of terminal olefins.[3e,h] Enantioselectivity is more difficult to control in these substrates than in trisubstituted olefins. There are two main reasons for this: a) the two substituents in the substrate can easily exchange positions in the chiral environment formed by the catalysts, thus reversing the face selectivity (Scheme 5.2.3(a)); and b) the terminal double bond can isomerize to form the more stable internal *E*-alkene, which usually leads to the predominant formation of the opposite enantiomer of the hydrogenated product (Scheme 5.2.3(b)). Few known catalytic systems provide high enantioselectivities for these substrates, and those that do are usually limited in substrate scope. In contrast to the hydrogenation of trisubstituted olefins, the enantioselectivity in the reduction of terminal alkenes is highly pressure dependent. Therefore, hydrogenation at an atmospheric pressure of H_2 gave, in general, significantly higher ee values than at higher pressures.[3e,h]



Scheme 5.2.3. (a) Face differentiation on the 1,1-disubstituted olefin coordination; (b) isomerization of the 1,1-disubstituted olefin once is coordinated to the iridium center.

As a model substrate, we have chosen the 3,3-dimethyl-2-phenyl-1-butene **S39** to assess the potential of the new ligand library. The results are summarized in Table 5.2.4. The best enantioselectivity was obtained with ligands **L3** (ee's up to 98%, Table 5.2.4, entries 9-11). The introduction of a methylene spacer between the oxazoline and the phenyl ring of the ligand backbone does not improve the enantioselectivities (*i.e.* entries 15 vs 9).

Table 5.2.4. Ir-catalyzed hydrogenation of **S39** using ligands **L1**-**L7a**-**g** [a]



Entry	Ligand	% Conv[b]	% ee[c]	Entry	Ligand	% Conv[b]	% ee[c]
1	**L1a**	100	88 (*S*)	13	**L4b**	100	66 (*S*)
2	**L1b**	100	61 (*S*)	14	**L4c**	100	93 (*S*)
3	**L1c**	100	90 (*S*)	15	**L5a**	100	78 (*S*)
4	**L1d**	100	65 (*S*)	16	**L5b**	100	84 (*S*)
5	**L1e**	100	84 (*S*)	17	**L5c**	100	54 (*R*)
6	**L1f**	100	66 (*S*)	18	**L6a**	100	96 (*S*)
7	**L1g**	100	82 (*S*)	19	**L6b**	100	93 (*S*)
8	**L2a**	100	84 (*S*)	20	**L6c**	100	57 (*S*)
9	**L3a**	100	98 (*S*)	21	**L7a**	100	90 (*S*)
10	**L3b**	100	97 (*S*)	22	**L7b**	87	66 (*S*)
11	**L3c**	100	97 (*S*)	23	**L7c**	42	15 (*S*)
12	**L4a**	100	84 (S)				

[a] Reactions carried out at room temperature by using 0.5 mmol of substrate and 1 mol% of Ir-catalyst precursor at 1 bar of H_2 using dichloromethane (2 mL) as solvent. [b] Conversion measured by ^1H NMR after 2 h. [c] Enantiomeric excess determined by GC.

We next studied the asymmetric hydrogenation of other terminal disubstituted olefins (Figure 5.2.3). We were pleased to see that substrates **S40**-**S46** also provided high enantioselectivities, albeit the presence of *ortho* substituents at the aryl ring (**S45** and

S46) led to lower activities. Lower enantioselectivities have been achieved in the reduction of several α-alkylstyrenes bearing decreasingly sterically demanding alkyl substituents (**S47**-**S50**). A plausible explanation is the competition between direct hydrogenation and isomerization. However, we were pleased to find that enantioselectivities for these substrates could be maximized by appropriately choosing the ligand parameters (ee's ranging from 83% to 91%). Interestingly, the excellent activities and enantioselectivities were maintained when introducing poorly coordinative groups in the substrate **S51**-**S54**. We were again able to fine tune the ligand to obtain high-to-excellent enantioselectivities (ee's up to 99%). The results are among the best in the literature for each substrate, even in the reduction of such highly appealing substrates as pinacolatoboron-containing substrates **S51** and **S52**,[19] and enol phosphinate **S53**[23] for which only very few catalytic systems have provided high enantioselectivities. Similarly, the hydrogenation of the allylic acetate **S54** also proceeds with high activity and enantioselectivity with the catalyst system Ir-**L3a**.

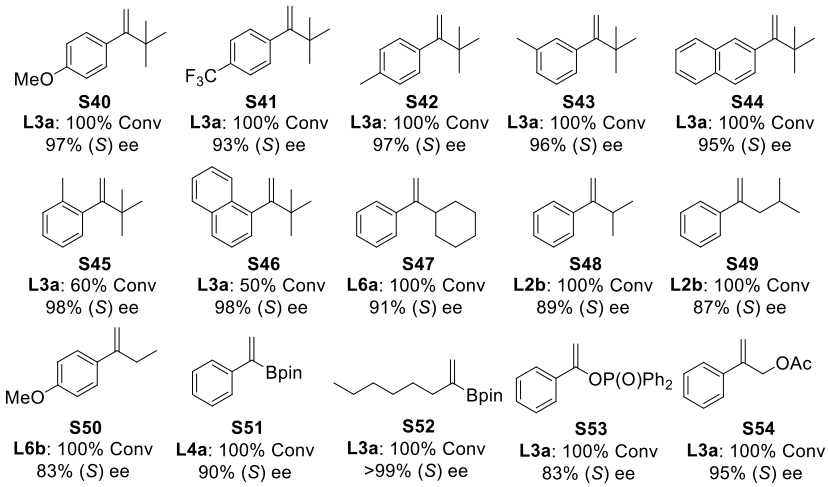


Figure 5.2.3. Selected results for the hydrogenation of disubstituted olefins **S40**-**S54** using [Ir(cod)(**L1**-**L7a**-**g**)]BAr_F catalyst precursors. Reaction conditions: 2 mol % catalyst precursor, CH_2Cl_2 as solvent, 1 bar H_2, 4 h.

5.2.3 Conclusions

We have successfully applied new Ir(I)-catalyst precursors ([Ir(cod)(**L1**-**L7a**-**g**)]BAr_F), modified with easily accessible PHOX-based phosphite-oxazoline ligands, for the asymmetric hydrogenation of demanding minimally functionalized alkenes and cyclic β-enamides. The catalytic results indicated that enantioselectivity is highly affected by the ligand parameters as well as the substrate. The new Ir-PHOX-based phosphite-oxazoline catalysts have been able to efficiently hydrogenate not only minimally functionalized model olefins, but also a wide range of challenging olefins that have

recently received a great deal of attention because the resulting hydrogenated compounds can be easily stereoselectively transformed into high-value organic compounds. The results are among the best reported so far. On the other hand, it should be noted the excellent enantioselectivities achieved in the hydrogenation of β-aryl enamides, which gave access to 2-aminotetralines and 3-aminochromanes in enantioselectivities up to 99%.

5.2.4 Experimental section

5.2.4.1 General considerations

All reactions were carried out using standard Schlenk techniques under an argon atmosphere. Commercial chemicals were used as received. Solvents were dried by means of standard procedures and stored under argon. ^{1}H, $^{13}C\{^{1}H\}$ and $^{31}P\{^{1}H\}$ NMR spectra were recorded using a Varian Mercury-400 MHz spectrometer. Chemical shifts are relative to that of $SiMe_4$ (^{1}H and $^{13}C\{^{1}H\}$) or H_3PO_4 ($^{31}P\{^{1}H\}$) as internal standard. Ligands **L1f**-**g** and **L5-L7a**-**c** have been prepared as described in Sections 3.2 and 3.3. Phosphorochloridites, [24] hydroxyl-oxazolines **1**-**3**, [25] ligands **L1**-**L4a**,[12,13] olefins **S1**-**S31**,[26] **S32**-**S38**[27] and **S39**-**S54**[28] were synthesized as previously reported.

5.2.4.2. Typical procedure for the preparation of phosphite-oxazoline ligands.

To a solution of *in situ* generated phosphochloridite (1.1 mmol) in dry toluene (6 mL), pyridine (0.16 mL, 2.0 mmol) was added. Then, this solution was placed in a -78 ºC bath. After 2 min at that temperature, a solution of the alcohol-oxazoline (1.0 mmol) and pyridine (0.16 mL, 2.0 mmol) in toluene (6 mL) was added dropwise at -78 °C. The mixture was left to warm to room temperature and stirred overnight at this temperature. The precipitate formed was filtered under argon and the solvent was evaporated under vacuum. The residue was purified by flash chromatography (under argon, using neutral alumina and dry toluene (1% NEt_3) as eluent system) to afford the corresponding phosphite-oxazoline as white solids.

L1b: Yield: 464.7 mg (70%); ^{31}P NMR (161.9 MHz, C_6D_6): $\delta = 138.7$ (s); ^{1}H NMR (400 MHz, C_6D_6): δ = 0.26 (s, 9H, CH_3, $SiMe_3$), 0.59 (s, 9H, CH_3, $SiMe_3$), 0.68 (d, 3H, CH_3, ^{i}Pr, $^{3}J_{H-H}$= 6.4 Hz), 0.88 (d, 3H, CH_3, ^{i}Pr, $^{3}J_{H-H}$= 7.2 Hz), 1.56 (m, 1H, CH, ^{i}Pr), 3.46 (m, 1H, CH-O), 3.78 (m, 2H, CH-O, CH-N) 6.68 (m, 3H, CH=), 6.87 (m, 2H, CH=), 7.11 (m, 2H, CH=), 7.33 (m, 2H, CH=), 7.64 (d, 1H, CH=, $^{3}J_{H-H}$= 8.0 Hz), 7.71 (d, 1H, CH=, $^{3}J_{H-H}$= 8.4 Hz), 8.02 (m, 3H, CH=), 8.18 (s, 1H, CH=). ^{13}C (100.6 MHz, C_6D_6): δ= 0.2 (d, CH_3, $SiMe_3$, J_{C-P}= 4.6 Hz), 0.5 (CH_3, $SiMe_3$), 18.2 (CH_3, ^{i}Pr), 18.7 (CH_3, ^{i}Pr), 33.9 (CH, ^{i}Pr), 69.4 (CH_2-O), 72.8 (CH-N), 121.4-152.9 (aromatic carbons), 160.8 (C=N). MS HR-ESI [found 686.2285, $C_{38}H_{42}NO_4PSi_2$ $(M-Na)^+$ requires 686.2282].

L1c: Yield: 471.4 mg (71%); ^{31}P NMR (161.9 MHz, C_6D_6): $\delta =$ 138.6 (s); ^{1}H NMR (400 MHz, C_6D_6): δ = 0.33 (s, 9H, CH_3, $SiMe_3$), 0.55 (s, 9H, CH_3, $SiMe_3$), 0.81 (d, 3H, CH_3, ^{i}Pr, $^{3}J_{H-H}$= 6.4 Hz), 0.98 (d, 3H, CH_3, ^{i}Pr, $^{3}J_{H-H}$= 7.2 Hz), 1.58 (m, 1H, CH, ^{i}Pr), 3.68 (m, 1H, CH-O), 3.87 (m, 2H, CH-O, CH-N) 5.9 (d, 1H, CH=, $^{3}J_{H-H}$= 8.0 Hz), 6.45 (m, 1H, CH=), 6.55 (m, 1H, CH=), 6.83 (m, 2H, CH=), 7.11 (m, 2H, CH=), 7.26 (m, 2H, CH=), 7.64 (d, 1H, CH=, $^{3}J_{H-H}$= 8.0 Hz), 7.74 (d, 1H, CH=, $^{3}J_{H-H}$= 8.4 Hz), 7.89 (dd, 1H, CH=, $^{3}J_{H-H}$= 8.0 Hz, $^{4}J_{H-H}$= 1.6 Hz), 8.03 (s, 1H, CH=), 8.21 (s, 1H, CH=). ^{13}C (100.6 MHz, C_6D_6): δ= -0.2 (d, CH_3, $SiMe_3$, J_{C-P}= 3.9 Hz), 0.0 (CH_3, $SiMe_3$), 18.5 (CH_3, ^{i}Pr), 18.6 (CH_3, ^{i}Pr), 33.0 (CH, ^{i}Pr), 69.4 (CH_2-O), 72.9 (CH-N), 120.6-152.9 (aromatic carbons), 160.5 (C=N). MS HR-ESI [found 686.2286, $C_{38}H_{42}NO_4PSi_2$ $(M-Na)^+$ requires 686.2282].

L1d: Yield: 423 mg (72%); ^{31}P NMR (C_6D_6), δ: 132.6 ppm (s); ^{1}H NMR (C_6D_6), δ: 0.62 (d, 6H, $^{3}J_{H-H}$= 6.4 Hz, CH_3, ^{i}Pr), 1.27 (s, 9H, CH_3, ^{t}Bu), 1.37 (s, 9H, CH_3, ^{t}Bu), 1.39 (m, 1H, CH, ^{i}Pr), 1.61 (s, 3H, CH_3), 1.68 (s, 3H, CH_3), 1.93 (s, 3H, CH_3), 2.03 (s, 3H, CH_3), 3.03 (dd, 1H, $^{2}J_{H-H}$= 11.6 Hz, $^{3}J_{H-H}$= 5.2 Hz, CH_2-O), 3.12 (dd, 1H, $^{2}J_{H-H}$= 11.2 Hz, $^{3}J_{H-H}$= 5.2 Hz, CH_2-O), 4.22 (m, 1H, CH-N), 6.7-7.5 (m, 6H, CH=), 8.59 (d, 1H, $^{3}J_{H-H}$= 6.4 Hz, CH=). ^{13}C NMR (C_6D_6), δ: 16.2 (CH_3, ^{i}Pr), 16.4 (CH_3, ^{i}Pr), 17.8 (CH_3), 19.1 (CH_3), 19.9 (CH_3), 20.0 (CH_3), 28.6 (CH, ^{i}Pr), 31.0 (d, CH_3, ^{t}Bu, J_{C-P}=5.3 Hz), 31.3 (CH_3, ^{t}Bu), 34.4 (C, ^{t}Bu), 34.8 (C, ^{t}Bu), 45.3 (CH_2-O), 55.4 (CH-N), 118.4-150.9 (aromatic carbons), 163.4 (C=N). MS HR-ESI [found 610.3067, $C_{36}H_{46}NO_4P$ $(M-Na)^+$ requires 610.3062].

L1e: Yield: 376 mg (64%); ^{31}P NMR (C_6D_6), δ: 133.9 ppm (s); ^{1}H NMR (C_6D_6), δ: 0.55 (d, 3H, $^{3}J_{H-H}$= 6.4 Hz, CH_3, ^{i}Pr), 0.63 (d, 3H, $^{3}J_{H-H}$= 6.8 Hz, CH_3, ^{i}Pr), 1.35 (s, 9H, CH_3, ^{t}Bu), 1.39 (s, 9H; CH_3, ^{t}Bu), 1.42 (m, 1H, CH, ^{i}Pr), 1.65 (s, 3H, CH_3), 1.79 (s, 3H, CH_3), 1.97 (s, 3H, CH_3), 2.06 (s, 3H, CH_3), 3.35 (m, 2H, CH_2-O), 4.28 (m, 1H, CH-N), 6.7-7.7 (m, 6H, CH=), 8.60 (d, 1H, $^{3}J_{H-H}$= 8.0 Hz, $^{4}J_{H-H}$= 2.0 Hz, CH=). ^{13}C NMR (C_6D_6), δ: 16.2 (CH_3, ^{i}Pr), 16.6 (CH_3, ^{i}Pr), 18.1 (CH_3), 19.1 (CH_3), 20.0 (CH_3), 21.4 (CH_3), 28.6 (CH, ^{i}Pr), 31.2 (d, CH_3, ^{t}Bu, J_{C-P}= 4.6 Hz), 31.4 (CH_3, ^{t}Bu), 34.4 (C, ^{t}Bu), 34.7 (C, ^{t}Bu), 45.6 (CH_2-O), 55.5 (CH-N), 119.3-150.4 (aromatic carbons), 163.4 (C=N). MS HR-ESI [found 610.3068, $C_{36}H_{46}NO_4P$ $(M-Na)^+$ requires 610.3062].

L3b: Yield: 495 mg (71%); ^{31}P NMR (161.9 MHz, C_6D_6): $\delta =$ 139.7 (s); ^{1}H NMR (400 MHz, C_6D_6): δ = 0.30 (s, 9H, CH_3, $SiMe_3$), 0.58 (s, 9H, CH_3, $SiMe_3$), 3.56 (pt, 1H, CH-O, J_{H-H}= 8.8 Hz), 4.08 (dd, 1H, CH-O, $^{2}J_{H-H}$= 10.4 Hz; $^{3}J_{H-H}$= 8.4 Hz), 5.05 (pt, 1H, CH-N, J_{H-H}= 9.6 Hz), 6.7-6.8 (m, 2H, CH=), 6.88 (m, 2H, CH=), 7.04 (m, 4H, CH=), 7.15 (m, 3H, CH=), 7.32 (m, 2H, CH=), 7.7 (m, 2H, CH=), 8.1 (m, 3H, CH=), 8.2 (s, 1H, CH=). ^{13}C (100.6 MHz, C_6D_6): δ= 0.2 (d, CH_3, $SiMe_3$, J_{C-P}= 4.62 Hz), 0.5 (CH_3, $SiMe_3$), 70.8 (CH-N), 74.6 (CH_2-O), 122.1-153.5 (aromatic carbons), 163.2 (C=N). MS HR-ESI [found 720.2130, $C_{41}H_{46}NO_4PSi_2$ $(M-Na)^+$ requires 720.2126].

L3c: Yield: 432 mg (62%); ^{31}P NMR (161.9 MHz, C_6D_6): δ = 138.2 (s); ^{1}H NMR (400 MHz, C_6D_6): δ = 0.35 (s, 9H, CH_3, $SiMe_3$), 0.57 (s, 9H, CH_3, $SiMe_3$), 3.81 (pt, 1H, CH-O, J_{H-H}= 8.4 Hz), 4.14 (dd, 1H, CH-O, $^{2}J_{H-H}$= 10.4 Hz; $^{3}J_{H-H}$= 8.4 Hz), 5.17 (pt, 1H, CH-N, J_{H-H}= 8.8 Hz), 6.20 (d, 1H, CH=, $^{3}J_{H-H}$= 7.6 Hz), 6.57-6.66 (m, 2H, CH=), 6.88 (m, 2H, CH=), 7.0-7.18 (m, 5H, CH=), 7.5 (d, 2H, CH=, $^{3}J_{H-H}$= 7.2 Hz), 7.32 (m, 2H, CH=), 7.68 (d, 1H, CH=, $^{3}J_{H-H}$= 8Hz), 7.75 (d, 1H, CH=, $^{3}J_{H-H}$ = 8.4 Hz), 8.04 (dd, 1H, CH=, $^{3}J_{H-H}$ = 7.2 Hz, $^{4}J_{H-H}$ = 2Hz), 8.06 (s, 1H, CH=), 8.22 (s, 1H, CH=). ^{13}C (100.6 MHz, C_6D_6): δ= 0.0 (d, CH_3, $SiMe_3$, J_{C-P}= 3.8 Hz), 0.5 (CH_3, $SiMe_3$), 70.9 (CH-N), 74.6 (CH_2-O), 121.4-153.6 (aromatic carbons), 163.1 (C=N). MS HR-ESI [found 720.2132, $C_{41}H_{46}NO_4PSi_2$ $(M-Na)^+$ requires 720.2126].

L4b: Yield: 542.3 mg (80%); ^{31}P NMR (161.9 MHz, C_6D_6): δ = 139.2 (s); ^{1}H NMR (400 MHz, C_6D_6): δ = 0.29 (s, 9H, CH_3, $SiMe_3$), 0.64 (s, 9H, CH_3, $SiMe_3$), 0.80 (s, 9H, CH_3, ^{t}Bu), 3.59 (m, 1H, CH-O), 3.81 (m, 2H, CH-O, CH-N), 6.0 (d, 1H, CH=, $^{3}J_{H-H}$ = 8.0 Hz), 6.61 (m, 1H, CH=), 6.72 (m, 1H, CH=), 7.0 (m, 2H, CH=), 7.11 (m, 1H, CH=), 7.25 (m, 3H, CH=), 7.39 (m, 1H, CH), 7.81 (d, 1H, CH=, $^{3}J_{H-H}$ = 8.0 Hz), 7.90 (d, 1H, CH=, $^{3}J_{H-H}$ = 8.0 Hz), 8.02 (d, 1H, CH=, $^{3}J_{H-H}$ = 8.0 Hz), 8.18 (s, 1H, CH=), 8.36 (s, 1H, CH=). ^{13}C (100.6 MHz, C_6D_6): δ= -0.7 (d, CH_3, $SiMe_3$, J_{C-P}= 4.3 Hz), -0.1 (CH_3, $SiMe_3$), 25.7 (CH_3, ^{t}Bu), 33.8 (C, ^{t}Bu), 67.6 (CH-N), 76.5 (CH_2-O), 120.6-152.9 (aromatic carbons), 160.5 (C=N). MS HR-ESI [found 700.2443, $C_{39}H_{44}NO_4PSi_2$ $(M-Na)^+$ requires 700.2439].

L4c: Yield: 474.5 mg (70%); ^{31}P NMR (161.9 MHz, C_6D_6): δ = 138.7 (s); ^{1}H NMR (400 MHz, C_6D_6): δ = 0.48 (s, 9H, CH_3, $SiMe_3$), 0.71 (s, 9H, CH_3, $SiMe_3$), 1.04 (s, 9H, CH_3, ^{t}Bu), 4.06 (m, 3H, CH_2-O, CH-N), 6.74 (m, 1H, CH=), 6.91 (m, 2H, CH=), 7.01 (m, 1H, CH=), 7.13 (m, 3H, CH=), 7.35 (m, 2H, CH), 7.68 (d, 1H, CH=, $^{3}J_{H-H}$ = 8.0 Hz), 7.75 (d, 1H, CH=, $^{3}J_{H-H}$ = 8.0 Hz), 8.05 (m, 2H, CH=), 8.22 (s, 1H, CH=). ^{13}C (100.6 MHz, C_6D_6): δ= -0.4 (d, CH_3, $SiMe_3$, J_{C-P}= 5.0 Hz), 0.0 (CH_3, $SiMe_3$), 25.7 (CH_3, ^{t}Bu), 33.7 (C, ^{t}Bu), 67.7 (CH-N), 76.3 (CH_2-O), 121.4-152.9 (aromatic carbons), 160.8 (C=N). MS HR-ESI [found 700.2445, $C_{39}H_{44}NO_4PSi_2$ $(M-Na)^+$ requires 700.2439].

5.2.4.3. Typical procedure for the preparation of [Ir(cod)(L1-L7a-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 40 °C for 1 hour. After 5 min at room temperature, $NaBAr_F$ (38.6 mg, 0.041 mmol) and water (2.5 mL) were added and the reaction mixture was stirred vigorously for 30 min at room temperature. The phases were separated and the aqueous phase was extracted twice with CH_2Cl_2. The combined organic phases were dried with $MgSO_4$, filtered through a plug of celite and the solvent was evaporated to give the products as red-orange solids.

[Ir(cod)(L1a)]BAr$_F$: Yield: 62 mg (92%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ=108.1 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.61 (m, 6H, CH_3, ^{i}Pr), 1.66 (s, 9H, CH_3, ^{t}Bu), 1.97 (s, 9H, CH_3, ^{t}Bu), 2.0 (s, 9H, CH_3, ^{t}Bu,), 2.1 (s, 9H, CH_3, ^{t}Bu), 2.37 (m, 1H, CH_2, cod), 2.4 (m, 1H, CH, ^{i}Pr), 2.50 (m, 1H, CH_2, cod), 2.63 (m, 1H, CH_2, cod), 2.82-2.97 (m, 4H, CH_2, cod), 3.2 (m, 1H, CH_2, cod), 4.05 (m, 1H, CH=, cod), 4.75 (m, 1H, CH=, cod), 4.89 (m, 1H, CH-N), 5.04 (pt, 1H, CH-O, J_{H-H} = 9.6 Hz), 5.09 (m, 1H, CH-O), 5.96 (m, 1H, CH=, cod), 6.09 (m, 1H, CH=, cod), 6.87 (d, 1H, CH=, $^3J_{H-H}$ = 7.6 Hz), 7.87 (m, 3H, CH=), 8.14 (m, 6H, CH=), 8.3 (m, 11H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=15.9 (CH_3, ^{i}Pr), 18.9 (CH_3, ^{i}Pr), 25.9 (CH_2, cod), 29.1 (CH_2, cod), 30.9 (CH_3, ^{t}Bu), 31.4 (CH_3, ^{t}Bu), 31.6 (CH_2, cod), 31.9 (CH_3, ^{t}Bu), 32.0 (CH_3, ^{t}Bu), 33.4 (CH, ^{i}Pr), 35.4 (C, ^{t}Bu), 35.5 (C, ^{t}Bu), 35.8 (C, ^{t}Bu), 36.2 (C, ^{t}Bu), 36.4 (d, CH_2, cod, J_{C-P}= 6.1 Hz), 63.5 (CH=, cod), 67.0 (CH=, cod), 69.2 (CH_2-O), 73.6 (CH-N), 106.9 (CH=, cod), 107.6 (CH=, cod), 118.0-150.4 (aromatic carbons), 162.3 (q, C-B, BArF, $^1J_{C-B}$ =49.7 Hz), 170.0 (C=N). MS HR-ESI [found 944.4363, $C_{48}H_{66}IrNO_4P$ $(M\text{-}BAr_F)^+$ requires 944.4359].

[Ir(cod)(L1b)]BAr$_F$: Yield: 65 mg (96%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ=121.1(s). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 0.03 (s, 9H, CH_3, $SiMe_3$), 0.68 (s, 9H, CH_3, $SiMe_3$), 0.78 (d, 3H, CH_3, ^{i}Pr, $^3J_{H-H}$ = 6.4 Hz), 0.96 (d, 3H, CH_3, ^{i}Pr, $^3J_{H-H}$ = 7.2 Hz), 1.32 (m, 1H, CH_2, cod), 1.76 (m, 1H, CH_2, cod), 1.93 (m, 1H, CH_2, cod), 2.17 (m, 1H, CH_2, cod), 2.30 (m, 2H, CH_2, cod), 2.38 (m, 1H, CH, ^{i}Pr), 2.46 (m, 2H, CH_2, cod), 3.70 (m, 1H, CH=, cod), 3.97 (m, 1H, CH=, cod), 4.23 (m, 1H, CH-N), 4.36 (pt, 1H, CH-O, J_{H-H} = 9.2 Hz), 4.56 (m, 1H, CH-O), 5.29 (m, 1H, CH=, cod), 5.56 (m, 1H, CH=, cod), 6.26 (d, 1H, CH=, $^3J_{H-H}$ = 8.4 Hz), 6.67 (d, 1H, CH=, $^3J_{H-H}$ = 8.4 Hz), 7.10 (d, 1H, CH=, $^3J_{H-H}$ = 7.6 Hz), 7.19 (t, 1H, CH=, $^3J_{H-H}$ = 7.2 Hz), 7.3-7.7 (m, 16H, CH=), 7.77 (d, 1H, CH=, $^3J_{H-H}$ = 8.0 Hz), 7.94 (d, 1H, CH=, $^3J_{H-H}$ = 8.4 Hz), 8.03 (d, 1H, CH=, $^3J_{H-H}$ = 8.8 Hz), 8.17 (s, 2H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=-0.8 (CH_3, $SiMe_3$), 0.9 (CH_3, $SiMe_3$), 14.0 (CH_3, ^{i}Pr), 18.3 (CH_3, ^{i}Pr), 25.3 (CH_2, cod), 28.5 (CH_2, cod), 29.7 (CH, ^{i}Pr), 31.1 (CH_2, cod), 35.7 (CH_2, cod), 62.6 (CH=, cod), 67.8 (CH_2-O), 69.3 (CH=, cod), 73.6 (CH-N), 105.5 (d, CH=, cod, J_{C-P}= 19.8 Hz), 108.2 (d, CH=, cod, J_{C-P}= 14.4 Hz), 118.0-151.2 (aromatic carbons), 162.1 (q, C-B, BArF, $^1J_{C-B}$ = 50.5 Hz), 167.6 (C=N). MS HR-ESI [found 964.2961, $C_{46}H_{54}IrNO_4PSi_2$ $(M\text{-}BAr_F)^+$ requires 964.2958].

[Ir(cod)(L1c)]BAr$_F$: Yield: 61 mg (90%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ=113.1 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 0.07 (s, 9H, CH_3, $SiMe_3$), 0.52 (s, 9H, CH_3, $SiMe_3$), 0.95 (d, 3H, CH_3, ^{i}Pr, $^3J_{H-H}$ = 6.4 Hz), 1.04 (d, 3H, CH_3, ^{i}Pr, $^3J_{H-H}$ = 7.2 Hz), 1.76 (m, 1H, CH_2, cod), 1.94 (m, 1H, CH_2, cod), 2.17-2.34 (m, 6H, CH_2, cod), 2.4 (m, 1H, CH, ^{i}Pr), 2.98 (m, 1H, CH=, cod), 3.84 (m, 1H, CH=, cod), 4.17 (m, 1H, CH-N), 4.44 (pt, 1H, CH-O, J_{H-H} = 9.2 Hz), 4.59 (m, 1H, CH-O), 5.38 (m, 1H, CH=, cod), 5.57 (m, 1H, CH=, cod), 6.78 (d, 1H, CH=, $^3J_{H-H}$ = 8.8 Hz), 6.81 (d, 1H, CH=, $^3J_{H-H}$ = 8.4 Hz), 7.08 (d, 1H, CH=, $^3J_{H-H}$ = 8.8 Hz), 7.19-7.7 (m, 17H, CH=), 7.77 (d, 1H, CH=, $^3J_{H-H}$ = 7.6

Hz), 7.91 (d, 1H, CH=, $^3J_{H-H}$ = 8.0 Hz), 7.97 (m, 2H, CH=), 8.18 (s, 1H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=0.8 (CH_3, $SiMe_3$), 0.2 (CH_3, $SiMe_3$), 15.1 (CH_3, ^{i}Pr), 18.9 (CH_3, ^{i}Pr), 25.1 (CH_2, cod), 29.0 (CH_2, cod), 29.7 (CH, ^{i}Pr), 32.7 (CH_2, cod), 36.4 (CH_2, cod), 58.1 (CH=, cod), 67.4 (CH=, cod), 68.2 (CH_2-O), 72.2 (CH-N), 106.3 (d, CH=, cod, J_{C-P}= 22.1 Hz), 108.2 (d, CH=, cod, J_{C-P}= 16.8 Hz), 111.4-150.2 (aromatic carbons), 161.8 (q, C-B, BArF, $^1J_{C-B}$ = 49.8 Hz), 170.8 (C=N). MS HR-ESI [found 964.2962, $C_{46}H_{54}IrNO_4PSi_2$ (M-BAr_F)$^+$ requires 964.2958].

[Ir(cod)(L1d)]BAr_F: Yield: 59 mg (91%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ=114.4 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 0.82 (d, 3H, CH_3, ^{i}Pr, $^3J_{H-H}$ = 6.4 Hz), 0.98 (d, 3H, CH_3, ^{i}Pr, $^3J_{H-H}$ = 7.2Hz), 1.08 (s, 9H, CH_3, ^{t}Bu), 1.63 (s, 9H, CH_3, ^{t}Bu), 1.97 (s, 3H, CH_3), 2.14 (s, 3H, CH_3), 2.24 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 2.4 (m, 1H, CH, iPr), 1.72-2.52 (m, 8H, CH_2, cod), 3.87 (m, 1H, CH=, cod), 4.10 (m, 1H, CH=, cod), 4.25 (m, 1H, CH-N) 4.39 (pt, 1H, CH-O, J_{H-H} = 10.0 Hz), 4.54 (m, 1H, CH-O), 5.22 (m, 1H, CH=, cod), 5.35 (m, 1H, CH=, cod), 6.17 (d, 1H, CH=, $^3J_{H-H}$ = 8.0 Hz), 7.87-7.27 (m, 3H, CH=), 7.53 (s, 4H, CH=), 7.71 (s, 10H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=14.0 (CH_3, ^{i}Pr), 16.3 (CH_3), 16.8 (CH_3), 18.9 (CH_3, ^{i}Pr), 20.3 (CH_3), 20.5 (CH_3), 25.6 (CH_2, cod), 28.9 (CH_2, cod), 30.8 (CH_3, ^{t}Bu), 31.0 (CH_2, cod), 31.4 (CH_3, ^{t}Bu), 34.7 (CH, ^{i}Pr), 34.9 (C, ^{t}Bu), 35.4 (d, CH_2, cod, J_{C-P}= 6.1 Hz), 62.9 (CH=, cod), 67.9 (CH_2-O), 69.4 (CH=, cod), 73.6 (CH-N), 103.9 (d, CH=, cod, J_{C-P}= 20.6 Hz), 107.6 (d, CH=, cod, J_{C-P}= 15.3 Hz), 117.4-146.4 (aromatic carbons), 161.7 (q, C-B, BArF, $^1J_{C-B}$ =49.7 Hz), 167.6 (C=N). MS HR-ESI [found 888.3737, $C_{44}H_{58}IrNO_4P$ (M-BAr_F)$^+$ requires 888.3733].

[Ir(cod)(L1e)]BAr_F: Yield: 60 mg (93%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ=106.6 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 0.97 (d, 3H, CH_3, ^{i}Pr, $^3J_{H-H}$ = 6.4 Hz), 1.02 (s, 9H, CH_3, ^{t}Bu), 1.03 (m, 3H, CH_3, ^{i}Pr), 1.49 (s, 9H, CH_3, ^{t}Bu), 1.68 (s, 3H, CH_3), 1.85 (s, 3H, CH_3), 1.92-2.22 (m, 5H, CH_2, cod), 2.24 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 2.4 (m, 1H, CH, ^{i}Pr), 2.37-2.51 (m, 3H, CH_2, cod), 2.61 (m, 1H, CH=, cod), 4.05 (m, 1H, CH=, cod), 4.22 (m, 1H, CH-N) 4.41 (pt, 1H, CH-O, J_{H-H} = 10.0 Hz), 4.52 (m, 1H, CH-O), 5.24 (m, 1H, CH=, cod), 5.53 (m, 1H, CH=, cod), 6.88 (d, 1H, CH=, $^3J_{H-H}$ = 8.0 Hz), 7.06 (s, 1H, CH=), 7.28-7.36 (m, 2H, CH=), 7.53-7.58 (m, 5H, CH=), 7.71 (s, 9H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=15.0 (CH_3, iPr), 16.4 (CH_3), 16.6 (CH_3), 18.3 (CH_3, iPr), 20.2 (CH_3), 20.6 (CH_3), 25.0 (CH_2, cod), 28.8 (CH_2, cod), 30.8 (CH_2, cod), 31.0 (CH_3, ^{t}Bu), 31.4 (CH_3, ^{t}Bu), 33.1 (CH, ^{i}Pr), 34.6 (C, ^{t}Bu), 34.9 (C, ^{t}Bu), 36.5 (CH_2, cod), 56.9 (CH=, cod), 68.4 (CH_2-O), 69.2 (CH=, cod), 72.4 (CH-N), 105.5 (d, CH=, cod, J_{C-P}= 15.3 Hz), 106.5 (d, CH=, cod, J_{C-P}= 18.3 Hz), 117.4-146.3 (aromatic carbons), 161.6 (q, C-B, BArF, $^1J_{C-B}$ =49.7 Hz), 170.6 (C=N). MS HR-ESI [found 888.3736, $C_{44}H_{58}IrNO_4P$ (M-BAr_F)$^+$ requires 888.3733].

[Ir(cod)(L1f)]BAr_F: Yield: 63 mg (94%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ=114.9 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 0.84 (d, 3H, CH_3, ^{i}Pr, $^3J_{H-H}$ = 6.8 Hz), 0.97 (d, 3H, CH_3, ^{i}Pr, $^3J_{H-H}$ = 6.8Hz), 1.08 (s, 9H, CH_3, ^{t}Bu), 1.65 (s, 9H, CH_3, ^{t}Bu), 1.68-2.48 (m, 16H,

CH_2), 2.41 (m, 1H, CH, ^{i}Pr), 2.01-2.48 (m, 4H, CH_2, cod), 2.75-2.91 (m, 4H, CH_2, cod), 3.88 (m, 1H, CH=, cod), 4.09 (m, 1H, CH=, cod), 4.25 (m, 1H, CH-N), 4.38 (pt, 1H, CH-O, J_{H-H} = 10.0 Hz), 4.53 (m, 1H, CH-O), 5.19 (m, 1H, CH=, cod), 5.30 (m, 1H, CH=, cod), 6.15 (d, 1H, CH=, $^{3}J_{H-H}$ = 8.8 Hz), 7.15 (m, 2H, CH=), 7.28 (m, 1H, CH=), 7.53 (s, 5H, CH=), 7.72 (s, 9H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=14.1 (CH_3, ^{i}Pr), 18.4 (CH_3, ^{i}Pr), 22.5 (CH_2), 22.6 (CH_2), 22.7 (CH_2), 22.8 (CH_2), 25.6 (CH_2, cod), 27.0 (CH_2), 27.1 (CH_2), 28.9 (CH_2, cod), 29.5 (CH_2), 30.8 (CH_3, ^{t}Bu), 30.9 (CH_2, cod), 31.0 (CH_2), 31.3 (CH_3, ^{t}Bu), 34.7 (CH, ^{i}Pr), 34.8 (C, ^{t}Bu), 35.5 (CH_2, cod), 62.9 (CH=, cod), 67.9 (CH_2-O), 69.2 (CH=, cod), 73.5 (CH-N), 103.8 (d, CH=, cod, J_{C-P}= 20.6 Hz), 106.7 (d, CH=, cod, J_{C-P}= 14.5 Hz), 117.4-146.3 (aromatic carbons), 161.6 (q, C-B, BArF, $^{1}J_{C-B}$ =50.5 Hz), 167.6 (C=N). MS HR-ESI [found 940.4051, $C_{48}H_{62}IrNO_4P$ $(M\text{-}BAr_F)^+$ requires 940.4046].

[Ir(cod)(L1g)]BAr$_F$: Yield: 64 mg (95%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ=107.1 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 0.98 (d, 3H, CH_3, ^{i}Pr, $^{3}J_{H-H}$ = 6.8 Hz), 1.01 (s, 9H, CH_3, ^{t}Bu), 1.02 (d, 3H, CH_3, ^{i}Pr, $^{3}J_{H-H}$ = 7.2 Hz), 1.47 (s, 9H, CH_3, ^{t}Bu), 1.62-2.46 (m, 16H, CH_2), 2.55 (m, 1H, CH, ^{i}Pr), 2.06-2.51 (m, 4H, CH_2, cod), 2.74-2.90 (m, 4H, CH_2, cod), 2.71 (m, 1H, CH=, cod), 4.01 (m, 1H, CH=, cod), 4.20 (m, 1H, CH-N), 4.40 (pt, 1H, CH-O, J_{H-H} = 9.6 Hz), 4.50 (m, 1H, CH-O), 5.21 (m, 1H, CH=, cod), 5.50 (m, 1H, CH=, cod), 6.90 (d, 1H, CH=, $^{3}J_{H-H}$ = 8.0 Hz), 6.95 (s, 1H, CH=), 7.17 (s, 1H, CH=), 7.33 (m, 1H, CH=), 7.57 (m, 1H, CH=), 7.53 (s, 4H, CH=), 7.72 (s, 9H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=15.1 (CH_3, ^{i}Pr), 18.4 (CH_3, ^{i}Pr), 22.6 (CH_2), 22.7 (CH_2), 22.8 (CH_2), 24.9 (CH_2, cod), 27.1 (CH_2), 27.2 (CH_2), 28.7 (CH_2, cod), 29.2 (CH_2), 29.6 (CH_2, cod), 30.8 (CH_3, ^{t}Bu), 31.1 (CH_3, ^{t}Bu), 33.1 (CH, ^{i}Pr), 34.5 (C, ^{t}Bu), 34.7 (C, ^{t}Bu), 35.5 (d, CH_2, cod, J_{C-P}= 4.5 Hz), 57.1 (CH=, cod), 68.5 (CH_2-O), 69.0 (CH=, cod), 72.4 (CH-N), 105.3 (d, CH=, cod, J_{C-P}= 15.3 Hz), 106.0 (d, CH=, cod, J_{C-P}= 18.4 Hz), 117.4-146.3 (aromatic carbons), 161.6 (q, C-B, BArF, $^{1}J_{C-B}$ =49.7 Hz), 170.4 (C=N). MS HR-ESI [found 940.4049, $C_{48}H_{62}IrNO_4P$ $(M\text{-}BAr_F)^+$ requires 940.4046].

[Ir(cod)(L2a)]BAr$_F$: Yield: 62 mg (94%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ= 108.2 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.03 (d, 3H, CH_3, $^{3}J_{H-H}$= 7.6 Hz), 1.1 (s, 9H, CH_3, ^{t}Bu), 1.35 (s, 9H, CH_3, ^{t}Bu), 1.39 (s, 9H, CH_3, ^{t}Bu), 1.57 (s, 9H, CH_3, ^{t}Bu), 1.77 (b, 2H, CH_2, cod), 1.88-2.10 (b, 3H, CH_2, cod), 2.18 (m, 2H, CH_2), 2.36 (m, 2H, CH_2, cod), 2.56 (m, 1H, CH_2, cod), 3.6 (m, 1H, CH=, cod), 4.21 (m, 1H, CH=, cod), 4.28 (m, 1H, CH-N), 4.38 (dd, 1H, CH-O, $^{2}J_{H-H}$= 9.6Hz, $^{3}J_{H-H}$= 6.4 Hz), 4.57 (pt, 1H, CH-O, J_{H-H}=9.6 Hz), 5.27 (m, 1H, CH=, cod), 5.48 (m, 1H, CH=, cod), 6.10 (d, 1H, CH=, $^{3}J_{H-H}$ = 8.4 Hz), 7.10 (d, 1H, CH=, $^{2}J_{H-H}$ = 1.6 Hz) 7.26 (m, 1H, CH=), 7.39-7.75 (m, 7H, CH=), 7.63 (dd, 1H, CH= $^{3}J_{H-H}$ = 8.0 Hz, $^{4}J_{H-H}$ = 1.6 Hz), 7.70 (s, 9H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 9.3 (CH_3, Et), 25.5 (CH_2, cod), 28.6 (CH_2, cod), 29.9 (CH_2, cod), 30.6 (CH_3, ^{t}Bu), 30.9 (CH_3, ^{t}Bu), 31.1 (CH_2, Et), 31.5(CH_3, ^{t}Bu), 31.6 (CH_3, ^{t}Bu), 34.9 (C, ^{t}Bu), 35.1 (C, ^{t}Bu), 35.4 (C, ^{t}Bu), 35.8 (C, ^{t}Bu), 36.1 (d, CH_2, cod, J_{C-P}= 6.1 Hz), 64.4 (CH=,

cod), 66.5 (CH=, cod), 60.4 (CH-N), 72.4 (CH_2-O), 104.9 (d, CH=, cod, J_{C-P} =19.9 Hz), 106.7 (d, CH=, cod, J_{C-P} =15.3 Hz), 117.6-149.8 (aromatic carbons), 162.1 (q, C-B, BArF, $^1J_{C-B}$ =49.6 Hz), 169.5 (C=N). MS HR-ESI [found 930.4206, $C_{47}H_{64}IrNO_4P$ $(M\text{-}BAr_F)^+$ requires 930.4202].

[Ir(cod)(L3a)]BAr_F: Yield: 65 mg (96%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ=107.0 (s). ^1H NMR (400 MHz, $CDCl_3$): δ= 1.16 (s, 9H, CH_3, ^{t}Bu), 1.31 (s, 9H, CH_3, ^{t}Bu), 1.35 (s, 9H, CH_3, ^{t}Bu), 1.53 (s, 9H, CH_3, ^{t}Bu), 1.3-1.7 (b, 4H, CH_2, cod), 2.0 (b, 2H, CH_2, cod), 2.11 (m, 2H, CH_2, cod), 2.8 (m, 1H, CH=, cod), 3.96 (m, 1H, CH=, cod), 4.47 (dd, 1H, CH-O, $^2J_{H-H}$ = 9.2 Hz, $^3J_{H-H}$ = 7.2 Hz), 4.57 (pt, 1H, CH-O, $^3J_{H-H}$ = 9.6 Hz), 5.30 (m, 1H, CH=, cod), 5.48 (m, 1H, CH=, cod), 5.5 (m, 1H, CH-N), 6.86 (d, 1H, CH=, $^3J_{H-H}$= 8.8 Hz), 7.11 (d, 1H, CH=, $^4J_{H-H}$= 2.4 Hz), 7.21 (d, 1H, CH=, $^4J_{H-H}$= 2.4 Hz), 7.39 (m, 3H, CH=), 7.49 (m, 5H, CH=), 7.59 (m, 2H, CH=), 7.18 (m, 9H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=25.5 (CH_2, cod), 29.3 (CH_2, cod) 29.7 (d, CH_2, cod, J_{C-P}= 6.1 Hz), 31.0 (CH_3, ^{t}Bu), 31.3 (CH_3, ^{t}Bu), 31.5 (CH_3, ^{t}Bu), 31.6 (CH_3, ^{t}Bu), 34.6 (CH_2, cod), 34.8 (C, ^{t}Bu), 34.8 (C, ^{t}Bu), 35.2 (C, ^{t}Bu), 35.5 (C, ^{t}Bu), 58.3 (CH=, cod), 68.7 (CH=, cod), 71.7 (CH-N), 75.7 (CH_2-O), 105.6 (d, CH=, cod, J_{C-P} =11.5 Hz), 105.7 (d, CH=, cod, J_{C-P} =14.5 Hz), 117.6-149.5 (aromatic carbons), 161.6 (q, C-B, BArF, $^1J_{C-B}$ =49.7 Hz), 172.4 (C=N). MS HR-ESI [found 978.4208, $C_{51}H_{64}IrNO_4P$ $(M\text{-}BAr_F)^+$ requires 978.4202].

[Ir(cod)(L3b)]BAr_F: Yield: 63 mg (92%). ^{31}P NMR (161.9 MHz, $CDCl_3$): 120.8 (s). ^1H NMR (400 MHz, $CDCl_3$): δ= 0.07 (s, 9H, CH_3, $SiMe_3$), 0.17 (s, 9H, CH_3, $SiMe_3$), 1.26 (m, 1H, CH_2, cod), 1.57 (m, 1H, CH_2, cod), 1.77 (m, 1H, CH_2, cod), 1.99-2.06 (m, 2H, CH_2, cod), 2.21 (m, 3H, CH_2, cod), 3.53 (m, 1H, CH=, cod), 3.91 (m, 1H, CH=, cod), 4.47, (dd, 1H, CH-O, $^2J_{H-H}$ = 9.6 Hz, $^3J_{H-H}$ = 3.6 Hz), 4.78 (pt, 1H, CH-O, J_{H-H} = 9.2 Hz), 5.29 (m, 1H, CH-N), 5.40 (m, 1H, CH=, cod), 5.54 (m, 1H, CH=, cod), 6.58 (d, 1H, CH=, $^3J_{H-H}$ = 8.4 Hz), 6.75 (d, 1H, CH=, $^3J_{H-H}$ = 8.4 Hz), 7.06-7.34 (m, 7H, CH=), 7.42-7.56 (m, 7H, CH=), 7.66-7.73 (m, 10H, CH=), 7.90 (d, 1H, CH=, $^3J_{H-H}$ = 8.4 Hz), 7.96 (dd, 1H, CH=, $^3J_{H-H}$ = 7.6 Hz, $^4J_{H-H}$ = 1.2 Hz), 8.03 (d, 1H, CH=, $^3J_{H-H}$ = 8.4 Hz), 8.06 (s, 1H, CH=), 8.17 (s, 1H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): -0.7 (CH_3, $SiMe_3$), 0.3 (CH_3, $SiMe_3$), 26.3 (CH_2, cod), 29.7 (CH_2, cod), 30.4 (CH_2, cod), 34.9 (CH_2, cod), 60.6 (CH=, cod), 68.6 (CH=, cod), 72.4 (CH-N), 76.4 (CH_2-O), 106.2 (d, CH=, cod, J_{C-P}= 15.29 Hz), 106.5 (d, CH=, cod, J_{C-P}= 12.2 Hz), 117.4-150.8 (aromatic carbons), 161.7 (q, C-B, BArF, $^1J_{C-B}$ =49.7 Hz), 170.2 (C=N). MS HR-ESI [found 998.2805, $C_{49}H_{52}IrNO_4PSi_2$ $(M\text{-}BAr_F)^+$ requires 998.2802].

[Ir(cod)(L3c)]BAr_F: Yield: 65 mg (95%). ^{31}P NMR (161.9 MHz, $CDCl_3$): 112.9 (s). ^1H NMR (400 MHz, $CDCl_3$): δ= 0.24 (s, 9H, CH_3, $SiMe_3$), 0.49 (s, 9H, CH_3, $SiMe_3$), 1.46 (m, 1H, CH_2, cod), 1.57-1.71 (m, 4H, CH_2, cod), 1.80 (m, 1H, CH_2, cod), 2.15 (m, 2H, CH_2, cod), 2.73 (m, 1H, CH=, cod), 3.93 (m, 1H, CH=, cod), 4.51, (dd, 1H, CH-O, $^2J_{H-H}$ = 9.2 Hz, $^3J_{H-H}$ = 7.2 Hz), 4.96 (pt, 1H, CH-O, J_{H-H} = 9.2 Hz), 5.33 (m, 1H, CH=,cod),

5.55 (m, 1H, CH-N), 5.56 (m, 1H, CH=, cod), 6.81 (d, 1H, CH=, $^3J_{H-H}$ = 8.4 Hz), 6.88 (d, 1H, CH=, $^3J_{H-H}$ = 8.8 Hz), 7.03 (d, 1H, CH=, $^3J_{H-H}$ = 8.4 Hz) 7.23 (m, 3H, CH=), 7.36-7.59 (m, 12H, CH=), 7.72 (m, 8H, CH=), 7.79 (d, 1H, CH=, $^3J_{H-H}$ = 5.2 Hz), 7.93 (d, 1H, CH=, $^3J_{H-H}$ = 8Hz Hz), 8.00 (d, 1H, CH=, $^3J_{H-H}$ = 8.0 Hz), 8.06 (s, 1H, CH=), 8.21 (s, 1H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$= 0.1 (CH_3, $SiMe_3$), 0.4 (CH_3, $SiMe_3$), 26.1 (CH_2, cod), 29.7 (CH_2, cod), 30.3 (CH_2, cod), 34.1 (CH_2, cod), 57.6 (CH=, cod), 69.2 (CH=, cod), 72.1 (CH-N), 75.9 (CH_2-O), 105.9 (CH=, cod), 106.1 (CH=, cod), 117.4-150.6 (aromatic carbons), 161.7 (q, C-B, BArF, $^1J_{C-B}$ =49.7 Hz), 173.0 (C=N). MS HR-ESI [found 998.2807, $C_{49}H_{52}IrNO_4PSi_2$ $(M\text{-}BAr_F)^+$ requires 998.2802].

[Ir(cod)(L4a)]BAr$_F$: Yield: 64 mg (95%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ=107.4 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.02 (s, 9H, CH_3, ^{t}Bu), 1.15 (s, 9H, CH_3, ^{t}Bu), 1.35 (s, 9H, CH_3, ^{t}Bu), 1.38 (s, 9H, CH_3, ^{t}Bu,) 1.55 (s, 9H, CH_3, ^{t}Bu), 1.7 (m, 1H, CH_2, cod), 1.8 (m, 2H, CH_2, cod), 2.0 (m, 1H, CH_2, cod), 2.17 (m, 1H, CH_2, cod), 2.3 (m, 2H, CH_2, cod), 2.5 (m, 1H, CH_2, cod), 3.3 (m, 1H, CH=, cod), 4.1 (dd, 1H, CH-N, $^2J_{H-H}$ = 9.2 Hz, $^3J_{H-H}$ = 3.2 Hz), 4.18 (m, 1H, CH=, cod), 4.38 (pt, 1H, CH-O, J_{H-H} =9.6 Hz), 4.6 (dd, 1H, CH-O, $^2J_{H-H}$ = 10Hz, $^3J_{H-H}$ = 3.6 Hz), 5.25 (m, 1H, CH=, cod), 5.49 (m, 1H, CH=, cod), 6.23 (d, 1H, CH=, $^3J_{H-H}$= 7.2 Hz), 7.31 (t, 1H, CH=, $^3J_{H-H}$= 8 Hz), 7.39 (d, 3H, CH=, $^3J_{H-H}$= 6.4 Hz), 7.45 (t, 1H, CH=, $^3J_{H-H}$= 7.2 Hz), 7.52 (m, 5H, CH=), 7.71 (s, 9H, CH=) . ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=24.4 (CH_2, cod), 25.9 (CH_3, ^{t}Bu), 28.1 (CH_2, cod), 30.0 (CH_3, ^{t}Bu), 30.9 (CH_3, ^{t}Bu), 31.2 (CH_3, ^{t}Bu), 31.5 (CH_3, ^{t}Bu), 31.7 (d, CH_2, cod, J_{C-P}= 1.6Hz), 34.3 (C, ^{t}Bu), 34.7 (C, ^{t}Bu), 34.9 (C, ^{t}Bu), 35.0 (C, ^{t}Bu), 35.7(C, ^{t}Bu), 36.4 (d, CH_2, cod, J_{C-P}= 6.0 Hz), 61.6 (CH=, cod), 66.0 (CH=, cod), 69.1 (CH_2-O), 77.5 (CH-N), 104.4 (d, CH=, cod, J_{C-P} =19.9 Hz), 106.6 (d, CH=, cod, J_{C-P} =13.6 Hz), 117.4-149.8 (aromatic carbons), 161.5 (q, C-B, BArF, $^1J_{C-B}$ =49.7 Hz), 168.9 (C=N). MS HR-ESI [found 958.4521, $C_{49}H_{68}IrNO_4P$ $(M\text{-}BAr_F)^+$ requires 958.4515].

[Ir(cod)(L4b)]BAr$_F$: Yield: 63 mg (92%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ=116.9 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 0.0 (s, 9H, CH_3, $SiMe_3$), 0.61 (s, 9H, CH_3, $SiMe_3$), 1.08 (s, 9H, CH_3, ^{t}Bu), 1.58-1.79 (b, 2H, CH_2, cod), 2.0 (m, 1H, CH_2, cod), 2.13 (m, 1H, CH_2, cod), 2.30 (m, 2H, CH_2, cod), 2.58 (m, 2H, CH_2, cod), 3.9 (m, 1H, CH=, cod), 4.0 (m, 1H, CH-N), 4.1 (m, 1H, CH=, cod), 4.38 (pt, 1H, CH-O, J_{H-H} =10 Hz), 4.62 (dd, 1H, CH-O, $^2J_{H-H}$ = 9.6 Hz, $^3J_{H-H}$ = 3.6 Hz), 5.48 (m, 2H, CH=, cod), 6.44 (d, 1H, CH=, $^3J_{H-H}$= 8.8 Hz), 7.09 (t, 2H, CH=, $^3J_{H-H}$= 8.8 Hz), 7.30 (t, 2H, CH=, $^3J_{H-H}$= 7.6 Hz), 7.40 (m, 2H, CH=), 7.52 (m, 5H, CH=), 7.71 (s, 9H, CH=), 7.80 (dd, 1H, CH=, $^3J_{H-H}$= 8.0 Hz, $^2J_{H-H}$= 1.6 Hz), 7.89 (d, 1H, CH=, $^3J_{H-H}$= 7.6 Hz), 8.03 (d, 1H, CH=, $^3J_{H-H}$= 8.4 Hz), 8.07 (s, 1H, CH=), 8.13 (s, 1H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= -1.5 (CH_3, $SiMe_3$), 0.6 (CH_3, $SiMe_3$), 25.0 (CH_2, cod), 26.4 (CH_3, ^{t}Bu), 28.7 (CH_2, cod), 31.4 (CH_2, cod), 34.0 (C, ^{t}Bu), 36.0 (d, CH_2, cod, J_{C-P}= 6.8Hz), 60.7 (CH=, cod), 67.9 (CH=, cod), 69.0 (CH2-O), 78.5 (CH-N), 106.5 (d, CH=, cod, J_{C-P} =20.6 Hz), 108.4 (d, CH=, cod, J_{C-P} =15.3 Hz), 117.4-152.8 (aromatic carbons), 161.5 (q, C-B, BArF, $^1J_{C-B}$ =49.7 Hz),

168.3 (C=N). MS HR-ESI [found 978.3121, $C_{47}H_{56}IrNO_4PSi_2$ $(M\text{-}BAr_F)^+$ requires 978.3115].

[Ir(cod)(L4c)]BAr$_F$: Yield: 64 mg (94%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ=113.8 (s). ^1H NMR (400 MHz, $CDCl_3$): δ= 0.0 (s, 9H, CH_3, $SiMe_3$), 0.53 (s, 9H, CH_3, $SiMe_3$), 1.13 (s, 9H, CH_3, ^{t}Bu), 1.58 (m, 1H, CH_2, cod), 1.7 (m, 2H, CH_2, cod), 1.95 (m, 1H, CH_2, cod), 2.23 (m, 2H, CH_2, cod), 2.32 (m, 2H, CH_2, cod), 2.78 (m, 1H, CH=, cod), 3.89 (m, 1H, CH=, cod), 4.1 (m, 1H, CH-N), 4.4 (pt, 1H, CH-O, $^3J_{H\text{-}H}$ = 9.2 Hz), 4.67 (dd, 1H, CH-O, $^2J_{H\text{-}H}$ = 10.4 Hz, $^3J_{H\text{-}H}$ = 2.0 Hz), 5.43 (m, 1H, CH=, cod), 5.58 (m, 1H, CH=, cod), 6.70 (d, 1H, CH=, $^3J_{H\text{-}H}$= 8.8 Hz), 6.87 (d, 1H, CH=, $^3J_{H\text{-}H}$= 8.0 Hz), 7.03 (d, 1H, CH=, $^3J_{H\text{-}H}$= 8.0 Hz), 7.19 (t, 1H, CH=, $^3J_{H\text{-}H}$= 7.6 Hz), 7.29 (m, 1H, CH=), 7.37 (t, 1H, CH=, $^3J_{H\text{-}H}$= 7.6 Hz), 7.47-7.59 (m, 7H, CH=), 7.71 (s, 8H, CH=), 7.87-7.98 (m, 4H, CH=), 8.17 (s, 1H, CH=).^{13}C NMR (100.6 MHz, $CDCl_3$): δ=0.0 (CH_3, $SiMe_3$), 0.1 (CH_3, $SiMe_3$), 24.5 (CH_2, cod), 25.9 (CH_3, ^{t}Bu), 28.8 (CH_2, cod), 29.7 (C, tBu), 30.9 (CH_2, cod), 36.7 (CH_2, cod), 56.3 (CH=, cod), 66.6 (CH=, cod), 69.1 (CH_2-O), 76.5 (CH-N), 106.9 (d, CH=, cod, $J_{C\text{-}P}$ =15.3 Hz), 108.4 (d, CH=, cod, $J_{C\text{-}P}$ =18.4 Hz), 117.4-151.0 (aromatic carbons), 161.5 (q, C-B, BArF, $^1J_{C\text{-}B}$ =49.7 Hz), 170.1 (C=N). MS HR-ESI [found 978.3119, $C_{47}H_{56}IrNO_4PSi_2$ $(M\text{-}BAr_F)^+$ requires 978.3115].

[Ir(cod)(L5a)]BAr$_F$: Yield: 65 mg (94%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ=100.9 (s). ^1H NMR (400 MHz, $CDCl_3$): δ= 1.28 (s, 9H, CH_3, ^{t}Bu), 1.39 (s, 9H, CH_3, ^{t}Bu), 1.48 (s, 9H, CH_3, ^{t}Bu), 1.63 (s, 9H, CH_3, ^{t}Bu), 1.8-2.05 (b, 4H, CH_2, cod), 2.17-2.5 (b, 4H, CH_2, cod), 3.2 (m, 1H, CH=, cod), 3.66 (d, 1H, CH_2, $^2J_{H\text{-}H}$ = 12Hz), 4.16 (m, 1H, CH-O), 4.45 (m, 1H, CH=, cod), 4.7 (d, 1H, CH2, $^2J_{H\text{-}H}$ =11.2 Hz), 4.84 (m, 1H, CH-O), 5.07 (b, 1H, CH=, cod), 5.27 (m, 1H, CH-N), 5.9 (m, 1H, CH=, cod), 6.98-7.55 (m, 17H, CH=), 7.72 (m, 8H, CH=).^{13}C NMR (100.6 MHz, $CDCl_3$): δ=22.6 (CH_2, cod), 25.5 (CH_2, cod), 29.3 (CH2, cod) 29.7 (d, CH_2, cod, $_{JC\text{-}P}$= 6.1 Hz), 31.0 (CH_3, ^{t}Bu), 31.3 (CH_3, ^{t}Bu), 31.5 (CH_3, ^{t}Bu), 31.6 (CH_3, ^{t}Bu), 34.6 (CH_2), 34.8 (C, ^{t}Bu), 34.8 (C, ^{t}Bu), 35.2 (C, ^{t}Bu), 35.5 (C, ^{t}Bu), 58.3 (CH=, cod), 68.7 (CH=, cod), 71.7 (CH-N), 75.7 (CH_2-O), 105.6 (d, CH=, cod, $J_{C\text{-}P}$ =11.5 Hz), 105.7 (d, CH=, cod, $J_{C\text{-}P}$ =14.5 Hz), 117.6-149.5 (aromatic carbons), 161.6 (q, C-B, BArF, $^1J_{C\text{-}B}$ =49.7 Hz), 172.4 (C=N). MS HR-ESI [found 992.4363, $C_{52}H_{66}IrNO_4P$ $(M\text{-}BAr_F)^+$ requires 992.4359].

[Ir(cod)(L5b)]BAr$_F$: Yield: 63 mg (91%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ=104.1 (s). ^1H NMR (400 MHz, $CDCl_3$): δ= 0.3 (s, 9H, CH_3, $SiMe_3$), 0.61 (s, 9H, CH_3, $SiMe_3$), 1.30-1.5 (b, 2H, CH_2, cod), 1.74 (m, 1H, CH_2, cod), 1.9 (m, 2H, CH_2, cod), 2.20 (m, 1H, CH_2, cod), 2.3 (m, 2H, CH_2, cod), 3.3 (m, 1H, CH=, cod), 3.9 (d, 1H, CH_2, $^2J_{H\text{-}H}$ = 15.6 Hz), 4.4 (m, 1H, CH=, cod), 4.44 (m, 1H, CH-O), 4.6 (m, 1H, CH=, cod), 4.66 (m, 1H, CH_2), 4.74 (pt, 1H, CH-O, $J_{H\text{-}H}$ = 8.8 Hz), 5.2 (m, 1H, CH-N), 5.5 (m, 1H, CH=, cod), 6.68 (t, 1H, CH=, $^3J_{H\text{-}H}$ = 8.4 Hz), 6.76 (d, 1H, CH=, $^3J_{H\text{-}H}$ = 8.4 Hz), 7.00 (m, 3H, CH=), 7.34 (m, 2H, CH=), 7.39-7.54 (m, 10H, CH=), 7.71 (s, 10H, CH=), 7.89 (d, 1H, CH=, $^3J_{H\text{-}H}$= 8.0 Hz), 7.99 (s, 1H, CH=), 8.03 (d, 1H, CH=, $^3J_{H\text{-}H}$= 8.0 Hz), 8.26 (s, 1H,

CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 0.3 (CH_3, $SiMe_3$), 0.4 (CH_3, $SiMe_3$), 26.0 (CH_2, cod), 29.6 (CH_2, cod), 31.7 (CH_2, cod), 35.4 (CH_2), 35.7 (d, CH_2, cod, J_{C-P}= 4.5 Hz), 59.9 (CH=, cod), 70.1 (d, CH=, cod, J_{C-P}= 1.5 Hz), 71.5 (CH-N), 78.9 (CH_2-O), 105.9 (d, CH=, cod, J_{C-P} =18.3 Hz), 106.2 (d, CH=, cod, J_{C-P} =15.3 Hz), 117.4-151.3 (aromatic carbons), 161.8 (q, C-B, BArF, $^1J_{C-B}$ =49.7 Hz), 176.8 (d, C=N, JC-P= 4.5 Hz). MS HR-ESI [found 1012.2961, $C_{50}H_{54}IrNO_4PSi_2$ $(M\text{-}BAr_F)^+$ requires 1012.2958].

[Ir(cod)(L5c)]BAr$_F$: Yield: 67 mg (96%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ=102.2 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 0.48 (s, 9H, CH_3, $SiMe_3$), 0.62 (s, 9H, CH_3, $SiMe_3$), 1.48 (b, 2H, CH_2, cod), 1.65 (m, 2H, CH_2, cod), 1.85 (m, 2H, CH_2, cod), 2.08 (m, 1H, CH_2, cod), 2.4 (m, 1H, CH_2, cod), 2.6 (m, 1H, CH=, cod), 3.6 (d, 1H, CH_2, $^2J_{H-H}$ = 14.8 Hz), 4.12 (m, 1H, CH=, cod), 4.15 (m, 1H, CH-O), 4.69 (d, 1H, CH_2, $^2J_{H-H}$ = 14.4 Hz), 4.85 (pt, 1H, CH-O, J_{H-H} = 10 Hz), 5.2 (m, 1H, CH=, cod), 5.3 (m, 1H, CH-N), 5.7 (m, 1H, CH=, cod), 5.84 (d, 1H, CH=, $^3J_{H-H}$ =8.0 Hz), 6.72 (d, 1H, CH=, $^3J_{H-H}$ =8.8 Hz), 6.90 (t, 1H, CH=, $^3J_{H-H}$ =8.4 Hz), 6.98 (d, 1H, CH=, $^3J_{H-H}$ =8.8 Hz), 7.04 (t, 1H, CH=, $^3J_{H-H}$ =7.6 Hz), 7.17 (t, 1H, CH=, $^3J_{H-H}$ =7.6 Hz), 7.40 (m, 4H, CH=), 7.45-7.82 (m, 9H, CH=), 7.71 (s, 8H, CH=), 7.91 (d, 1H, CH=, $^3J_{H-H}$ =8.0 Hz), 8.00 (d, 1H, CH=, $^3J_{H-H}$ =8.0 Hz), 8.08 (s, 1H, CH=), 8.29 (s, 1H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 0.6 (CH_3, $SiMe_3$), 0.8 (CH_3, $SiMe_3$), 25.2 (CH_2, cod), 29.7 (CH_2, cod), 30.3 (CH_2, cod), 34.1 (CH_2, cod), 35.4 (CH_2), 57.6 (CH=, cod), 69.5 (CH=, cod), 70.9 (CH-N), 77.2 (CH_2-O), 103.5 (d, CH=, cod, J_{C-P} =19.8 Hz), 106.4 (d, CH=, cod, J_{C-P} =15.3 Hz), 117.4-151.8 (aromatic carbons), 161.8 (q, C-B, BArF, $^1J_{C-B}$ =49.7 Hz), 174.5 (C=N). MS HR-ESI [found 1012.2962, $C_{50}H_{54}IrNO_4PSi_2$ $(M\text{-}BAr_F)^+$ requires 1012.2958].

[Ir(cod)(L6a)]BAr$_F$: Yield: 63 mg (93%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ=101.1 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 0.79 (d, 3H, CH_3, ^{i}Pr, $^3J_{H-H}$ = 6.0 Hz), 1.00 (d, 3H, CH_3, ^{i}Pr, $^3J_{H-H}$ = 6.8 Hz), 1.30 (s, 9H, CH_3, ^{t}Bu), 1.39 (s, 9H, CH_3, ^{t}Bu), 1.44 (s, 9H, CH_3, ^{t}Bu), 1.57 (s, 9H, CH_3, ^{t}Bu), 2.05-2.5 (b, 8H, CH_2, cod), 2.32 (m, 1H, CH, ^{i}Pr), 3.5 (m, 1H, CH=, cod), 3.60 (d, 1H, CH_2, $^2J_{H-H}$ = 14.8Hz), 4.07 (m, 1H, CH-N), 4.31 (m, 2H, CH_2-O), 4.62 (d, 1H, CH_2, $^2J_{H-H}$ =14.4 Hz), 4.7 (m, 1H, CH=, cod), 5.12 (m, 1H, CH=, cod), 5.07 (b, 1H, CH=, cod), 5.42 (d, 1H, CH=, $^3J_{H-H}$ = 8.0 Hz), 5.7 (m, 1H, CH=, cod), 6.90 (t, 1H, CH=, $^3J_{H-H}$ = 8 Hz), 7.00 (t, 1H, CH=, $^3J_{H-H}$ = 7.6 Hz), 7.10 (d, 1H, CH=, $^3J_{H-H}$ = 8.4Hz), 7.16 (d, 1H, CH=, 3JH-H= 6.8Hz), 7.4 (m, 1H, CH=), 7.53 (s, 5H, CH=), 7.64 (m, 1H, CH=), 7.72 (s, 8H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=15.0 (CH_3, ^{i}Pr), 19.8 (CH_3, ^{i}Pr), 25.3 (CH_2, cod), 29.3 (CH_2, cod), 30.9 (CH_3, ^{t}Bu), 31.2 (CH_3, ^{t}Bu), 31.3 (CH_3, ^{t}Bu), 31.7 (CH_3, ^{t}Bu), 31.8 (CH_2, cod), 32.9 (CH, ^{i}Pr), 34.6 (C, ^{t}Bu), 34.9 (C, ^{t}Bu), 35.0 (CH_2), 35.2 (C, ^{t}Bu), 35.5 (C, ^{t}Bu), 36.0 (CH_2, cod), 58.8 (CH=, cod), 69.5 (CH=, cod), 69.6 (CH_2-O), 71.2(CH-N), 102.4 (d, CH=, cod, J_{C-P} =19.9 Hz), 106.6 (d, CH=, cod, J_{C-P} =14.5 Hz), 117.4-149.5 (aromatic carbons), 161.7 (q, C-B, BArF, $^1J_{C-B}$ =49.7 Hz), 171.9 (C=N). MS HR-ESI [found 958.4522, $C_{49}H_{68}IrNO_4P$ $(M\text{-}BAr_F)^+$ requires 958.4515].

[Ir(cod)(L6b)]BAr$_F$: Yield: 65 mg (95%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ=105.2 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 0.31 (s, 9H, CH_3, $SiMe_3$), 0.55 (s, 9H, CH_3, $SiMe_3$), 0.82 (d, 3H, CH_3, ^{i}Pr, $^3J_{H-H}$ = 6.4 Hz), 0.92 (d, 3H, CH_3, ^{i}Pr, $^3J_{H-H}$ = 7.2 Hz), 1.51 (m, 1H, CH_2, cod), 1.72 (m, 1H, CH_2, cod), 1.82 (m, 1H, CH, ^{i}Pr), 2.08 (m, 2H, CH_2, cod), 2.49 (m, 4H, CH_2, cod), 3.44 (m, 1H, CH=, cod), 3.74 (d, 1H, CH_2, $^2J_{H-H}$ = 16 Hz), 4.11 (m, 1H, CH-N), 4.29 (pt, 1H, CH-O, J_{H-H} = 8.4 Hz), 4.4 (m, 1H, CH=, cod), 4.47 (d, 1H, CH_2, $^2J_{H-H}$ =15.6 Hz), 4.49 (m, 1H, CH-O), 4.97 (d, 1H, CH=, $^3J_{H-H}$ = 8.4 Hz), 5.46 (m, 1H, CH=, cod), 5.8 (b, 1H, CH=, cod), 6.61 (t, 1H, CH=, $^3J_{H-H}$ = 8.0 Hz), 6.76 (d, 1H, CH=, $^3J_{H-H}$ = 8.8 Hz), 6.95 (t, 1H, CH=, $^3J_{H-H}$ = 7.6 Hz), 7.04 (d, 2H, CH=, $^3J_{H-H}$ = 8.4 Hz), 7.16 (d, 1H, CH=, $^3J_{H-H}$ = 7.6 Hz), 7.24 (m, 1H, CH=), 7.48 (t, 1H, CH=, $^3J_{H-H}$ = 7.6 Hz), 7.52 (s, 6H, CH=), 7.71 (s, 8H, CH=), 7.90 (d, 1H, CH=, $^3J_{H-H}$ = 8.4 Hz), 8.00 (s, 1H, CH=), 8.03 (d, 1H, CH=, $^3J_{H-H}$ = 8.4 Hz), 8.25 (s, 1H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=0.0 (CH_3, $SiMe_3$), 0.1 (CH_3, $SiMe_3$), 13.8 (CH_3, ^{i}Pr), 18.6 (CH_3, ^{i}Pr), 26.4 (CH_2, cod), 29.7 (CH_2, cod), 30.6 (CH, ^{i}Pr), 31.5 (CH_2, cod), 35.1 (CH_2), 35.4 (CH_2, cod), 60.5 (CH=, cod), 68.7 (CH=, cod), 71.2 (CH_2-O), 72.7 (CH-N), 103.0 (d, CH=, cod, J_{C-P} =15.9 Hz), 105.8 (d, CH=, cod, J_{C-P} =18.3 Hz), 117.4-151.0 (aromatic carbons), 161.6 (q, C-B, BArF, $^1J_{C-B}$ =50.5 Hz), 178.0 (C=N). MS HR-ESI [found 978.3119, $C_{47}H_{56}IrNO_4PSi_2$ (M-BAr$_F$)$^+$ requires 978.3115].

[Ir(cod)(L6c)]BAr$_F$: Yield: 63 mg (92%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ=103.3 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 0.46 (s, 9H, CH_3, $SiMe_3$), 0.58 (s, 9H, CH_3, $SiMe_3$), 0.80 (d, 3H, CH_3, ^{i}Pr, $^3J_{H-H}$ = 6.4 Hz), 0.97 (d, 3H, CH_3, ^{i}Pr, $^3J_{H-H}$ = 7.2 Hz), 1.52 (m, 1H, CH_2, cod), 1.67 (m, 1H, CH_2, cod), 1.95-2.07 (m, 2H, CH_2, cod), 2.27 (m, 2H, CH_2, cod), 2.34 (m, 1H, CH, ^{i}Pr), 2.49 (m, 2H, CH_2, cod), 3.09 (m, 1H, CH=, cod), 3.57 (d, 1H, CH_2, $^2J_{H-H}$ = 14.4 Hz), 4.03 (m, 1H, CH-N), 4.30 (m, 2H, CH_2-O), 4.31 (m, 1H, CH=, cod), 4.57 (d, 1H, CH_2, $^2J_{H-H}$ = 14.4 Hz), 5.33 (m, 1H, CH=, cod), 5.58 (m, 1H, CH=, cod), 5.59 (m, 1H, CH=), 6.73 (d, 1H, CH=, $^3J_{H-H}$ = 8.8 Hz), 6.78 (t, 1H, CH=, $^3J_{H-H}$ = 7.2 Hz), 7.00 (m, 2H, CH=), 7.16 (m, 2H, CH=), 7.47 (m, 1H, CH=), 7.53 (s, 5H, CH=), 7.71 (s, 9H, CH=), 7.91 (d, 1H, CH=, $^3J_{H-H}$ = 7.6 Hz), 8.00 (d, 1H, CH=, $^3J_{H-H}$ = 7.6 Hz), 8.06 (s, 1H, CH=), 8.27 (s, 1H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=0.6 (CH_3, $SiMe_3$), 0.7 (CH_3, $SiMe_3$), 14.9 (CH_3, ^{i}Pr), 19.7 (CH_3, ^{i}Pr), 25.7 (CH_2, cod), 29.7 (CH_2, cod), 30.2 (CH, ^{i}Pr), 32.5 (CH_2, cod), 35.3 (CH_2), 35.6 (CH_2, cod), 59.3 (CH=, cod), 69.1 (CH=, cod), 69.5 (CH_2-O), 70.4 (CH-N), 105.8 (d, CH=, cod, J_{C-P} =9.15 Hz), 106.0 (d, CH=, cod, J_{C-P} =11.46 Hz), 117.4-151.2 (aromatic carbons), 161.7 (q, C-B, BArF, $^1J_{C-B}$ =48.9 Hz), 172.0 (C=N). MS HR-ESI [found 978.3122, $C_{47}H_{56}IrNO_4PSi_2$ (M-BAr$_F$)$^+$ requires 978.3115].

[Ir(cod)(L7a)]BAr$_F$: Yield: 62 mg (91%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ=100.2 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.09 (s, 9H, CH_3, ^{t}Bu), 1.30 (s, 9H, CH_3, ^{t}Bu), 1.38 (s, 9H, CH_3, ^{t}Bu), 1.44 (s, 9H, CH_3, ^{t}Bu), 1.57 (s, 9H, CH_3, ^{t}Bu), 2.05 (m, 2H, CH_2, cod), 2.06 (m, 2H, CH_2, cod), 2.27 (m, 2H, CH_2, cod), 2.39 (m, 2H, CH_2, cod), 3.46 (m, 1H,

CH=, cod), 3.61 (d, 1H, CH_2, $^2J_{H-H}$ = 14.8 Hz), 3.97 (m, 1H, CH-N), 4.31 (pt, 1H, CH-O, J_{H-H} = 10.4 Hz), 4.31 (m, 1H, CH-O), 4.72 (m, 1H, CH=, cod), 4.88 (d, 1H, CH_2, $^2J_{H-H}$ =14.4 Hz), 5.03 (m, 1H, CH=, cod), 5.57 (d, 1H, CH=, $^3J_{H-H}$ = 7.6 Hz), 5.7 (m, 1H, CH=, cod), 6.92-7.044 (m, 3H, CH=), 7.16 (m, 2H, CH=), 7.26 (m, 1H, CH=), 7.41 (m, 1H, CH=), 7.53 (s, 3H, CH=), 7.64 (m, 1H, CH=), 7.72 (s, 8H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=24.8 (CH_2, cod), 26.0 (CH_3, ^{t}Bu), 29.5 (CH_2, cod), 30.9 (CH_3, ^{t}Bu), 31.2 (CH_3, ^{t}Bu), 31.3 (CH_3, ^{t}Bu), 31.8 (CH_3, ^{t}Bu), 32.5 (CH_2, cod), 34.5 (C, ^{t}Bu), 34.6 (C, ^{t}Bu), 34.9 (C, ^{t}Bu), 35.1 (C, ^{t}Bu), 35.8 (CH_2), 36.0 (CH_2, cod), 57.8 (CH=, cod), 68.8 (CH=, cod), 71.1 (CH_2-O), 75.7 (CH-N), 99.3 (d, CH=, cod, J_{C-P} =21.4 Hz), 106.7 (d, CH=, cod, J_{C-P} =14.5 Hz), 117.5-151.3 (aromatic carbons), 161.6 (q, C-B, BArF, $^1J_{C-B}$ =49.7 Hz), 171.8 (C=N). MS HR-ESI [found 972.4675, $C_{50}H_{70}IrNO_4P$ (M-BAr_F)$^+$ requires 972.4672].

[Ir(cod)(L7c)]BAr_F: Yield: 66 mg (96%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ=101.7 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 0.47 (s, 9H, CH_3, $SiMe_3$), 0.58 (s, 9H, CH_3, $SiMe_3$), 1.05 (s, 9H, CH_3, ^{t}Bu), 1.44 (m, 1H, CH_2, cod), 1.58 (m, 1H, CH_2, cod), 1.92 (m, 1H, CH_2, cod), 2.06 (m, 1H, CH_2, cod), 2.17 (m, 1H, CH_2, cod), 2.31 (m, 1H, CH_2, cod), 2.38 (m, 1H, CH_2, cod), 2.48 (m, 1H, CH_2, cod), 2.89 (m, 1H, CH=, cod), 3.58 (d, 1H, CH_2, $^2J_{H-H}$ = 14.4 Hz), 3.87 (m, 1H, CH-N), 4.29 (m, 1H, CH-O), 4.30 (m, 1H, CH=, cod), 4.63 (m, 1H, CH-O), 4.84 (d, 1H, CH_2, $^2J_{H-H}$ = 14.4 Hz), 5.34 (m, 1H, CH=, cod), 5.58 (m, 1H, CH=, cod), 5.90 (d, 1H, CH=, $^3J_{H-H}$ = 8.0Hz), 6.68 (d, 1H, CH=, $^3J_{H-H}$ = 8.4 Hz), 6.89-7.05 (m, 3H, CH=), 7.17 (m, 2H, CH=), 7.46 (m, 2H, CH=), 7.53 (s, 4H, CH=), 7.72 (s, 9H, CH=), 7.92 (d, 1H, CH=, $^3J_{H-H}$ = 8.0 Hz), 7.99 (d, 1H, CH=, $^3J_{H-H}$ = 8.4 Hz), 8.08 (s, 1H, CH=), 8.26 (s, 1H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=0.4 (CH_3, $SiMe_3$), 0.7 (CH_3, $SiMe_3$), 25.1 (CH_2, cod), 26.1 (CH_3, ^{t}Bu), 29.7 (CH_2, cod), 30.3 (d, CH_2, cod, J_{C-P}= 19.1 Hz), 34.6 (C, ^{t}Bu), 35.6 (d, CH_2, cod, J_{C-P}= 5.3 Hz), 36.1 (CH_2), 57.6 (CH=, cod), 68.1 (CH=, cod), 71.2 (CH_2-O), 74.9 (CH-N), 104.3 (d, CH=, cod, J_{C-P} =18.0 Hz), 106.8 (d, CH=, cod, J_{C-P} =15.3 Hz), 117.4-151.1 (aromatic carbons), 161.7 (q, C-B, BArF, $^1J_{C-B}$ =49.7 Hz), 171.8 (C=N). MS HR-ESI [found 992.3274, $C_{48}H_{58}IrNO_4PSi_2$ (M-BAr_F)$^+$ requires 992.3271].

5.2.4.4. 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-S54**[9] as well as for

cyclic β-enamides **S32**-**S38**[22] were determined using the conditions previously described.

5.2.5 References

1 a) Brown, J. M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds; Springer-Verlag: Berlin, **1999**; Vol. I, pp 121. b) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, **1994**. c) Wang, D.-S.; Chen, Q.-A.; Lu, S.-M.; Zhou, Y.-G. *Chem. Rev.* **2012**, *112*, 2557. d) Knowles, W. S.; Noyori, R. *Acc. Chem. Res*. **2007**, *40*, 1238.

2 a) Genêt, J. P. In *Modern Reduction Methods*; Andersson, P. G., Munslow, I. J., Eds.; Wiley-VCH: Weinheim, **2008**. b) Chi, Y., Tang, W., Zhang, X. In *Modern Rhodium-Catalyzed Organic Reactions*; Evans, P. A. Eds.; Wiley-VCH: Weinheim, **2005**. c) Kitamura, M., Noyori, R. in *Ruthenium in Organic Synthesis*; Murahashi, S.-I., Ed.; Wiley-VCH: Weinheim, **2004**. d) Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029. e) Johnson, N. B.; Lennon, I. C.; Moran, P. H.; Ramsden, J. A. *Acc. Chem. Res.* **2007**, *40*, 1291. f) Weiner, B.; Szymanski, W.; Janssen, D. B.; Minnaard, A. J.; Feringa, B. L. *Chem. Soc. Rev.* **2010**, *39*, 1656.

3 For reviews, see: a) Cui, X.; Burgess, K. *Chem. Rev.* **2005**, *105*, 3272. b) Källström, K.; Munslow, I.; Andersson, P. G. *Chem. Eur. J.* **2006**, *12*, 3194. c) Roseblade, S. J.; Pfaltz, A. *Acc. Chem. Res.* **2007**, *40*, 1402. d) Church, T. L.; Andersson, P. G. *Coord. Chem. Rev.* **2008**, *252*, 513. e) Pàmies, O.; Andersson, P. G.; Diéguez, M. *Chem. Eur. J.* **2010**, *16*, 14232. f) Woodmansee, D. H.; Pfaltz, A. *Chem. Commun.* **2011**, *47*, 7912. g) Zhu, Y.; Burgess, K. *Acc. Chem. Res.* **2012**, *45*, 1623. h) Verendel, J. J.; Pàmies, O.; Diéguez, M.; Andersson, P. G. *Chem. Rev.* **2014**, *114*, 2130.

4 a) Crabtree, R. H.; Felkin, H.; Morris, G. E. *J. Organomet. Chem.* **1977**, *141*, 205; b) Crabtree, R. H. *Acc. Chem. Res.* **1979**, *12*, 331.

5 Lightfoot, A.; Schnider, P.; Pfaltz, A. *Angew. Chem. Int. Ed.* **1998**, *37*, 2897.

6 See, for instance: a) Blankenstein, J.; Pfaltz, A. *Angew. Chem. Int. Ed.* **2001**, *40*, 4445. b) Hou, D.-R.; Reibenspies, J. H.; Colacot, T. J.; Burgess, K. *Chem. Eur. J.* **2001**, *7*, 5391. c) Menges, F.; Pfaltz, A. *Adv. Synth. Catal.* **2002**, *344*, 40. d) Perry, M. C.; Cui, X.; Powell, M. T.; Hou, D.-R.; Reibenspies, J. H.; Burgess, K. *J. Am. Chem. Soc.* **2003**, *125*, 113. e) Tang, W.; Wang, W.; Zhang, X. *Angew. Chem. Int. Ed.* **2003**, *42*, 943. f) Liu, D.; Tang, W.; Zhang, X. *Org. Lett.* **2004**, *6*, 513. g) McIntyre, S.; Hörmann, E.; Menges, F.; Smidt, S. P.; Pfaltz, A. *Adv. Synth. Catal.* **2005**, *347*, 282. h) Trifonova, A.; Diesen, J. S.; Andersson, P. G. *Chem. Eur. J.* **2006**, *12*, 2318. i) Lu, S.-M.; Bolm, C. *Angew. Chem. Int. Ed.* **2008**, *47*, 8920. j) Engman, M.; Cheruku, P.; Tolstoy, P.; Bergquist, J.; Völker, S. F.; Andersson, P. G. *Adv. Synth. Catal.* **2009**, *351*, 375. k) Zhao, J.; Burgess, K. *J. Am. Chem. Soc.* **2009**, *131*, 13236. l) Lu, W.-J.; Chen, Y.-W.; Hou, X.-L. *Adv. Synth. Catal.* **2010**, *352*, 103. m) Zhang, Y.; Han, Z.; Li, F.; Ding, K.; Zhang, A. *Chem. Commun.* **2010**, *46*, 156. n) Verendel, J. J.; Zhou, T.; Li, J.-Q.; Paptchikhine, A.; Lebedev, O.; Andersson, P. G. *J. Am. Chem. Soc*. **2010**, *132*, 8880. o)

Franzke, A.; Pfaltz, A. *Chem. Eur. J.* **2011**, *17*, 4131. p) Shang, J.; Han, Z.; Li, Y.; Wang, X.; Ding, K. *Chem. Commun.* **2012**, *48*, 5172. q) Wang, X.; Han, Z.; Wang, Z.; Ding, K. *Angew. Chem. Int. Ed.* **2012**, *51*, 936. r) Verendel, J. J.; Li, J.-Q.; Quan, X.; Peters, B.; Zhou, T.; Gautun, O. R.; Govender, T.; Andersson, P. G. *Chem. Eur. J.* **2012**, *18*, 6507. s) Mazuela, J.; Pàmies, O.; Diéguez, M. *Eur. J. Org. Chem.* **2013**, 2139. t) Khumsubdee, S.; Fan, Y.; Burgess, K. *J. Org. Chem*. **2013**, *78*, 9969. u) Zhu, Y.; Burgess, K. *RSC Advances* **2012**, *2*, 4728. v) Müller, M.-A.; Pfaltz, A. *Angew. Chem Int. Ed.* **2014**, *53*, 8668.

7 Källström, K.; Hedberg, C.; Brandt, P.; Bayer, A.; Andersson, P. G. *J. Am. Chem. Soc.* **2004**, *126*, 14308.

8 a) Hedberg, C.; Källström, K.; Brandt, P.; Hansen, L. K.; Andersson, P. G. *J. Am. Chem. Soc.* **2006**, *128*, 2995. b) Källström, K.; Andersson, P. G. *Tetrahedron Lett.* ***2006***, *47*, 7471. c) Engman, M.; Diesen, J. S.; Paptchikhine, A.; Andersson, P. G. *J. Am. Chem. Soc.* **2007**, *129*, 4536. d) Cheruku, P.; Paptchikhine, A.; Ali, M.; Neudoerfl, J.-M.; Andersson, P. G. *Org. Biomol. Chem.* **2008**, *6*, 366. e) Cheruku, P.; Paptchikhine, A.; Church, T. L.; Andersson, P. G. *J. Am. Chem. Soc.* **2009**, *131*, 8285. f) Tolstoy, P.; Engman, M.; Paptchikhine, A.; Bergquist, J.; Church, T. L.; Leung, A. W.-M.; Andersson, P. G. *J. Am. Chem. Soc.* **2009**, *131*, 8855. g) Li, J.-Q.; Paptchikhine, A.; Govender, T.; Andersson, P. G. *Tetrahedron: Asymmetry* **2010**, *21*, 1328. h) Paptchikhine, A.; Itto, K.; Andersson, P. G. *Chem. Commun.* **2011**, *47*, 3989. i) Li, J.-Q.; Quan, X.; Andersson, P. G. *Chem. Eur. J.* **2012**, *18*, 10609. j) Zhou, T.; Peters, B.; Maldonado, M. F.; Govender, T.; Andersson, P. G. *J. Am. Chem. Soc.* **2012**, *134*, 13592. k) Yotapan, N.; Paptchikhine, A.; Bera, M.; Avula, S. K.; Vilaivan, T.; Andersson, P. G. *Asian J. Org. Chem.* **2013**, *2*, 674.

9 See, for example: a) Bunlaksananusorn, T.; Polborn, K.; Knochel, P. *Angew. Chem. Int. Ed.* **2003**, *42*, 3941. b) Drury III, W. J.; Zimmermann, N.; Keenan, M.; Hayashi, M.; Kaiser, S.; Goddard, R.; Pfaltz, A. *Angew. Chem. Int. Ed.* **2004**, *43*, 70. c) Bell, S.; Wüstenberg, B.; Kaiser, S.; Menges, F.; Netscher, T.; Pfaltz, A. *Science* **2006**, *311*, 642. d) Kaiser, S.; Smidt, S. P.; Pfaltz, A. *Angew. Chem. Int. Ed.* **2006**, *45*, 5194. e) Margalef, J.; Lega, M.; Ruffo, F.; Pàmies, O.; Diéguez, M. *Tetrahedron: Asymmetry* **2012**, *23*, 945. f) Woodmansee, D. H.; Müller, M.-A.; Tröndlin, L.; Hörmann, E.; Pfaltz, A. *Chem. Eur. J.* **2012**, *18*, 13780. g) Schumacher, A.; Bernasconi, M.; Pfaltz, A. *Angew. Chem. Int. Ed.* **2013**, *52*, 7422. h) Bernasconi, M.; Müller, M.-A.; Pfaltz, A. *Angew. Chem. Int. Ed.* **2014**, *53*, 5385.

10 van Leeuwen, P. W. N. M.; Kamer, P. C. J.; Claver, C.; Pàmies, O.; Diéguez, M. *Chem. Rev.* **2011**, *111*, 2077.

11 Mazuela, J.; Pàmies, O.; Diéguez, M. *Chem. Eur. J.* **2010**, *16*, 3434.

12 a) Pàmies, O.; Diéguez, M.; Claver, C. *J. Am. Chem. Soc.* **2005**, *127*, 3646. b) Bellini, R.; Magre, M.; Biosca, M.; Norrby, P.-O.; Pàmies, O.; Diéguez, M.; Moberg, C. *ACS Catal.* **2016**, *6*, 1701.

13 Magre, M.; Biosca, M.; Pàmies, O.; Diéguez, M. *ChemCatChem* **2015**, *7*, 114.

[14] See for instance: a) Diéguez, M.; Mazuela, J.; Pàmies, O.; Verendel, J. J.; Andersson, P. G. *J. Am. Chem. Soc.* **2008**, *130*, 7208. b) Mazuela, J.; Verendel, J. J.; Coll, M.; Schäfner, B.; Börner, A.; Andersson, P. G.; Pàmies, O.; Diéguez, M. *J. Am. Chem. Soc.* **2009**, *131*, 12344. c). Mazuela, J.; Norrby, P.-O.; Andersson, P. G.; Pàmies, O.; Diéguez, M. *J. Am. Chem. Soc.* **2011**, *133*, 13634.

[15] Bunlaksananusorn, T.; Polborn, K.; Knochel, P. *Angew. Chem. Int. Ed.* **2003**, *42*, 3941 (ee's up to 96% in the hydrogenation of dehydroaminoacids).

[16] Chiral carboxylic esters can also be obtained by asymmetric conjugated reduction of α,β–unsaturated esters with $NaBH_4$ using Co-catalysts and by the asymmetric 1,4-reduction with moisture-sensitive hydrosilane reagents using Rh- and Cu-catalysts. See for instance: a) Leutenegger, U.; Madin, A.; Pfaltz, A. *Angew. Chem. Int. Ed.* **1989**, *28*, 60. b) Yamada, T. M; Ohtsuka, Y.; Ikeno, T. *Chem. Lett.* **1998**, 1129. c) Appella, D. H.; Moritani, Y.; Shintani, R.; Ferreira, E. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9473. d) Hughes, G.; Kimura, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 11253. e) Tsuchiya, Y.; Kanazwa, Y.; Shiomo, T.; Kobayashi, K.; Nishiyama, H. *Synlett* **2004**, 2493.

[17] a) Lu, W.-J.; Chen, Y.-W.; Hou, X.-L. *Angew. Chem. Int. Ed.* **2008**, *47*, 10133. b) Maurer, F.; Huch, V.; Ullrich, A.; Kazmaier, U. *J. Org. Chem.* **2012**, *77*, 5139. c) ref 6i. d) ref 6q. e) ref 6r.

[18] For successful application, see: a) Lu, W.-J.; Hou, X.-L. *Adv. Synth. Catal.* **2009**, *351*, 1224. b) ref 6p.

[19] For successful applications, see: a) Ganić, A.; Pfaltz, A. *Chem. Eur. J.* **2012**, *18*, 6724. b) Margalef, J.; Caldentey, X.; Karlsson, E. A.; Coll, M.; Mazuela, J.; Pàmies, O.; Diéguez, M.; Pericàs, M. A. *Chem. Eur. J.* **2014**, *20*, 12201. c) ref 14b. d) Paptchikhine, A.; Cheruku, P.; Engman, M.; Andersson, P. G. *Chem. Commun.* **2009**, 5996.

[20] For successful applications, see: a) Cheruku, P.; Diesen, J.; Andersson, P. G. *J. Am. Chem. Soc.* **2008**, *130*, 5595. b) Mazuela, J.; Paptchikhine, A.; Pàmies, O.; Andersson, P. G.; Diéguez, M. *Chem. Eur. J.* **2010**, *16*, 4567.

[21] See for example: a) Hoen, R.; van den Berg, M.; Bernsmann, H.; Minnaard, A. J.; de Vries, J. G.; Feringa, B. L. *Org. Lett.* **2004**, *6*, 1433. b) Sandee, A. J.; van der Burg, A. M.; Reek, J. N. H. *Chem. Commun.* **2007**, 864. c) Pignataro, L.; Boghi, M.; Civera, M.; Carboni, S.; Piarulli, U.; Gennari, C. *Chem. Eur. J.* **2012**, *18*, 1383. d) Frank, D. J.; Franzke, A.; Pfaltz, A. *Chem. Eur. J.* **2013**, *19*, 2405. e) Bravo, M. J.; Ceder, R. M.; Muller, G.; Rocamora, M. *Organometallics* **2013**, *32*, 2632.

[22] a) Renaud, J. L.; Dupau, P.; Hay, A.-E.; Guingouain, M.; Dixneouf, P. H.; Bruneau, C. *Adv. Synth. Catal.* **2003**, *345*, 230. b) Jiang, X.-B.; Lefort, L.; Goudriaan, P. E.; de VRies, A. H. M.; van Leeuwen, P. W. N. M. Reek, J. N. H. *Angew. Chem. Int. Ed.* **2006**, *45*, 1223. c) Revés, M.; Ferrer, C.; León, T.; Doran, S.; Etayo, P.; Vidal-Ferran, A.; Riera, A.; Verdaguer, X. *Angew. Chem. Int. Ed.* **2010**, *49*, 9452. d) Wu, Z.; Ayad, T.; Ratovelomanana-Vidal, V. *Org. Lett.* **2011**, *13*, 3782. e) Arribas, I.; Rubio, M.; Kleman, P.; Pizzano, A. *J. Org. Chem.* **2013**, *78*, 3997. f) Liu, G.; Liu, X.; Cai, Z.; Jiao, G.; Xu, G.; Tang, W. *Angew. Chem. Int. Ed.* **2013**, *52*, 4235.

[23] Only three catalytic systems have provided high enantioselectivities, see: a) Cheruku, P.; Gohil, S.; Andersson, P. G. *Org. Lett.* **2007**, *9*, 1659 (ee's up to 95%). b) ref 20b (ee's up to 82%). C) Biosca, M.; Paptchikhine, A.; Pàmies, O.; Andersson, P. G.; Diéguez, M. *Chem. Eur. J.* **2015**, *21*, 3455 (ee's up to 97%).

[24] Buisman, G. J. H.; Kamer, P. C. J.; van Leeuwen, P. W. M. N. Tetrahedron: Asymmetry 1993, 4, 1625.

[25] Gómez-Simón, M.; Jansat, S.; Muller, G.; Panyella, D.; Font-Bardía, M; Solans, X. *J. Chem. Soc., Dalton Trans.* **1997**, 3755.

[26] a) Randy, M.; Duhaime, D. A.; Lombardo, I. A.; Alan, C. W. *J. Org. Chem.* **1985**, *50*, 873. b) Prepared by stereoselective Horner-Wadsworth-Emmons olefination: Paterson, I.; Yeung, K.-S.; Smaill, J. B. *Synlett* **1993**, 774. Followed by reduction of the α,β-unsaturated ester: c) Corey, E. J.; Kirst, H. A.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1970**, *92*, 6314. For the synthesis of α,β-Unsaturated Carbonyl Compounds, see: d) Tian, F.; Yao, D.; Liu, Y.; Xie, F.; Zhang, W. *Adv. Synth. Catal.* **2010**, *352*, 1841.

[27] a) Pautigny, C.; Debouit, C.; Vayron, P.; Ayad, T.; Ratovelomanana-Vidal, V. *Tetrahedron Asymmetry* **2010**, *21*, 1382. b) Wu, Z.; Ayad, T.; Ratovelomanana-Vidal, V. *Org. Lett.* **2011**, *13*, 3782. c) Arribas, I.; Rubio, M.; Kleman, P.; Pizzano, A. *J. Org. Chem.* **2013**, *78*, 3997. d) Liu, G.; Liu, X.; Cai, Z.; Jiao, G.; Xu, G.; Tang, W. *Angew. Chem. Int. Ed.* **2013**, *52*, 4235.

[28] Lo Fiego, M. J.; Lockhart, M. T.; Chopa, A. B. *J. Organomet. Chem.* **2009**, *694*, 3674.

5.3. Asymmetric Ir-catalyzed hydrogenation of challenging olefins using phosphite/phosphinite-oxazoline PHOX-based ligands containing an alkyl backbone chain

Magre, M.; Coll, M.; Pàmies, O.; Diéguez, M. *Manuscript in preparation*

Abstract: *We report the successful application of Ir(I)-catalyst precursors modified with easily accessible phosphite/phosphinite-oxazoline ligands* ***L8-L14a-h*** *for the asymmetric hydrogenation of several substrate types. The ligands used differ from previously phosphite-oxazoline PHOX ligands presented in Section 5.3 in the presence of an alkyl chain instead of the flat ortho-phenylene tether. By suitable choosing the ligands parameters, however, we have been able to achieve high enantioselectivities (typically ee's>95%) not only for a wide range of minimally functionalized tri- and disubstituted olefins, with examples containing poorly coordinative groups; but also in the hydrogenation of challenging functionalized β-aryl enamides, which provide easy access to 2-aminotetralines and 3-aminochromanes.*

5.3.1. Introduction

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

An important breakthrough in the asymmetric hydrogenation of minimally functionalized olefins came when Pfaltz and coworkers used phosphine-oxazoline PHOX ligands to design [Ir(PHOX)(cod)]PF_6, a chiral analogue of Crabtree's catalyst[5].[6] The authors early found that the new catalyst was unstable to the reaction conditions. Pfaltz and co-workers overcame this limitation by changing the hexafluorophosphate anion to [(3,5-$(CF_3)_2$-$C_6H_3)_4$B]$^-$ ([BAr_F]$^-$).[7] Since then, most of the research in this field

have been dedicated to develop new Ir-catalysts modified with heterodonor P,N-ligands. Among them, the use of phosphine/phosphinite-oxazoline ligands has played a predominant role.[8] Our group has also shown that the substrate versatility of this process could be improved by the replacement of the phosphine/phosphinite moiety by a biaryl phosphite group.[9] Since this discovery, our group has contributed to the Ir-hydrogenation of minimally functionalized olefins with an improved series of ligands.[10,11] Although the number of substrates that can be successfully reduced has increased with the new ligand designs, there are still important substrate classes that give unsatisfactory results with known catalysts. More research is therefore needed to find more versatile ligand systems that can be synthesized on an efficient and modular synthetic route using simple starting materials.

In this chapter we therefore report the synthesis and application of new Ir-complexes modified with a chiral phosphite/phosphinite-oxazoline ligand library (**L8**-**L14a**-**g**; Figure 5.3.1). The ligand backbone resembles to that of phosphite-oxazoline PHOX ligands **L1**-**L4** (Section 5.2) in which the flat *ortho*-phenylene tether in PHOX ligands has been replaced by an alkyl chain. The modular ligand design allowed us to systematically investigate the effect of varying: (a) the substituents and the introduction of a new stereogenic center in the alkyl backbone chain (ligands **L8**, **L9** and **L13**-**L14**); (b) the substituents and configuration of the oxazoline moiety (ligands **L9**-**L12**); (c) the substituents and configurations in the biaryl phosphite moiety (**a**-**f**); and (d) the replacement of the phosphite group by a phosphinite moiety (**g**-**h**). By carefully selecting these elements, we achieved high enantioselectivities in the asymmetric hydrogenation of a wide range of minimally functionalized olefins, with examples containing poorly coordinative groups, as well as a range of challenging cyclic β-enamides.

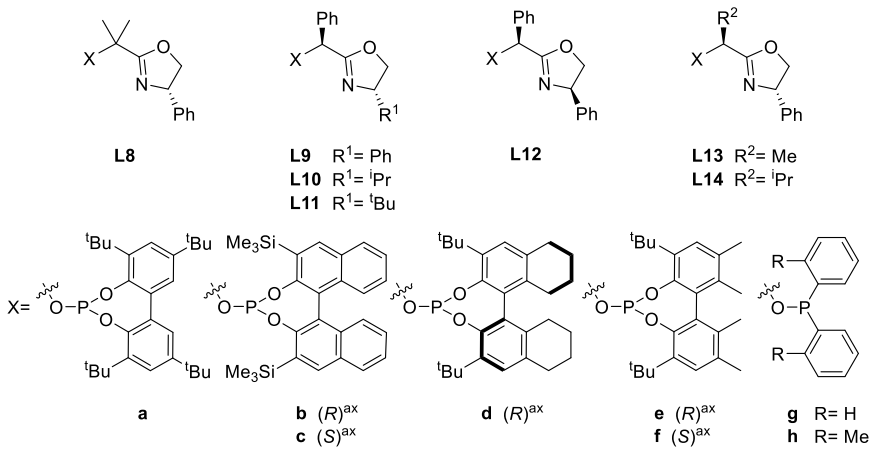
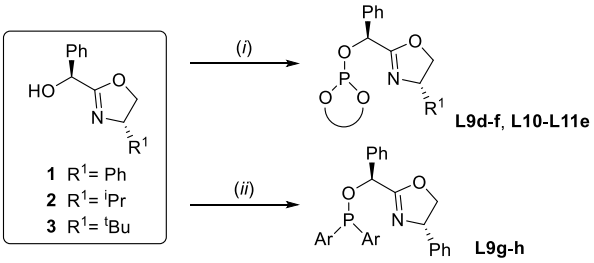


Figure 5.3.1. Phosphite/phosphinite-oxazoline ligands **L8**-**L14a**-**h**.

5.3.2. Results

5.3.2.1. Preparation of Ligands

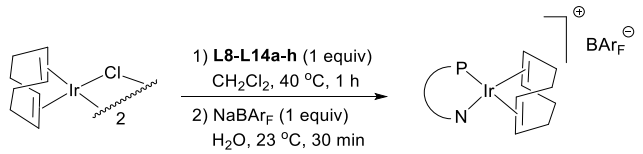
The synthesis of the new phosphite/phosphinite-oxazoline ligands **L9d**-**h** and **L10**-**L11e** is shown in Scheme 5.3.1. As previously described in Section 3.4, phosphite-oxazoline ligands **L9d**-**f** and **L10**-**L11e** were prepared by coupling the corresponding hydroxyl-oxazoline intermediates **1**-**3** with the desired phosphorochloridites ($ClP(OR)_2$; $(OR)_2$ = **d**-**f**; step *i*). Similarly, phosphinite-oxazoline ligands were synthesized by treating the corresponding hydroxyl-oxazoline **1** with one equivalent of the corresponding chlorophosphine ($ClPR_2$; R= **g**-**h**; step *ii*). All ligands were stable during purification on neutral alumina under an atmosphere of argon and they were isolated as white solids. They were stable at room temperature and very stable to hydrolysis. HRMS-ESI spectra were in agreement with the assigned structures. The ^1H and ^{13}C NMR spectra were as expected for these C_1 ligands. One singlet for each compound was observed in the ^{31}P NMR spectrum.



Scheme 5.3.1. Synthesis of new phosphite/phosphinite-oxazoline ligands **L9d**-**h** and **L10**-**L11e**. (i) $ClP(OR)_2$; $(OR)_2$ = **d**-**f**, Py, toluene, 16 h. (ii) $ClPR_2$; NEt_3, DMAP, toluene, rt, 30 min.

5.3.2.2. Preparation of Ir-catalyst precursors

The reaction of the corresponding phosphite/phosphinite-oxazoline ligands **L8**-**L14a**-**h** with $[Ir(\mu\text{-}Cl)(cod)]_2$ in dichloromethane for 1 h followed by in situ chlorine abstraction with $NaBAr_F$ produced the desired cationic catalyst precursors [Ir(cod)(**L8**-**L14a**-**h**)]BAr_F (Scheme 5.3.2). 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. The HRMS-ESI spectra were in agreement with the assigned structures, displaying the heaviest ions at m/z which correspond to the loss of the BAr_F anion from the molecular species. The ^1H, ^{13}C, and ^{31}P NMR spectra show the expected pattern for these C_1-complexes.



Scheme 5.3.2. Synthesis of catalyst precursors [Ir(cod)(**L8**-**L14a**-**h**)]BAr_F.

5.3.2.3 Asymmetric hydrogenation of trisubstituted olefins

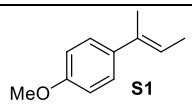
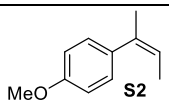
As previously mentioned the effectiveness in the asymmetric hydrogenation of minimally functionalized olefins is highly dependent on the substrate geometry. In general, high enantioselectivities are achieved in the hydrogenation of *E*-trisubstituted olefins, while the reduction of *Z*-olefins proceeds with much low enantiocontrol. Catalytic systems that are able to reduce both substrate classes in high enantioselectivities are therefore rare. For this purpose, in a first set of experiments we used the Ir-catalyzed hydrogenation of substrates (*E)*-2-(4-methoxyphenyl)-2-butene **S1** and (*Z)*-2-(4-methoxyphenyl)-2-butene **S2** to study the potential of phosphite/phosphinite-oxazoline ligands **L8**-**L14a**-**g**. Substrates **S1** and **S2** were chosen as models for the hydrogenation of *E*- and *Z*-isomers, respectively, because they have been reduced with a wide range of ligands, which enable the efficiency of the various ligand systems to be compared directly. The results, which are summarized in Table 5.3.1, indicate that enantioselectivities are highly affected by a subtle balance of the substituents at the alkyl backbone, the substituents/configuration at both the oxazoline and the biaryl phosphite group. However, the effect of these parameters strongly depends on the substrate geometry. Nevertheless, we have been able to achieve both isomers of the hydrogenated product in high enantioselectivities (ee's up to 95%) at low catalysts loadings (0.25 mol% Ir-catalyst) for both substrates using Ir-**L13b** for **S1** and Ir-**L10e** for **S2** (entries 20 and 13, respectively).

The effect of the presence of a chiral center at the alkyl backbone chain was studied comparing ligands **L8**-**L9a**-**c** (entries 1-3 vs 4-6). The results indicated that while for substrate **S1**, the introduction of a chiral center in the alkyl backbone chain has little effect on enantioselectivity; in the reduction of **S2,** the presence of a chiral alkyl backbone chain has a positive effect on enantioselectivity.

The effect of the different biaryl phosphite and phosphinite moieties on catalytic performance was studied using ligands **L9a**-**h**. The results indicated that the presence of an enantiopure (*R*)-biaryl phosphite group is necessary for enantioselectivities to be high (entries 4-11). Moreover, while for substrate **S1**, enantioselectivity is also highly affected by the substituents and the dihedral angle of the biaryl phosphite group, these parameters hardly affected the enantiocontrol in the reduction of **S2**. Thus, while the highest enantioselectivity in the hydrogenation of **S1** was achieved using ligand **L9b**

(entry 5), similarly high ee's were obtained using ligands **L9b**, **L9d** and **L9e** (entries 5, 7 and 8).

Table 5.3.1. Ir-catalyzed hydrogenation of **S1** and **S2** using ligands Ir(cod)(**L8**-**L14a**-**h**)BAr_F[a]

		 S1		 S2	
Entry	Ligand	% Conv[b]	% ee[c]	% Conv[b]	% ee[c]
1	**L8a**	100	91 (*R*)	100	40 (*S*)
2	**L8b**	100	93 (*R*)	100	53 (*S*)
3	**L8c**	100	24 (*R*)	100	40 (*S*)
4	**L9a**	100	58 (*R*)	100	21 (*S*)
5	**L9b**	100	92 (*R*)	100	86 (*S*)
6	**L9c**	100	68 (*S*)	100	41 (*R*)
7	**L9d**	100	60 (*R*)	100	91 (*S*)
8	**L9e**	100	75 (*R*)	100	91 (*S*)
9	**L9f**	100	67 (*S*)	100	44 (*R*)
10	**L9g**	100	60 (*R*)	100	53 (*S*)
11	**L9h**	100	70 (*R*)	100	50 (*S*)
12	**L10a**	100	30 (*R*)	100	33 (*S*)
13[d]	**L10e**	100	64 (*R*)	100	92 (*S*)
14	**L11a**	100	9 (*R*)	60	37 (*S*)
15	**L11e**	100	88 (*R*)	60	25 (*S*)
16	**L12a**	100	76 (*S*)	100	71 (*R*)
17	**L12b**	100	0	100	33 (*R*)
18	**L12c**	100	90 (*S*)	100	91 (*R*)
19	**L13a**	100	78 (*R*)	100	5 (*S*)
20[d]	**L13b**	100	95 (*R*)	100	80 (*S*)
21	**L13c**	100	40 (*S*)	100	45 (*R*)
22	**L14a**	100	81 (*R*)	100	70 (*S*)
23	**L14b**	100	94 (*R*)	100	78 (*S*)
24	**L14c**	100	30 (*R*)	100	8 (*S*)

[a] Reactions carried out at room temperature by using 0.5 mmol of substrate and 1 mol% of Ir-catalyst precursor at 50 bar of H_2 using dichloromethane (2 mL) as solvent. [b] Conversion measured by ^1H NMR after 2 h. [c] Enantiomeric excess determined by GC. [d] Reaction carried out at 0.25 mol% of Ir-catalyst precursor for 3 h.

The effect of the different oxazoline substituents on enantioselectivity was studied using ligands **L9**-**L11**. The results indicated that the nature of this substituent has a different effect on enantioselectivity, which is difficult to rationalize, depending on the geometry of the olefin. Thus, while the use of ligands with a *tert*-butyl oxazoline substituent (ligands **L11**) has a positive effect on enantioselectivity in the reduction of

S1, in the hydrogenation of **S2** the use of ligands **L11** provides the lowest enantiocontrol (*i.e.* entry 15 vs 8 and 13).

The results using ligands **L12**, with different configuration at the oxazoline than **L9**, indicated that there is a cooperative effect between the configuration of the biaryl phosphite group and that of the oxazoline group, which led to a matched combination for ligands **L9b** and **L12c** (entries 5 and 18 vs 4, 6 and 16-17). It should be highlighted that the use of ligands **L9b** and **L12c** give access to the different enantiomers of the hydrogenated product.

Finally, the effect of the nature of the substituent at the alkyl backbone chain was studied with ligands **L9**, **L13** and **L14**. The results indicated that while in the reduction of **S1** the nature of this substituent has almost no effect on enantioselectivity (*i.e.* entries 5, 20 and 23), for substrate **S2**, the presence of an isopropyl substituent has a detrimental effect on enantioselectivity (*i.e.* entry 23 vs 5 and 20).

We next studied the asymmetric hydrogenation of other *E*- and *Z*-trisubstituted olefins (**S3**-**S30**), including examples containing neighbouring polar groups, by using ligands **L8**-**L14a**-**g**. The most noteworthy results are shown in Figure 5.3.2. We found that the correct choice of the ligand parameters is crucial to achieve the highest levels of enantioselectivity. We initially studied the hydrogenation of *E*-substrates **S3**-**S4**, related to **S1,** that differ in the substituents in both the aryl ring and the substituents *trans* to the aryl group. Enantioselectivities followed the same trends as those observed for substrate **S1**. High enantioselectivities were therefore obtained using Ir-**L13b** catalytic system (ee's up to 98%). We next studied the hydrogenation of dehydronaphthalene **S5**, which has a Z-configuration. The results followed a different trend than in the reduction of model Z-substrate **S2**, providing enantioselectivities up to 67% ee using Ir-**L13b** catalytic system.

We next studied the hydrogenation of a range of trisubstituted olefins containing several types of neighboring poorly coordinative groups **S6**-**S30** (Figure 5.3.2). The hydrogenation of this type of substrates is especially relevant, because they allow for further functionalization and could therefore led to important intermediates for the synthesis of more complex chiral molecules. We found that enantioselectivities up to 90% ee could be achieved in the reduction of allylic alcohol **S6** using Ir-**L9c** catalytic system.

A range of α,β-unsaturated esters (**S7**-**S12**) were also hydrogenated in high enantioselectivities (ee's ranging from 98% to 99%) using Ir-**L13b** catalyst. It should be noted that ee's are highly independent of the nature of the alkyl substituent and the electronic nature of the substrate phenyl ring. These results are noteworthy because the resulting chiral carboxylic ester derivatives are present in many relevant products.

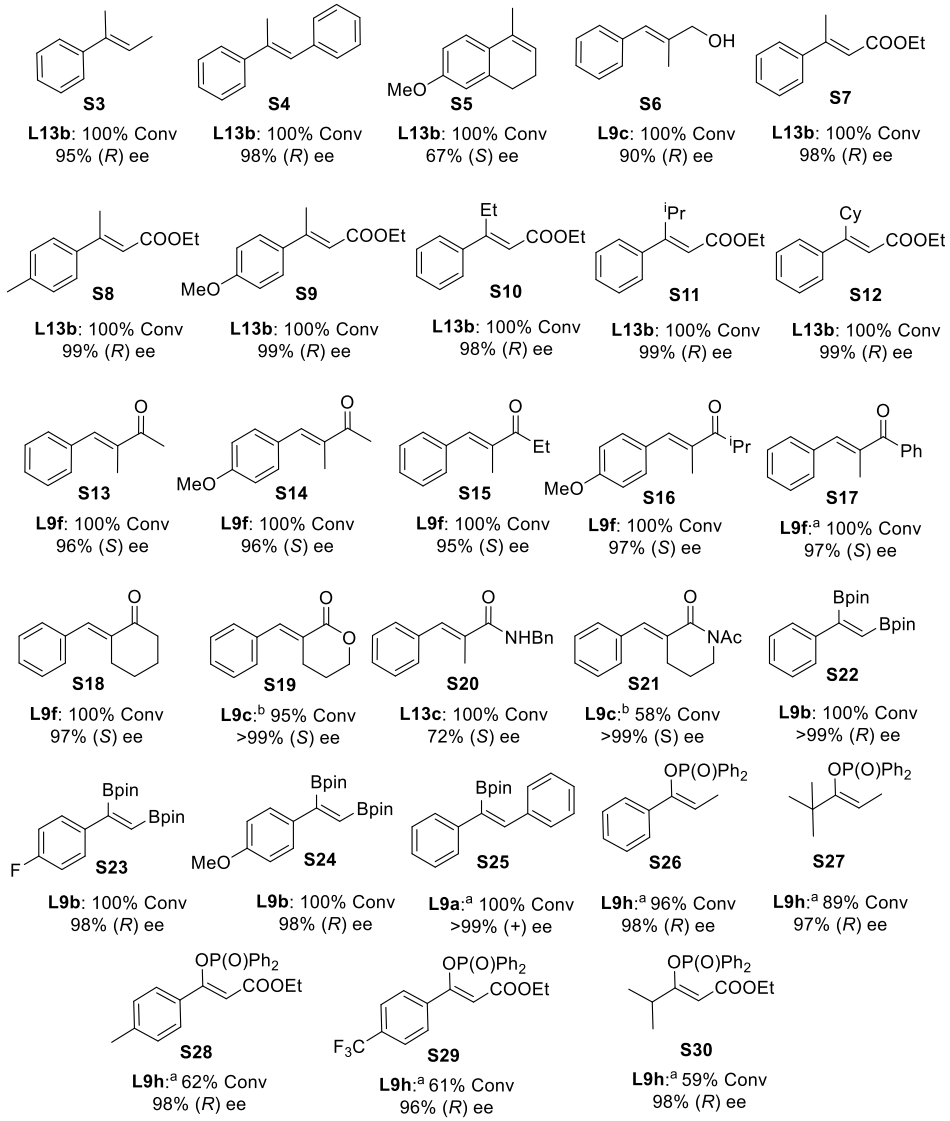


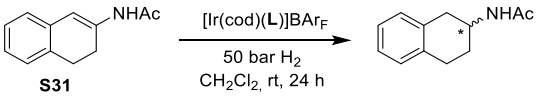
Figure 5.3.2. Selected results for the hydrogenation of trisubstituted olefins **S3**-**S30** using [Ir(cod)(**L9**-**L14a**-**g**)]BAr_F catalyst precursors. Reaction conditions: 2 mol % catalyst precursor, CH_2Cl_2 as solvent, 50 bar H_2, 2 h. [a] Reactions carried out for 24 h.

We were pleased to find out that a range of α,β-unsaturated ketones (**S13**-**S18**) could also be efficiently hydrogenated using Ir-**L9f** catalytic system (ee's up to 97%). Again, ee's are highly independent of the nature of the alkyl substituent and the electronic nature of the substrate phenyl ring. This represents an important entry point to the synthesis of ketones with stereogenic centres in the α-position to the carbonyl group. Despite this, they have been less studied than other trisubstituted olefins with neighboring polar groups.[12] α,β-Unsaturated lactones and amides (substrates **S19**-

S21) represent other challenging substrate classes that have been overlooked, despite their potential utility for the construction of complex molecules. Thus, for instance, amides with stereogenic centers in the α-position are present in several natural products and that the amide group can be easily transformed into other useful compounds (i.e. amines).[13] Interestingly the reduction of unsaturated lactone **S19** and amide **S21** proceeded with similar excellent enantiocontrol than α,β-unsaturated ketones, albeit the highest enantiomeric excesses (up to >99% ee) were achieved with Ir-**L9c** catalyst. Nevertheless, the hydrogenation of α,β-unsaturated amide **S20** proceeds with low enantiocontrol, which contrast with the excellent enantioselectivities also achieved using phosphite-oxazoline PHOX-based ligands (see Section 5.2). We also evaluated our new ligand library in the reduction of alkenylboronic esters **S22**-**S25**.[14] Full conversions and high enantioselectivities (ee's ranging from 98% to >99%) were achieved. The hydrogenation of alkenylboronic esters provides easy access to chiral borane compounds, which are valuable organic intermediates since the C-B bond can be easily transformed to C-O, C-N and C-C bonds with retention of the chirality. Finally, we focused our attention to the hydrogenation of a range of challenging enol phosphinites, including examples of pure alkyl-substituted ones (**S26**-**S30**). We were satisfied to find out that Ir-**L9h** is highly efficient in the hydrogenation of this substrate class (ee's ranging from 96% to 98%), providing slightly better enantioselectivities than those achieved using ligands **L1**-**L7** (see Section 5.2). The effective hydrogenation of this type of substrates opens up an appealing route for obtaining chiral organophosphinates, which can be easily transformed into high-value compounds such as alcohols and phosphines.

Encouraged by these results and the excellent performance of previously presented Ir-**L1**-**L7** catalytic system in the hydrogenation of cyclic β-aryl-N-acetyl enamides (Section 5.2), we decided to also explore the Ir-**L8**-**L14a**-**g** catalysts in the hydrogenation of arrange of enamides **S31**-**S37**. As mentioned in Section 5.2, the hydrogenation of this substrate class is still a challenge because in contrast to the parent α-enamides most of the Rh- and Ru-catalysts provided low enantiomeric excesses; nevertheless, some successful protocols are available.[15] Thus, for instance, Tang and coworkers have designed a new P-stereogenic diphosphine ligand with deep chiral pockets that has shown high efficiency in the Rh-catalyzed hydrogenation of this substrate class (ee's ranging from 94% to 98%). As a model, we choose N-(3,4-dihydronaphthalen-2-yl)acetamide **S31** to assess the potential of the new ligand library. The results are summarized in Table 5.3.2.

Table 5.3.2. Selected results for the Ir-catalyzed hydrogenation of **S31** using the phosphite/phosphinite-oxazoline ligand library **L8**-**L14a**-**h**[a]



Entry	Ligand	% Conv[b]	% ee[b]
1	**L8a**	100	84 (*S*)
2	**L8b**	100	88 (*S*)
3	**L8c**	100	22 (*R*)
4	**L9a**	100	20 (*R*)
5	**L9b**	100	85 (*S*)
6	**L9c**	100	53 (*R*)
7	**L9d**	100	84 (*S*)
8	**L9e**	100	85 (*S*)
9	**L9h**	100	37 (*S*)
10	**L10e**	100	91 (*S*)
11	**L11e**	100	40 (*S*)
12	**L12b**	100	66 (S)
13	**L12c**	100	97 (*R*)
14	**L13b**	100	94 (*S*)
15	**L14b**	100	92 (*S*)

[a] Reactions carried out using 0.5 mmol of **S31** and 1 mol% of Ir-catalyst precursor. [b] Conversion determined by ^{1}H NMR. [c] Enantiomeric excesses determined by chiral HPLC.

The results indicate that the effect of the different ligand parameters on enantioselectivity is very similar to that observed for the hydrogenation of **S1**. The main difference can be found in the cooperative effect between the configurations at the biaryl phosphite moiety and at the oxazoline group that led to a matched combination for Ir-**L12c** catalytic system (entry 13 vs 12, 5 and 6). Thus, as observed for the hydrogenation of **S1**, both enantiomers of the hydrogenation product can be achieved in high enantioselectivities (up to 97% ee) using Ir-**L12c** and Ir-**L13b** catalysts (entries 13 and 14).

We next studied the asymmetric hydrogenation of other β-aryl-N-acetyl enamides **S32**-**S37** using [Ir(cod)(**L12c**)]BAr$_F$ and [Ir(cod)(**L13b**)]BAr$_F$ as catalyst precursors (Figure 5.3.3). Advantageous, the results indicate that both activities and enantioselectivities are relatively insensitive to the different substitution pattern in the aryl ring. Ir-**L12c** and Ir-**L13b** catalytic systems are therefore able to give access to both enantiomers of a range of 2-aminotetralines and 3-aminochromanes in excellent enantioselectivities (ee's ranging from 91% to 99%). This is of great importance because both moieties are present in numerous biologically active natural products and therapeutic agents, such as *Rotigotine*[16] and *Robalzotan* (NAD-299)[17].

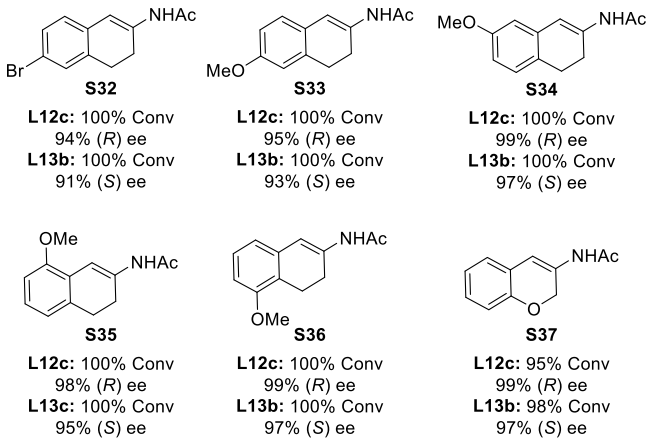


Figure 5.3.3. Asymmetric hydrogenation of several β-aryl-N-acetyl enamides. Reaction conditions: 1 mol % catalyst precursor, CH_2Cl_2 as solvent, 50 bar H_2, 24 h.

5.3.2.4. Asymmetric hydrogenation of disubstituted olefins

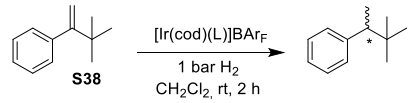
To further study the potential of the phosphite/phosphinite-oxazoline ligand library **L8**-**L14a**-**g**, we also screened it in the Ir-catalyzed hydrogenation of terminal olefins.[4e,h] As mentioned in Section 5.2, enantioselectivity is more difficult to control in these substrates than in trisubstituted olefins. Few known catalytic systems provide high enantioselectivities for these substrates, and those that do are usually limited in substrate scope. In contrast to the hydrogenation of trisubstituted olefins, the enantioselectivity in the reduction of terminal alkenes is highly pressure dependent. Therefore, hydrogenation at an atmospheric pressure of H_2 gave, in general, significantly higher ee values than at higher pressures.[4e,h]

As a model substrate, we have chosen the 3,3-dimethyl-2-phenyl-1-butene **S38** to assess the potential of the new ligand library. The results are summarized in Table 5.3.3.

The main difference with the hydrogenation of trisubstituted olefins is that the highest enantioselectivities are achieved with ligands containing a configurationally flexible biphenyl phosphite group **a** (comparing L9a-h; *i.e.* entry 4 vs 5-11). This not only indicates that for this substrate the ligand backbone is able to control the tropoisomerization of the biphenyl phosphite group (the results suggest that biaryl phosphite **a** adopts an *R*-configuration for ligands **L8**-**L11** and **L13**-**L14** and an *S*-configuration with ligands **L12**); but also that the flexibility of biphenyl phosphite group (**a**) helps to perfectly accommodate the catalyst's chiral pocket to the substrate. In contrast to other phosphite-oxazoline ligands and in line with the results achieved with **L1**-**L7** ligands (see Section 5.2) the sense of enantioselectivity is controlled by the configuration of the oxazoline moiety. Both enantiomers of the hydrogenated product

can therefore be achieved by simply changing the configuration of the oxazoline group (*i.e.* entries 4 and 16). In summary, we have been therefore able to fine-tune the ligand parameters to produce both enantiomers of the hydrogenated product in high enantioselectivities (ee's up to 99%) at low hydrogen pressures (1 bar) using low catalyst loadings (0.25 mol% Ir-catalyst).

Table 5.3.3. Selected results for the Ir-catalyzed hydrogenation of **S38** using phosphite/phosphinite-oxazoline ligand library **L8**-**L14a**-**g**[a]



Entry	Ligand	% Conv[b]	% ee[c]	Entry	Ligand	% Conv[b]	% ee[c]
1[d]	**L8a**	100	99 (*S*)	13	**L10e**	100	89 (*S*)
2	**L8b**	100	95 (*S*)	14	**L11a**	100	97 (*S*)
3	**L8c**	100	74 (*S*)	15	**L11e**	100	77 (*S*)
4	**L9a**	100	96 (*S*)	16[d]	**L12a**	100	98 (*R*)
5	**L9b**	100	93 (*S*)	17	**L12b**	100	74 (*R*)
6	**L9c**	100	42 (*S*)	18	**L12c**	100	92 (*R*)
7	**L9d**	100	82 (*S*)	19	**L13a**	100	92 (*S*)
8	**L9e**	100	88 (*S*)	20	**L13b**	100	92 (*S*)
9	**L9f**	100	40 (*S*)	21	**L13c**	100	10 (*S*)
10	**L9g**	100	81 (*S*)	22	**L14a**	100	96 (*S*)
11	**L9h**	100	82 (*S*)	23	**L14b**	100	91 (*S*)
12	**L10a**	100	95 (*S*)	24	**L14c**	100	60 (*S*)

[a] Reactions carried out at room temperature by using 0.5 mmol of substrate and 1 mol% of Ir-catalyst precursor at 1 bar of H_2 using dichloromethane (2 mL) as solvent. [b] Conversion measured by ^{1}H NMR after 2 h. [c] Enantiomeric excess determined by GC. [d] Reactions carried out at 0.25 mol% of Ir-catalyst for 2 h.

We next studied the asymmetric hydrogenation of other terminal disubstituted olefins (Figure 5.3.4). In first place, we studied several α-*tert*-butylstyrene type substrates (**S39**-**S44**) to evaluate how the electronic and steric properties of the aryl group of the substrate affected the catalytic performance. The results indicated that the presence of *ortho* substituents at the aryl ring (**S44**) led to lower activities. Nevertheless, enantioselectivity is hardly affected by the substitution pattern and the electronic nature of the substituents (ee's ranging 97% to >99%). Lower enantioselectivities have been achieved in the reduction of several α-alkylstyrenes bearing decreasingly sterically demanding alkyl substituents (**S45**-**S48**). A plausible explanation is the competition between direct hydrogenation and isomerization. However, we were pleased to find that enantioselectivities for these substrates could be maximized by appropriately choosing the ligand parameters (ee's ranging from 86% to 92%). Finally, we tested our ligands in the hydrogenation of the

terminal boronic esters **S49** and **S50** and enol phosphinates **S51** and **S52**. The hydrogenation of these substrate types, which are very appealing due to the importance and versatility of chiral organoboranes and organophosphinates, is still a challenge.[18] We were pleased to find that our ligands are able to hydrogenate this substrate with enantioselectivities as high as 95% ee. It should be mentioned that for these challenging classes of substrates the scope of the previously presented **L1**-**L7** ligand (Section 5.2) is complementary with that of ligands **L8**-**L14**. Thus, while ligands **L1**-**L7** provide high enantioselectivities (up to >99% ee) in the hydrogenation of terminal boronic esters, the reduction of enol phosphinites proceeds with high enantiocontrol (ee's up to 95%) using ligands **L8**-**L14**.

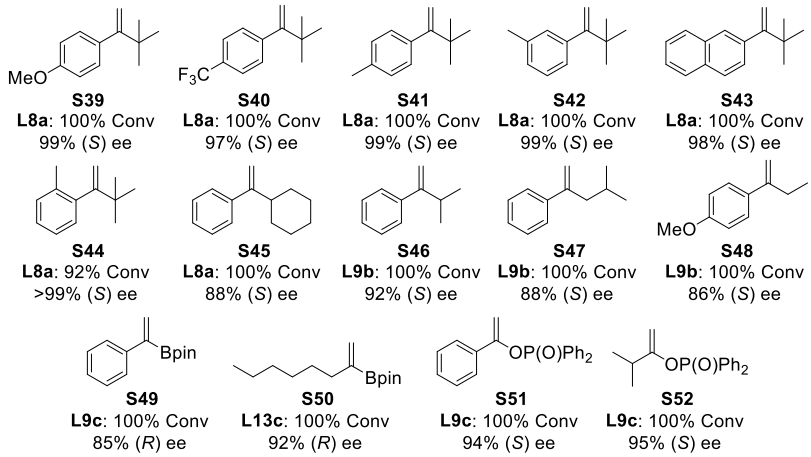


Figure 5.3.4. Selected results for the hydrogenation of trisubstituted olefins **S39**-**S52** using [Ir(cod)(**L9**-**L14a**-**g**)]BAr_F catalyst precursors. Reaction conditions: 1 mol % catalyst precursor, CH_2Cl_2 as solvent, 1 bar H_2, 2 h.

5.3.3. Conclusions

We have successfully applied new Ir(I)-catalyst precursors ([Ir(cod)(**L8**-**L14a**-**g**)]BAr_F), modified with easily accessible phosphite/phosphinite-oxazoline ligands, for the asymmetric hydrogenation of several substrate types. The ligands used differ from previously phosphite-oxazoline PHOX ligands presented in Section 5.2 in the presence of an alkyl chain instead of the flat *ortho*-phenylene tether. The catalytic results indicated that enantioselectivity is highly affected by the ligand parameters as well as the substrate. By suitable choosing the ligands parameters, however, we have been able to achieve high enantioselectivities (typically ee's>95%) not only for a wide range of minimally functionalized tri- and disubstituted olefins, with examples containing poorly coordinative groups (*i.e.* α,β-unsaturated ketones, amides and esters, alkenylboronic esters, enol phosphinates, …); but also in the hydrogenation of

challenging functionalized olefins such as the β-aryl enamides, which provide easy access to 2-aminotetralines and 3-aminochromanes.

5.3.4. Experimental Part

5.3.4.1. General Procedures.

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 $^{13}C\{^{1}H\}$) or H_3PO_4 ($^{31}P\{^{1}H\}$) as internal standard. Hydroxyl-oxazolines **1**-**6** and ligands **L8**-**L14a**-**c** have been prepared as described in Section 5.2. Phosphorochloridites,[19] olefins **S1**-**S30**,[20] **S31**-**S37**[21] and **S38**-**S52**[22] were synthesized as previously reported.

5.3.4.2. Typical procedure for the preparation of phosphite-oxazoline ligands.

To a solution of *in situ* generated phosphochloridite (1.1 mmol) in dry toluene (6 mL), pyridine (0.16 mL, 2.0 mmol) was added. Then, this solution was placed in a -78 ºC bath. After 2 min at that temperature, a solution of the alcohol-oxazoline (1.0 mmol) and pyridine (0.16 mL, 2.0 mmol) in toluene (6 mL) was added dropwise at -78 °C. The mixture was left to warm to room temperature and stirred overnight at this temperature. The precipitate formed was filtered under argon and the solvent was evaporated under vacuum. The residue was purified by flash chromatography (under argon, using neutral alumina and dry toluene (1% NEt_3) as eluent system) to afford the corresponding phosphite-oxazoline as white solids.

L9d: Yield: 508 mg (74%); ^{31}P NMR (161.9 MHz, C_6D_6): $\delta = 133.0$ (s); ^{1}H NMR (400 MHz, C_6D_6): δ = 1.23-1.63 (m, 9H, CH_2), 1.39 (s, 9H, CH_3, ^{t}Bu), 1.53 (s, 9H, CH_3, ^{t}Bu), 2.43-2.73 (m, 7H, CH_2), 3.62 (pt, 1H, CH-O_{ox}, J_{H-H}= 8.0 Hz), 4.19 (pt, 1H, CH-O_{ox}, J_{H-H}= 8.4 Hz), 4.96 (pt, 1H, CH-N, J_{H-H}= 9.6 Hz), 5.55 (d, 1H, CH-OP, $^{3}J_{H-P}$= 9.2 Hz), 6.88 (d, 2H, CH=, $^{3}J_{H-H}$= 3.6 Hz), 6.95-7.17 (m, 8H, CH=), 7.50 (d, 2H, CH=, $^{3}J_{H-H}$= 7.2 Hz). ^{13}C (100.6 MHz, C_6D_6): δ= 23.4 (CH_2), 23.6 (CH_2), 23.8 (CH_2), 27.9 (CH_2), 28.2 (CH_2), 30.3 (CH_2), 31.6 (CH_3, ^{t}Bu), 31.7 (CH_3, ^{t}Bu), 35.1 (C, ^{t}Bu), 35.2 (C, ^{t}Bu), 70.1 (CH-N), 73.9 (CH-OP), 75.3 (CH_2-O_{ox}), 126.0-146.0 (aromatic carbons), 167.1 (C=N). MS HR-ESI [found 710.3372, $C_{44}H_{50}NO_4P$ $(M-Na)^+$ requires 710.3370].

L9e: Yield: 394 mg (62%); ^{31}P NMR (161.9 MHz, C_6D_6): $\delta = 133.0$ (s); ^{1}H NMR (400 MHz, C_6D_6): δ = 1.4 (s, 9H, CH_3, ^{t}Bu), 1.51 (s, 9H, CH_3, ^{t}Bu), 1.69 (s, 3H, CH_3), 1.83 (s, 3H, CH_3), 2.06 (s, 3H, CH_3), 2.12 (s, 3H, CH_3), 3.66 (pt, 1H, CH-O_{ox}, J_{H-H}= 8.4 Hz), 4.17 (dd, 1H, CH-O_{ox}, $^{2}J_{H-H}$= 10.0 Hz, $^{3}J_{H-H}$= 8.4 Hz), 4.95 (dd, 1H, CH-N, $^{2}J_{H-H}$= 10.0

Hz, $^{3}J_{H-H}$= 8.4 Hz), 5.74 (d, 1H, CH-OP, $^{3}J_{H-P}$= 9.2 Hz), 6.9 (m, 2H, CH=), 6.96-7.15 (m, 4H, CH=), 7.19 (s, 1H, CH=), 7.23 (s, 1H, CH=), 7.47-7.50 (m, 2H, CH=). ^{13}C (100.6 MHz, C_6D_6): δ= 16.8 (CH_3), 17.1 (CH_3), 20.7 (CH_3), 20.8 (CH_3), 31.7 (CH_3, ^{t}Bu), 31.8(d, CH_3, ^{t}Bu, J_{C-P}= 2.31 Hz), 35.1 (C, ^{t}Bu), 35.2 (C, ^{t}Bu), 70.1 (CH-N), 73.9 (d, CH-OP, J_{C-P}= 2.3 Hz), 75.3 (CH_2-O_{ox}), 126.0-146.5 (aromatic carbons), 167.0 (C=N). MS HR-ESI [found 658.3061, $C_{40}H_{46}NO_4P$ $(M-Na)^+$ requires 658.3057].

L9f: Yield: 425 mg (67%); ^{31}P NMR (161.9 MHz, C_6D_6): δ = 116.5 (s); ^{1}H NMR (400 MHz, C_6D_6): δ = 3.64 (pt, 1H, CH-O_{ox}, J_{H-H}= 7.6 Hz), 3.87 (dd, 1H, CH-O_{ox}, $^{2}J_{H-H}$= 10.0 Hz, $^{3}J_{H-H}$= 8.0 Hz), 4.82 (dd, 1H, CH-N, $^{2}J_{H-H}$= 10.0 Hz, $^{3}J_{H-H}$= 8.0 Hz), 5.86 (d, 1H, CH-OP, $^{3}J_{H-P}$= 8.4 Hz), 6.95-7.11 (m, 14H, CH=), 7.56 (dt, 2H, CH=, $^{3}J_{H-H}$= 8.0 Hz, $^{4}J_{H-H}$= 2.0 Hz), 7.62 (d, 2H, CH=, $^{3}J_{H-H}$= 7.2 Hz), 7.39 (t, 2H, CH=, $^{3}J_{H-H}$= 7.2 Hz). ^{13}C (100.6 MHz, C_6D_6): δ= 69.4 (CH-N), 74.6 (CH_2-O_{ox}), 77.2 (CH-OP), 125.3-142.6 (aromatic carbons), 166.6 (C=N). MS HR-ESI [found 658.3060, $C_{40}H_{46}NO_4P$ $(M-Na)^+$ requires 658.3057].

L10e: Yield: 409 mg (68%); ^{31}P NMR (161.9 MHz, C_6D_6): δ = 133.6 (s); ^{1}H NMR (400 MHz, C_6D_6): δ = 0.53 (d, 3H, CH_3, ^{i}Pr, $^{3}J_{H-H}$= 6.8 Hz), 0.74 (d, 3H, CH_3, ^{i}Pr, $^{3}J_{H-H}$= 6.8 Hz), 1.35 (m, 1H, CH, ^{i}Pr), 1.38 (s, 9H, CH_3, ^{t}Bu), 1.50 (s, 9H, CH_3, ^{t}Bu), 1.68 (s, 3H, CH_3), 1.81 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 2.12 (s, 3H, CH_3), 3.51 (pt, 1H, CH-O_{ox}, J_{H-H}= 8.0 Hz), 3.63 (m, 1H, CH-N), 3.85 (pt, 1H, CH-O_{ox}, J_{H-H}= 8.8 Hz), 6.65 (d, 1H, CH-OP, $^{3}J_{H-P}$= 9.2 Hz), 6.99-7.14 (m, 3H, CH=), 7.17 (s, 1H, CH=), 7.20 (s, 1H, CH=), 7.39 (s, 1H, CH=), 7.41 (s, 1H, CH=). ^{13}C (100.6 MHz, C_6D_6): δ= 16.8 (CH_3), 17.1 (CH_3), 18.8 (CH_3, ^{i}Pr), 19.2 (CH_3, ^{i}Pr), 20.7 (CH_3), 20.8 (CH_3), 31.8 (d, CH_3, ^{t}Bu, J_{C-P}= 4.62 Hz), 32.0 (CH_3, ^{t}Bu), 33.4 (CH, ^{i}Pr), 35.1 (C, ^{t}Bu), 35.2 (C, ^{t}Bu), 71.0 (CH_2-O_{ox}), 72.8 (CH-N), 74.0 (CH-OP), 126.0-146.4 (aromatic carbons), 165.4 (C=N). MS HR-ESI [found 624.3216, $C_{37}H_{48}NO_4P$ $(M-Na)^+$ requires 624.3213].

L11e: Yield: 412 mg (67%); ^{31}P NMR (161.9 MHz, C_6D_6): δ = 134.2 (s); ^{1}H NMR (400 MHz, C_6D_6): δ = 0.61 (s, 9H, CH_3, ^{t}Bu), 1.41 (s, 9H, CH_3, ^{t}Bu), 1.49 (s, 9H, CH_3, ^{t}Bu), 1.68 (s, 3H, CH_3), 1.80 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 2.12 (s, 3H, CH_3), 3.69 (m, 2H, CH-O_{ox}, CH-N), 3.91 (m, 1H, CH-O_{ox}), 5.70 (d, 1H, CH-OP, $^{3}J_{H-P}$= 9.6 Hz), 6.99-7.15 (m, 3H, CH=), 7.18 (s, 1H, CH=), 7.20 (s, 1H, CH=), 7.41 (s, 1H, CH=), 7.44 (s, 1H, CH=). ^{13}C (100.6 MHz, C_6D_6): δ= 16.8 (CH_3), 17.1 (CH_3), 20.7 (CH_3), 20.8 (CH_3), 26.1 (CH_3, ^{t}Bu), 31.7 (d, CH_3, ^{t}Bu, J_{C-P}= 5.33 Hz), 31.9 (CH_3, ^{t}Bu), 34.2 (C, ^{t}Bu), 35.1 (C, ^{t}Bu), 35.2 (C, ^{t}Bu), 69.2 (CH_2-O_{ox}), 74.0 (d, CH-OP, J_{C-P}= 4.62 Hz), 76.2 (CH-N), 126.0-146.4 (aromatic carbons), 165.4 (C=N). MS HR-ESI [found 638.3372, $C_{38}H_{50}NO_4P$ $(M-Na)^+$ requires 638.3370].

5.3.4.3. Typical procedure for the preparation of phosphinite-oxazoline ligands.

The corresponding hydroxyl-oxazoline 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.

L9g: Yield: 121 mg (58%); ^{31}P NMR (161.9 MHz, C_6D_6): $\delta = 105.0$ (s); ^1H NMR (400 MHz, C_6D_6): δ = 2.31 (s, 3H, CH_3), 2.44 (s, 3H, CH_3), 3.59 (m, 1H, CH-O_{ox}), 3.87 (m, 1H, CH-O_{ox}), 4.82 (m, 1H, CH-N), 5.92 (d, 1H, CH-OP, $^3J_{H-P}$= 8.4 Hz), 6.88 (m, 1H, CH=), 6.95-7.15 (m, 14H, CH=), 7.63 (d, 1H, CH=, $^3J_{H-H}$= 8.4 Hz), 7.72 (m, 1H, CH=), 8.09 (m, 1H, CH=). ^{13}C (100.6 MHz, C_6D_6): δ= 20.2 (d, CH_3, J_{C-P}= 9.15 Hz), 20.4 (d, CH_3, J_{C-P}= 9.15 Hz) 69.3 (CH-N), 74.4 (CH_2-O_{ox}), 77.6 (d, CH-OP, J_{C-P}= 24.4 Hz), 125.9-142.6 (aromatic carbons), 166.8 (C=N). MS HR-ESI [found 440.1754, $C_{26}H_{28}NO_2P$ $(M-Na)^+$ requires 440.1750].

L9h: Yield: 149 mg (67%); ^{31}P NMR (161.9 MHz, C_6D_6): $\delta = 135.7$ (s); ^1H NMR (400 MHz, C_6D_6): δ = 1.42 (s, 9H, CH_3, ^{t}Bu), 1.54 (s, 9H, CH_3, ^{t}Bu), 1.69 (s, 3H, CH_3), 1.77 (s, 3H, CH_3), 2.04 (s, 3H, CH_3), 2.09 (s, 3H, CH_3), 3.63 (pt, 1H, CH-O_{ox}, J_{H-H}= 8.0 Hz), 4.05 (dd, 1H, CH-O_{ox}, $^2J_{H-H}$= 10.0 Hz, $^3J_{H-H}$= 8.8 Hz), 4.90 (dd, 1H, CH-N, $^2J_{H-H}$= 10.0 Hz, $^3J_{H-H}$= 8.4 Hz), 5.93 (d, 1H, CH-OP, $^3J_{H-P}$= 8.8 Hz), 6.92 (m, 2H, CH=), 6.96-7.15 (m, 6H, CH=), 7.18 (s, 1H, CH=), 7.26 (s, 1H, CH=), 7.53 (d, 2H, CH=, $^3J_{H-H}$= 7.6 Hz). ^{13}C (100.6 MHz, C_6D_6): δ= 16.9 (CH_3), 17.1 (CH_3), 20.7 (CH_3), 20.8 (CH_3), 31.6 (d, CH_3, ^{t}Bu, J_{C-P}= 4.62 Hz), 32.0 (CH_3, ^{t}Bu), 35.1 (C, ^{t}Bu), 35.4 (C, ^{t}Bu), 70.1 (CH-N), 74.1 (d, CH-OP, J_{C-P}= 7.64 Hz), 75.4 (CH_2-O_{ox}), 126.0-146.2 (aromatic carbons), 166.6 (C=N). MS HR-ESI [found 468.2067, $C_{28}H_{32}NO_2P$ $(M-Na)^+$ requires 468.2063].

5.3.4.4. Typical procedure for the preparation of [Ir(cod)(L8-L14a-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)(L8a)]BAr$_F$: Yield: 63 mg (94%); ^{31}P NMR (161.9 MHz, $CDCl_3$): δ = 97.8 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.33 (s, 9H, CH_3, ^{t}Bu), 1.36 (s, 9H, CH_3, ^{t}Bu), 1.47 (s, 9H, CH_3, ^{t}Bu), 1.58 (s, 9H, CH_3, ^{t}Bu), 1.83 (s, 6H, CH_3), 1.75-2.2 (m, 8H, CH_2, cod), 3.21 (m, 1H, CH=, cod), 3.64 (m, 1H, CH=, cod), 4.54 (dd, 1H, CH-O$_{ox}$, $^2J_{H-H}$= 9.6 Hz, $^3J_{H-H}$= 3.6 Hz), 4.74 (m, 1H, CH=, cod), 4.81 (pt, 1H, CH-O$_{ox}$, J_{H-H}= 9.6 Hz), 5.21 (m, 1H, CH-N), 5.24 (m, 1H, CH=, cod), 7.12 (m, 3H, CH=), 7.19 (d, 1H, CH=, $^4J_{H-H}$= 2.0 Hz), 7.42 (m, 3H, CH=), 7.52 (m, 6H, CH=), 7.71 (s, 8H, CH=).^{13}C (100.6 MHz, $CDCl_3$): δ= 27.8 (CH_2, cod), 28.6 (CH_3), 28.9 (CH_3), 30.2 (CH_2, cod), 31.3 (CH_3, ^{t}Bu), 31.4 (CH_3, ^{t}Bu), 31.9 (CH_3, ^{t}Bu), 31.7 (CH_2, cod), 32.2 (CH_2, cod), 34.7 (C, ^{t}Bu), 34.8 (C, ^{t}Bu), 35.4 (C, ^{t}Bu), 35.6 (C, ^{t}Bu), 62.2 (CH=, cod), 65.8 (CH=, cod), 71.5 (CH-N), 78.7 (CH_2-O$_{ox}$), 79.5 (d, CH-OP, $^2J_{C-P}$= 1.5 Hz), 102.4 (d, CH=, cod, J_{C-P}= 16.0 Hz), 104.2 (d, CH=, cod, J_{C-P}= 16.1 Hz), 117.4-149.1 (aromatic carbons), 161.6 (q, C-B, BArF, $^1J_{C-B}$= 50.4 Hz), 176.3 (d, C=N, $^3J_{C-P}$= 6.13 Hz). MS HR-ESI [found 944.4362, $C_{48}H_{66}IrNO_4P$ (M-BAr$_F$)$^+$ requires 944.4359].

[Ir(cod)(L8b)]BAr$_F$: Yield: 63 mg (95%); ^{31}P NMR (161.9 MHz, $CDCl_3$): δ = 103.8 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.53 (s, 9H, CH_3, $SiMe_3$), 0.61 (s, 9H, CH_3, $SiMe_3$), 1.83 (s, 3H, CH_3), 1.93 (s, 3H, CH_3), 1.58-2.0 (m, 7H, CH_2, cod), 2.17 (m, 1H, CH_2, cod), 2.93 (m, 1H, CH=, cod), 3.96 (m, 1H, CH=, cod), 4.54 (dd, 1H, CH-O$_{ox}$, $^2J_{H-H}$= 8.8 Hz, $^3J_{H-H}$= 2.8 Hz), 4.81 (m, 2H, CH=, cod; CH-O$_{ox}$), 5.35 (m, 2H, CH-N; CH=, cod), 6.63 (d, 1H, CH=, $^3J_{H-H}$= 8.8 Hz), 7.02 (d, 1H, CH=, $^3J_{H-H}$= 8.8 Hz), 7.16 (m, 2H, CH=), 7.24 (m, 3H, CH=), 7.42-7.51 (m, 8H, CH=), 7.71 (s, 8H, CH=), 7.96 (d, 2H, CH=, $^3J_{H-H}$= 8.4 Hz), 8.16 (d, 2H, CH=, $^3J_{H-H}$= 8.4 Hz).^{13}C (100.6 MHz, $CDCl_3$): δ= 0.6 (CH_3, $SiMe_3$), 1.3 (CH_3, $SiMe_3$), 28.2 (CH_2, cod), 28.9 (CH_3), 29.4 (CH_2, cod), 29.9 (CH_3), 31.5 (CH_2, cod), 33.1 (d, CH_2, cod, J_{C-P}= 4.62 Hz), 59.3 (CH=, cod), 68.3 (CH=, cod), 71.5 (CH-N), 78.7 (CH_2-O$_{ox}$), 79.7 (d, CH-OP, $^2J_{C-P}$= 2.91 Hz), 105.5 (d, CH=, cod, J_{C-P}= 15.49 Hz), 106.0 (d, CH=, cod, J_{C-P}= 16.7 Hz), 117.6-150.6 (aromatic carbons), 161.9 (q, C-B, BArF, $^1J_{C-B}$= 50.0 Hz), 176.8 (d, C=N, $^3J_{C-P}$= 6.43 Hz). MS HR-ESI [found 964.2859, $C_{46}H_{54}IrNO_4PSi_2$ (M-BAr$_F$)$^+$ requires 964.2858].

[Ir(cod)(L8c)]BAr$_F$: Yield: 60 mg (91%); ^{31}P NMR (161.9 MHz, $CDCl_3$): δ = 104.7 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.43 (s, 9H, CH_3, $SiMe_3$), 0.50 (s, 9H, CH_3, $SiMe_3$), 1.56 (s, 3H, CH_3), 1.62 (m, 2H, CH_2, cod), 1.68 (s, 3H, CH_3), 1.78 (m, 1H, CH_2, cod), 1.96-2.07 (m, 3H, CH_2, cod), 2.30 (m, 1H, CH_2, cod), 3.30 (m, 1H, CH=, cod), 4.03 (m, 1H, CH=, cod), 4.47 (dd, 1H, CH-O$_{ox}$, $^2J_{H-H}$= 9.2 Hz, $^3J_{H-H}$= 4.0 Hz), 4.79 (pt, 1H, CH-O$_{ox}$, J_{H-H}= 9.2 Hz), 4.97 (m, 1H, CH=, cod), 5.30 (m, 1H, CH-N), 5.71 (m, 1H, CH=, cod), 6.95 (d, 1H, CH=, $^3J_{H-H}$= 8.4 Hz), 7.00 (d, 1H, CH=, $^3J_{H-H}$= 84 Hz), 7.10 (m, 2H, CH=), 7.24 (m, 3H, CH=), 7.44-7.51 (m, 8H, CH=), 7.70 (s, 8H, CH=), 7.90 (d, 1H, CH=, $^3J_{H-H}$= 8.4 Hz), 7.96 (d, 1H, CH=, $^3J_{H-H}$= 8.4 Hz), 8.07 (s, 1H, CH=), 8.11 (s, 1H, CH=).^{13}C (100.6 MHz, $CDCl_3$): δ= 0.4 (CH_3, $SiMe_3$), 0.9 (CH_3, $SiMe_3$), 26.1 (CH_2, cod), 29.0 (d, CH_2, cod, J_{C-P}= 6.94 Hz), 29.5 (CH_3), 29.7 (CH_3), 31.4 (CH_2, cod), 34.7 (d,

CH_2, cod, J_{C-P}= 6.03 Hz), 61.4 (CH=, cod), 68.8 (CH=, cod), 70.7 (CH-N), 78.0 (CH_2-O_{ox}), 79.3 (d, CH-OP, $^2J_{C-P}$= 3.82 Hz), 100.8 (d, CH=, cod, J_{C-P}= 18.30 Hz), 106.4 (d, CH=, cod, J_{C-P}= 14.48 Hz), 117.4-150.9 (aromatic carbons), 161.7 (q, C-B, BArF, $^1J_{C-B}$= 49.7 Hz), 175.3 (d, C=N, $^3J_{C-P}$= 5.33 Hz MS HR-ESI [found 964.2862, $C_{46}H_{54}IrNO_4PSi_2$ $(M\text{-}BAr_F)^+$ requires 964.2858].

[Ir(cod)(L9a)]BAr_F: Yield: 63 mg (92%); ^{31}P NMR (161.9 MHz, $CDCl_3$): δ = 102.4 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.29 (s, 9H, CH_3, ^{t}Bu), 1.32 (s, 9H, CH_3, ^{t}Bu), 1.34 (s, 9H, CH_3, ^{t}Bu), 1.44 (s, 9H, CH_3, ^{t}Bu), 1.80-2.00 (m, 7H, CH_2, cod), 2.12 (m, 1H, CH_2, cod), 3.30 (m, 1H, CH=, cod), 3.60 (m, 1H, CH=, cod), 4.55 (dd, 1H, CH-O_{ox}, $^2J_{H-H}$= 12.0 Hz, $^3J_{H-H}$= 4.0 Hz), 4.80 (pt, 1H, CH-O_{ox}, J_{H-H}= 8.0 Hz), 4.90 (m, 1H, CH=, cod), 5.19 (dd, 1H, CH-N, $^2J_{H-H}$= 12.0 Hz, $^3J_{H-H}$= 4.0 Hz), 5.33 (m, 1H, CH=, cod), 6.33 (d, 1H, CH-OP, $^3J_{H-P}$= 16.0 Hz), 7.13 (d, 1H, CH=, $^4J_{H-H}$= 2.6 Hz), 7.18 (m, 3H, CH=), 7.42-7.52 (m, 12H, CH=), 7.61 (m, 2H, CH=), 7.72 (m, 8H, CH=). ^{13}C (100.6 MHz, $CDCl_3$): δ= 28.7 (CH_2, cod), 28.9 (CH_2, cod), 31.2 (CH_2, cod), 31.4 (CH_3, ^{t}Bu), 31.6 (CH_2, cod), 31.7 (CH_3, ^{t}Bu), 32.0 (CH_2, cod), 34.7 (C, ^{t}Bu), 34.8 (C, ^{t}Bu), 35.3 (C, ^{t}Bu), 35.4 (C, ^{t}Bu), 62.9 (CH=, cod), 65.8 (CH=, cod), 71.2 (CH-N), 74.8 (CH-OP), 79.4 (CH_2-O_{ox}), 103.5 (d, CH=, cod, J_{C-P}= 18.0 Hz), 104.4 (d, CH=, cod, J_{C-P}= 16.09 Hz), 117.4-149.2 (aromatic carbons), 161.6 (q, C-B, BArF, $^1J_{C-B}$= 50.30 Hz), 173.6 (C=N). MS HR-ESI [found 992.4362, $C_{52}H_{66}IrNO_4P$ $(M\text{-}BAr_F)^+$ requires 992.4359].

[Ir(cod)(L9b)]BAr_F: Yield: 64 mg (92%); ^{31}P NMR (161.9 MHz, $CDCl_3$): δ = 107.2 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.37 (s, 9H, CH_3, $SiMe_3$), 0.49 (s, 9H, CH_3, $SiMe_3$), 1.53 (m, 2H, CH_2, cod), 1.63 (m, 1H, CH_2, cod), 1.76 (m, 1H, CH_2, cod), 1.94 (m, 1H, CH_2, cod), 2.09 (m, 1H, CH_2, cod), 2.15 (m, 1H, CH_2, cod), 2.37 (m, 1H, CH_2, cod), 3.11 (m, 1H, CH=, cod), 4.07 (m, 1H, CH=, cod), 4.42 (m, 1H, CH-O_{ox}), 4.76 (m, 1H, CH-O_{ox}), 5.43 (m, 1H, CH-N), 5.82 (m, 1H, CH=, cod), 6.00 (m, 1H, CH-OP), 6.95 (m, 2H, CH=), 7.22 (m, 5H, CH=), 7.33-7.52 (m, 10H, CH=), 7.71 (m, 8H, CH=), 7.93 (m, 5H, CH=), 8.13 (m, 2H, CH=). ^{13}C (100.6 MHz, $CDCl_3$): δ= 0.2 (CH_3, $SiMe_3$), 1.4 (CH_3, $SiMe_3$), 26.4 (CH_2, cod), 29.4 (CH_2, cod), 31.4 (CH_2, cod), 34.7 (CH_2, cod), 61.4 (CH=, cod), 67.0 (CH=, cod), 71.5 (CH-N), 74.4 (CH-OP), 80.3 (CH_2-O_{ox}), 102.3 (d, CH=, cod, J_{C-P}= 15.9 Hz), 106.5 (d, CH=, cod, J_{C-P}= 16.2 Hz), 117.4-150.1 (aromatic carbons), 161.6 (q, C-B, BArF, $^1J_{C-B}$= 49.7 Hz), 172.8 (C=N). MS HR-ESI [found 1012.2961, $C_{50}H_{54}IrNO_4PSi_2$ $(M\text{-}BAr_F)^+$ requires 1012.2958].

[Ir(cod)(L9c)]BAr_F: Yield: 65 mg (94%); ^{31}P NMR (161.9 MHz, $CDCl_3$): δ = 108.3 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.35 (s, 9H, CH_3, $SiMe_3$), 0.62 (s, 9H, CH_3, $SiMe_3$), 1.55 (m, 1H, CH_2, cod), 1.62 (m, 1H, CH_2, cod), 1.75 (m, 1H, CH_2, cod), 1.89 (m, 2H, CH_2, cod), 1.99 (m, 3H, CH_2, cod), 2.99 (m, 1H, CH=, cod), 3.99 (m, 1H, CH=, cod), 4.50 (dd, 1H, CH-O_{ox}, $^2J_{H-H}$= 12.0 Hz, $^3J_{H-H}$= 4.0 Hz), 4.89 (m, 2H, CH-O_{ox}; CH=, cod), 5.19 (m, 1H, CH=, cod), 5.32 (m, 1H, CH-N), 6.48 (d, 1H, CH-OP, $^3J_{H-H}$= 12.0 Hz), 6.99 (d, 1H, CH=, $^3J_{H-H}$= 8.0 Hz), 7.03 (d, 1H, CH=, $^3J_{H-H}$= 8.0 Hz), 7.25 (m, 3H, CH=), 7.37-

7.53 (m, 14H, CH=), 7.73 (m, 9H, CH=), 6.92 (d, 1H, CH=, $^{3}J_{H-H}$= 8.0 Hz), 7.99 (d, 1H, CH=, $^{3}J_{H-H}$= 8.0 Hz), 8.04 (s, 1H, CH=), 8.21 (s, 1H, CH=). ^{13}C (100.6 MHz, $CDCl_3$): δ= 0.0 (CH_3, $SiMe_3$), 1.2 (CH_3, $SiMe_3$), 27.3 (CH_2, cod), 30.2 (CH_2, cod), 30.5 (CH_2, cod), 33.4 (CH_2, cod), 61.8 (CH=, cod), 69.8 (CH=, cod), 71.8 (CH-N), 74.6 (d, CH-OP, $^{2}J_{C-P}$= 6.0 Hz), 79.6 (CH_2-O_{ox}), 104.4 (d, CH=, cod, J_{C-P}= 17.1 Hz), 106.0 (d, CH=, cod, J_{C-P}= 14.08 Hz), 117.4-150.2 (aromatic carbons), 161.7 (q, C-B, BArF, $^{1}J_{C-B}$= 49.3 Hz), 174.3 (d, C=N, $^{3}J_{C-P}$= 5.0 Hz). MS HR-ESI [found 1012.2960, $C_{50}H_{54}IrNO_4PSi_2$ (M-BAr_F)$^+$ requires 1012.2958].

[Ir(cod)(L9d)]BAr_F: Yield: 64 mg (94%); ^{31}P NMR (161.9 MHz, $CDCl_3$): δ = 100.7 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.99 (s, 9H, CH_3, ^{t}Bu), 1.19 (s, 9H, CH_3, ^{t}Bu), 1.21-2.77 (m, 16H, CH_2), 1.21-2.77 (m, 8H, CH_2, cod), 1.70 (m, 1H, CH=, cod), 3.98 (m, 1H, CH=, cod), 4.54 (m, 1H, CH-O_{ox}), 4.64 (pt, 1H, CH-O_{ox}, J_{H-H}= 9.2 Hz), 5.19 (m, 1H, CH-N), 5.20 (m, 1H, CH=, cod), 5.58 (m, 1H, CH=, cod), 6.00 (d, 1H, CH-OP, $^{3}J_{H-P}$= 16.4 Hz), 6.97 (m, 1H, CH=), 7.08 (m, 1H, CH=), 7.20 (m, 2H, CH=), 7.26 (m, 1H, CH=), 7.46-7.52 (m, 9H, CH=), 7.71 (s, 8H, CH=), 7.83 (d, 2H, CH=, $^{3}J_{H-H}$= 6.8 Hz). ^{13}C (100.6 MHz, $CDCl_3$): δ= 22.6 (CH_2), 26.5 (CH_2), 26.0 (d, CH_2, cod, J_{C-P}= 11.46 Hz), 29.3 (CH_2), 30.15 (CH_2, cod), 31.1 (CH_2, cod), 31.1 (CH_3, ^{t}Bu), 32.1 (CH_3, ^{t}Bu), 34.3 (C, ^{t}Bu), 34.4 (d, CH_2, cod, J_{C-P}= 4.62 Hz), 34.6 (C, ^{t}Bu), 61.1 (CH=, cod), 66.6 (CH=, cod), 70.4 (CH-N), 76.2 (CH-OP), 78.7 (CH_2-O_{ox}), 100.4 (d, CH=, cod, J_{C-P}= 18.3 Hz), 103.6 (d, CH=, cod, J_{C-P}= 15.3 Hz), 117.4-143.1 (aromatic carbons), 161.6 (q, C-B, BArF, $^{1}J_{C-B}$= 46.5 Hz), 170.8 (d, C=N, $^{3}J_{C-P}$= 7.6 Hz). MS HR-ESI [found 988.4048, $C_{52}H_{62}IrNO_4P$ (M-BAr_F)$^+$ requires 988.4046].

[Ir(cod)(L9e)]BAr_F: Yield: 61 mg (91%); ^{31}P NMR (161.9 MHz, $CDCl_3$): δ = 100.7 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.05 (s, 9H, CH_3, ^{t}Bu), 1.25 (s, 9H, CH_3, ^{t}Bu), 1.74 (s, 3H, CH_3), 1.76 (s, 3H, CH_3), 1.89 (m, 3H, CH_2, cod), 2.10 (m, 1H, CH_2, cod), 2.18 (s, 3H, CH_3), 2.19 (m, 1H, CH_2, cod), 2.26 (s, 3H, CH_3), 2.30-2.47 (m, 3H, CH_2, cod), 2.85 (m, 1H, CH=, cod),4.03 (m, 1H, CH=, cod), 4.55 (m, 1H, CH-O_{ox}), 4.67 (pt, 1H, CH-O_{ox}, J_{H-H}= 9.6 Hz), 4.95 (m, 2H, CH-N, CH=, cod), 5.66 (m, 1H, CH=, cod), 6.01 (d, 1H, CH-OP, $^{3}J_{H-P}$= 14.8 Hz), 7.09-7.28 (m, 4H, CH=), 7.47-7.54 (m, 10H, CH=), 7.77 (m, 10H, CH=).^{13}C (100.6 MHz, $CDCl_3$): δ= 16.4 (CH_3), 16.5 (CH_3), 20.2 (CH_3), 20.3 (CH_3), 26.3 (CH_2, cod), 29.9 (CH_2, cod), 31.3 (CH_3, ^{t}Bu), 31.4 (CH_2, cod), 32.2 (CH_3, ^{t}Bu), 35.1 (C, ^{t}Bu), 34.6 (d, CH_2, cod, J_{C-P}= 5.33 Hz), 34.8 (C, ^{t}Bu), 61.5 (CH=, cod), 66.7 (CH=, cod), 70.5 (CH-N), 76.0 (CH-OP), 78.7 (CH_2-O_{ox}), 100.1 (d, CH=, cod, J_{C-P}= 18.3 Hz), 103.6 (d, CH=, cod, J_{C-P}= 13.8 Hz), 117.4-143.5 (aromatic carbons), 161.6 (q, C-B, BArF, $^{1}J_{C-B}$= 49.7 Hz), 170.8 (d, C=N, $^{3}J_{C-P}$= 7.6 Hz). MS HR-ESI [found 936.3735, $C_{48}H_{58}IrNO_4P$ (M-BAr_F)$^+$ requires 936.3733].

[Ir(cod)(L9h)]BAr_F: Yield: 55 mg (94%); ^{31}P NMR (161.9 MHz, $CDCl_3$): δ = 101.9 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.23 (s, 9H, CH_3, ^{t}Bu), 162 (s, 9H, CH_3, ^{t}Bu), 1.70 (m, 2H, CH_2, cod), 1.78 (s, 3H, CH_3), 1.83 (s, 3H, CH_3), 1.80-1.99 (m, 5H, CH_2, cod), 2.05

(m, 1H, CH_2, cod), 2.24 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 2.75 (m, 1H, CH=, cod), 3.97 (m, 1H, CH=, cod), 4.51 (m, 1H, CH-O_{ox}), 4.86 (m, 1H, CH=, cod), 4.85 (pt, 1H, CH-O_{ox}, J_{H-H}= 10.0 Hz), 5.05 (m, 1H, CH=, cod), 5.13 (m, 1H, CH-N), 6.45 (d, 1H, CH-OP, $^3J_{H-P}$= 9.2 Hz), 7.11-7.17 (m, 3H, CH=), 7.26 (m, 1H, CH=), 7.31 (m, 1H, CH=), 7.34-7.46(m, 6H, CH=), 7.52 (s, 5H, CH=), 7.72 (s, 8H, CH=). ^{13}C (100.6 MHz, $CDCl_3$): δ= 16.5 (CH_3), 16.6 (CH_3), 20.2 (CH_3), 20.43 (CH_3), 27.4 (CH_2, cod), 30.2 (CH_2, cod), 30.6 (CH_2, cod), 31.2 (CH_3, ^{t}Bu), 32.5 (CH_3, ^{t}Bu), 33.3 (d, CH_2, cod, J_{C-P}= 5.01 Hz), 34.6 (C, ^{t}Bu), 35.1 (C, ^{t}Bu), 61.0 (CH=, cod), 69.7 (CH=, cod), 71.7 (CH-N), 74.1 (d, CH-OP, $^2J_{C-P}$= 8.34 Hz), 79.9 (CH_2-O_{ox}), 103.5 (d, CH=, cod, J_{C-P}= 16.8 Hz), 104.3 (d, CH=, cod, J_{C-P}= 13.8 Hz), 117.4-143.6 (aromatic carbons), 161.7 (q, C-B, BArF, $^1J_{C-B}$= 49.7 Hz), 174.8 (C=N). MS HR-ESI [found 766.2429, $C_{38}H_{40}IrNO_2P$ $(M\text{-}BAr_F)^+$ requires 766.2426].

[Ir(cod)(L10a)]BAr_F: Yield: 63 mg (92%); ^{31}P NMR (161.9 MHz, $CDCl_3$): $\delta = 101.7$ (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.90 (m, 6H, CH_3, ^{i}Pr), 1.04 (s, 9H, CH_3, ^{t}Bu), 1.29 (s, 9H, CH_3, ^{t}Bu), 1.36 (s, 9H, CH_3, ^{t}Bu), 1.57 (s, 9H, CH_3, ^{t}Bu), 1.71 (m, 2H, CH_2, cod), 2.05 (m, 1H, CH, ^{i}Pr), 2.06 (m, 3H, CH_2, cod), 2.26 (m, 1H, CH_2, cod), 2.39 (m, 2H, CH_2, cod), 3.29 (m, 1H, CH=, cod), 3.85 (m, 1H, CH=, cod), 4.07 (m, 1H, CH-N), 4.21 (pt, 1H, CH-O_{ox}, J_{H-H}= 9.6 Hz), 4.58 (dd, 1H, CH-O_{ox}, $^2J_{H-H}$= 10.4 Hz, $^3J_{H-H}$= 3.2 Hz), 5.03 (m, 1H, CH=, cod), 5.59 (m, 1H, CH=, cod), 5.93 (d, 1H, CH-OP, $^3J_{H-P}$= 17.6 Hz), 7.08 (d, 1H, CH=, $^4J_{H-H}$= 2.4 Hz), 7.15 (d, 1H, CH=, $^4J_{H-H}$= 2.0 Hz), 7.38 (d, 1H, CH=, $^4J_{H-H}$= 2.4 Hz), 7.51 (m, 7H, CH=), 7.56 (d, 1H, CH=, $^4J_{H-H}$= 2.0 Hz), 7.70 (m, 10H, CH=). ^{13}C (100.6 MHz, $CDCl_3$): δ= 14.5 (CH_3, ^{i}Pr), 18.8 (CH_3, ^{i}Pr), 26.0 (CH_2, cod), 29.7 (CH_2, cod), 30.9 (CH_3, ^{t}Bu), 31.0 (CH, ^{i}Pr), 31.3 (CH_3, ^{t}Bu), 31.4 (CH_3, ^{t}Bu), 31.8 (CH_2, cod), 32.2 (CH_3, ^{t}Bu), 34.6 (C, ^{t}Bu), 34.7 (C, ^{t}Bu), 34.9 (C, ^{t}Bu), 35.2 (d, CH_2, cod, J_{C-P}= 7.08 Hz), 35.6 (C, ^{t}Bu), 64.2 (CH=, cod), 66.5 (CH=, cod), 70.7 (CH-N), 70.8 (CH_2-O_{ox}), 76.2 (CH-OP), 98.7 (d, CH=, cod, J_{C-P}= 19.1 Hz), 104.7 (d, CH=, cod, J_{C-P}= 13.8 Hz), 117.4-149.1 (aromatic carbons), 161.8 (q, C-B, BArF, $^1J_{C-B}$= 49.7 Hz), 169.7 (C=N). MS HR-ESI [found 958.4517, $C_{49}H_{68}IrNO_4P$ $(M\text{-}BAr_F)^+$ requires 958.4515].

[Ir(cod)(L10e)]BAr_F: Yield: 59 mg (90%); ^{31}P NMR (161.9 MHz, $CDCl_3$): $\delta = 101.0$ (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.91 (m, 6H, CH_3, ^{i}Pr), 0.98 (s, 9H, CH_3, ^{t}Bu), 1.58 (s, 9H, CH_3, ^{t}Bu), 1.73 (s, 3H, CH_3), 1.74 (s, 3H, CH_3), 1.75 (m, 2H, CH_2, cod), 2.09 (m, 1H, CH, ^{i}Pr), 2.09-2.16 (m, 4H, CH_2, cod), 2.17 (s, 3H, CH_3), 2.28 (s, 3H, CH_3), 2.43 (m, 2H, CH_2, cod), 3.24 (m, 1H, CH=, cod), 4.05 (m, 1H, CH=, cod), 4.06 (m, 1H, CH-N), 4.16 (pt, 1H, CH-O_{ox}, J_{H-H}= 9.2 Hz), 4.55 (dd, 1H, CH-O_{ox}, $^2J_{H-H}$= 10.0 Hz, $^3J_{H-H}$= 2.8 Hz), 4.87 (m, 1H, CH=, cod), 5.59 (m, 1H, CH=, cod), 5.83 (d, 1H, CH-OP, $^3J_{H-P}$= 12.8 Hz), 7.06 (s, 1H, CH=), 7.26 (s, 2H, CH=), 7.46 (m, 2H, CH=), 7.52 (s, 4H, CH=), 7.63 (m, 2H, CH=), 7.71 (s, 8H, CH=). ^{13}C (100.6 MHz, $CDCl_3$): δ= 14.6 (CH_3, ^{i}Pr), 16.4 (CH_3), 16.5 (CH_3), 18.8 (CH_3, ^{i}Pr), 20.2 (CH_3), 20.3 (CH_3), 25.4 (CH_2,

cod), 29.1 (CH_2, cod), 31.0 (CH, ^{i}Pr), 31.3 (CH_3, ^{t}Bu), 32.4 (CH_3, ^{t}Bu), 32.6 (CH_2, cod), 34.4 (C, ^{t}Bu), 34.8 (C, ^{t}Bu), 35.9 (d, CH_2, cod, J_{C-P}= 5.43Hz), 63.3 (CH=, cod), 67.4 (CH=, cod), 70.4 (CH-N), 70.7 (CH_2-O_{ox}), 76.0 (CH-OP), 97.1 (d, CH=, cod, J_{C-P}= 19.9 Hz), 104.3 (d, CH=, cod, J_{C-P}= 13.8 Hz), 117.4-143.9 (aromatic carbons), 161.6 (q, C-B, BArF, $^{1}J_{C-B}$= 49.7 Hz), 169.0 (d, C=N, $^{3}J_{C-P}$= 8.34 Hz). MS HR-ESI [found 902.3892, $C_{45}H_{60}IrNO_4P$ $(M\text{-}BAr_F)^+$ requires 902.3889].

[Ir(cod)(L11a)]BAr_F: Yield: 64 mg (94%); ^{31}P NMR (161.9 MHz, $CDCl_3$): δ = 103.2 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.93 (s, 9H, CH_3, ^{t}Bu), 1.12 (s, 9H, CH_3, ^{t}Bu), 1.33 (s, 9H, CH_3, ^{t}Bu), 1.34 (s, 9H, CH_3, ^{t}Bu), 1.55 (s, 9H, CH_3, ^{t}Bu), 1.70 (m, 2H, CH_2, cod), 2.02 (m, 2H, CH_2, cod), 2.33 (m, 2H, CH_2, cod), 2.43 (m, 1H, CH_2, cod), 2.59 (m, 1H, CH_2, cod), 3.81 (m, 1H, CH=, cod), 4.04 (m, 1H, CH-N), 4.35 (pt, 1H, CH-O_{ox}, J_{H-H}= 8.8 Hz), 4.72 (dd, 1H, CH-O_{ox}, $^{2}J_{H-H}$= 10.0 Hz, $^{3}J_{H-H}$= 2.4 Hz), 5.00 (m, 1H, CH=, cod), 5.71 (m, 1H, CH=, cod), 5.83 (d, 1H, CH-OP, $^{3}J_{H-P}$= 20.8 Hz), 7.04 (d, 1H, CH=, $^{4}J_{H-H}$= 2.4 Hz), 7.17 (d, 2H, CH=, $^{3}J_{H-H}$= 7.6 Hz), 7.22 (d, 1H, CH=, $^{4}J_{H-H}$= 2.0 Hz), 7.29 (d, 1H, CH=, $^{4}J_{H-H}$= 2.0 Hz), 7.41 (t, 2H, CH=, $^{3}J_{H-H}$= 7.6 Hz), 7.47-7.52 (m, 4H, CH=), 7.71 (s, 8H, CH=). ^{13}C (100.6 MHz, $CDCl_3$): δ= 23.9 (CH_2, cod), 25.6 (CH_3, ^{t}Bu), 27.9 (CH_2, cod), 29.7 (CH_2, cod), 30.1 (CH_3, ^{t}Bu), 31.1 (CH_3, ^{t}Bu), 31.2 (CH_3, ^{t}Bu), 33.6 (CH_2, cod), 34.7 (C, ^{t}Bu), 34.8 (C, ^{t}Bu), 35.6 (C, ^{t}Bu), 36.9 (d, CH_2, cod, J_{C-P}= 6.84 Hz), 63.3 (CH=, cod), 67.4 (CH=, cod), 72.1 (CH_2-O_{ox}), 74.5 (CH-N), 75.0 (CH-OP), 97.5 (d, CH=, cod, J_{C-P}= 22.2 Hz), 104.8 (d, CH=, cod, J_{C-P}= 12.1 Hz), 117.4-148.7 (aromatic carbons), 161.6 (q, C-B, BArF, $^{1}J_{C-B}$= 49.7 Hz), 169.6 (d, C=N, $^{3}J_{C-P}$= 7.6 Hz). MS HR-ESI [found 972.4675, $C_{50}H_{70}IrNO_4P$ $(M\text{-}BAr_F)^+$ requires 972.4672].

[Ir(cod)(L11e)]BAr_F: Yield: 60 mg (92%); ^{31}P NMR (161.9 MHz, $CDCl_3$): δ = 102.9 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.95 (s, 9H, CH_3, ^{t}Bu), 1.11 (s, 9H, CH_3, ^{t}Bu), 1.58 (s, 9H, CH_3, ^{t}Bu), 1.65 (s, 3H, CH_3), 1.65 (m, 1H, CH_2, cod), 1.73 (m, 1H, CH_2, cod), 1.80 (s, 3H, CH_3), 1.99 (m, 1H, CH_2, cod), 2.15 (m, 1H, CH_2, cod), 2.23 (s, 3H, CH_3), 2.25 (s, 3H, CH_3), 2.26 (m, 1H, CH_2, cod), 2.43 (m, 2H, CH_2, cod), 2.54 (m, 1H, CH_2, cod), 3.98 (m, 1H, CH-N), 3.69 4.07 (m, 1H, CH=, cod), 4.16 (m, 1H, CH=, cod), 4.25 (pt, 1H, CH-O_{ox}, J_{H-H}= 9.6 Hz), 4.64 (dd, 1H, CH-O_{ox}, $^{2}J_{H-H}$= 10.0 Hz, $^{3}J_{H-H}$= 2.4 Hz), 4.92 (m, 1H, CH=, cod), 5.63 (m, 1H, CH=, cod), 5.74 (d, 1H, CH-OP, $^{3}J_{H-P}$= 12.4 Hz), 6.99 (s, 1H, CH=), 7.21 (s, 1H, CH=), 7.32 (m, 2H, CH=), 7.40-749 (m, 1H, CH=), 7.52 (s, 6H, CH=), 7.71 (s, 8H, CH=). ^{13}C (100.6 MHz, $CDCl_3$): δ= 16.5 (CH_3), 16.6 (CH_3), 20.1 (CH_3), 20.3 (CH_3), 23.8 (CH_2, cod), 26.0 (CH_3, ^{t}Bu), 28.0 (CH_2, cod), 30.9 (CH_3, ^{t}Bu), 32.2 (CH_3, ^{t}Bu), 33.9 (CH_2, cod), 34.3 (C, ^{t}Bu), 34.6 (C, ^{t}Bu), 35.1 (C, ^{t}Bu), 37.0 (d, CH_2, cod, J_{C-P}= 7.64 Hz), 65.5 (CH=, cod), 66.9 (CH=, cod), 71.9 (CH_2-O_{ox}), 74.7 (CH-N), 75.2 (d, CH-OP, J_{C-P}= 4.62 Hz), 95.5 (d, CH=, cod, J_{C-P}= 22.1 Hz), 103.5 (d, CH=, cod, J_{C-P}= 12.3 Hz), 117.4-145.1 (aromatic carbons), 161.6 (q, C-B, BArF, $^{1}J_{C-B}$= 49.7 Hz), 169.8 (d, C=N, $^{3}J_{C-P}$= 7.64 Hz). MS HR-ESI [found 916.4049, $C_{46}H_{62}IrNO_4P$ $(M\text{-}BAr_F)^+$ requires 916.4046].

[Ir(cod)(L12a)]BAr$_F$: Yield: 61 mg (92%); ^{31}P NMR (161.9 MHz, $CDCl_3$): $\delta = 101.5$ (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.26 (s, 9H, CH_3, ^{t}Bu), 1.32 (s, 9H, CH_3, ^{t}Bu), 1.33 (s, 9H, CH_3, ^{t}Bu), 1.52 (s, 9H, CH_3, ^{t}Bu), 1.75-2.1 (m, 8H, CH_2, cod), 3.28 (m, 1H, CH=, cod), 3.61 (m, 1H, CH=, cod), 4.50 (dd, 1H, CH-O_{ox}, $^2J_{H-H}$= 9.2 Hz, $^3J_{H-H}$= 3.6 Hz), 4.77 (pt, 1H, CH-O_{ox}, J_{H-H}= 10.0 Hz), 5.13 (m, 1H, CH=, cod), 5.18 (m, 1H, CH-N), 5.26 (m, 1H, CH=, cod), 6.22 (d, 1H, CH-OP, $^3J_{H-P}$= 8.4 Hz), 6.97 (d, 1H, CH=, $^3J_{H-H}$= 7.6 Hz), 7.13 (m, 3H, CH=), 7.36-7.52 (m, 10H, CH=), 7.60 (d, 1H, CH=, $^3J_{H-H}$= 6.4 Hz), 7.72 (m, 9H, CH=).^{13}C (100.6 MHz, $CDCl_3$): δ= 28.3 (CH_2, cod), 29.1 (CH_2, cod), 29.7 (CH_2, cod), 31.2 (CH_3, ^{t}Bu), 31.4 (CH_3, ^{t}Bu), 31.6 (CH_3, ^{t}Bu), 31.7 (CH_2, cod), 34.7 (C, ^{t}Bu), 35.3 (C, ^{t}Bu), 35.4 (C, ^{t}Bu), 63.5 (CH=, cod), 66.2 (CH=, cod), 70.8 (CH-N), 74.6 (CH-OP), 79.5 (CH_2-O_{ox}), 103.4 (d, CH=, cod, J_{C-P}= 15.3 Hz), 104.9 (d, CH=, cod, J_{C-P}= 12.2 Hz), 117.4-149.0 (aromatic carbons), 161.6 (q, C-B, BArF, $^1J_{C-B}$= 50.5 Hz), 172.5 (C=N). MS HR-ESI [found 992.4361, $C_{52}H_{66}IrNO_4P$ (M-BAr$_F$)$^+$ requires 992.4359].

[Ir(cod)(L12b)]BAr$_F$: Yield: 62 mg (94%); ^{31}P NMR (161.9 MHz, $CDCl_3$): $\delta = 107.2$ (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.30 (s, 9H, CH_3, $SiMe_3$), 0.66 (s, 9H, CH_3, $SiMe_3$), 1.56 (m, 1H, CH_2, cod), 1.69 (m, 1H, CH_2, cod), 1.96-2.17 (m, 6H, CH_2, cod), 3.08 (m, 1H, CH=, cod), 3.85 (m, 1H, CH=, cod), 4.41 (dd, 1H, CH-O_{ox}, $^2J_{H-H}$= 8.8 Hz; $^3J_{H-H}$= 3.2 Hz), 4.80 (pt, 1H, CH-O_{ox}, J_{H-H}= 9.2 Hz), 4.93 (m, 1H, CH=, cod), 5.10 (m, 1H, CH=, cod), 5.33 (m, 1H, CH-N), 5.97 (d, 1H, CH-OP, $^3J_{H-P}$= 4.4 Hz), 6.91 (d, 2H, CH=, $^3J_{H-H}$= 7.6 Hz), 6.96 (d, 1H, CH=, $^3J_{H-H}$= 8.8 Hz), 7.07 (d, 1H, CH=, $^3J_{H-H}$= 8.0 Hz), 7.22-7.56 (m, 14H, CH=), 7.62 (d, 1H, CH=, $^3J_{H-H}$= 6.0 Hz), 7.71 (s, 8H, CH=), 7.89 (d, 1H, CH=, $^3J_{H-H}$= 8.0 Hz), 8.00 (d, 1H, CH=, $^3J_{H-H}$= 8.0 Hz), 8.03 (s, 1H, CH=), 8.22(s, 1H, CH=). ^{13}C (100.6 MHz, $CDCl_3$): δ= 0.1 (CH_3, $SiMe_3$), 1.2 (CH_3, $SiMe_3$), 26.1 (CH_2, cod), 28.9 (CH_2, cod), 32.1 (CH_2, cod), 35.0 (CH_2, cod), 61.4 (CH=, cod), 66.8 (CH=, cod), 72.5 (CH-N), 74.6 (CH-OP), 78.6 (CH_2-O_{ox}), 103.3 (d, CH=, cod, J_{C-P}= 18.3 Hz), 104.9 (d, CH=, cod, J_{C-P}= 13.7 Hz), 117.4-150.2 (aromatic carbons), 161.6 (q, C-B, BArF, $^1J_{C-B}$= 49.7 Hz), 172.0 (d, C=N, $^3J_{C-P}$= 7.64 Hz). MS HR-ESI [found 1012.2960, $C_{50}H_{54}IrNO_4PSi_2$ (M-BAr$_F$)$^+$ requires 1012.2958].

[Ir(cod)(L12c)]BAr$_F$: Yield: 64 mg (96%); ^{31}P NMR (161.9 MHz, $CDCl_3$): $\delta = 105.8$ (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.48 (s, 9H, CH_3, $SiMe_3$), 0.71 (s, 9H, CH_3, $SiMe_3$), 1.91 (m, 1H, CH_2, cod), 2.04 (m, 1H, CH_2, cod), 2.49 (m, 4H, CH_2, cod), 2.37 (m, 1H, CH_2, cod), 2.51 (m, 1H, CH_2, cod), 3.11 (m, 1H, CH=, cod), 4.27 (m, 1H, CH=, cod), 4.75 (m, 1H, CH-O_{ox}), 5.00 (pt, 1H, CH-O_{ox}, J_{H-H}= 10.0 Hz), 5.40 (m, 1H, CH-N), 5.75 (m, 1H, CH=, cod), 5.81 (m, 1H, CH=, cod), 6.66 (d, 1H, CH-OP, $^3J_{H-P}$= 6.8 Hz), 7.19 (t, 2H, CH=, $^3J_{H-H}$= 9.6 Hz), 7.32 (d, 2H, CH=, $^3J_{H-H}$= 6.8 Hz), 7.48 (m, 3H, CH=), 7.62-7.79 (m, 13H, CH=), 7.98 (s, 8H, CH=), 8.11 (d, 1H, CH=, $^3J_{H-H}$= 8.0 Hz), 8.18 (d, 1H, CH=, $^3J_{H-H}$= 8.0 Hz), 8.25 (s, 1H, CH=), 8.34 (s, 1H, CH=). ^{13}C (100.6 MHz, $CDCl_3$): δ= 0.5 (CH_3, $SiMe_3$), 0.6 (CH_3, $SiMe_3$), 26.4 (CH_2, cod), 30.1 (CH_2, cod), 30.6

(CH_2, cod), 34.3 (d, CH_2, cod, J_{C-P}= 7.45 Hz), 61.3 (CH=, cod), 68.6 (CH=, cod), 69.8 (CH-N), 74.6 (CH-OP), 78.8 (CH_2-O_{ox}), 102.5 (d, CH=, cod, J_{C-P}= 18.3 Hz), 107.5 (d, CH=, cod, J_{C-P}= 14.4 Hz), 117.5-149.9 (aromatic carbons), 161.6 (q, C-B, BArF, $^1J_{C-B}$= 49.7 Hz), 172.4 (C=N). MS HR-ESI [found 1012.2962, $C_{50}H_{54}IrNO_4PSi_2$ $(M\text{-}BAr_F)^+$ requires 1012.2958].

[Ir(cod)(L13a)]BAr_F: Yield: 64 mg (96%); ^{31}P NMR (161.9 MHz, $CDCl_3$): δ = 103.4 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.35 (s, 9H, CH_3, ^{t}Bu), 1.37 (s, 9H, CH_3, ^{t}Bu), 1.48 (s, 9H, CH_3, ^{t}Bu), 1.61 (s, 9H, CH_3, ^{t}Bu), 1.74 (d, 3H, CH_3, $^3J_{H-H}$= 6.8 Hz), 1.75-2.06 (m, 8H, CH_2, cod), 3.17 (m, 1H, CH=, cod), 3.76 (m, 1H, CH=, cod), 4.58 (dd, 1H, CH-O_{ox}, $^2J_{H-H}$= 9.2 Hz, $^3J_{H-H}$= 4.0 Hz), 4.71 (m, 1H, CH=, cod), 4.90 (pt, 1H, CH-O_{ox}, J_{H-H}= 9.2 Hz), 5.17 (m, 1H, CH-N), 5.18 (m, 1H, CH=, cod), 5.55 (m, 1H, CH-OP), 7.17 (m, 4H, CH=), 7.40 (m, 3H, CH=), 7.53 (m, 6H, CH=), 7.32 (s, 8H, CH=).^{13}C (100.6 MHz, $CDCl_3$): δ= 17.1 (d, CH_3, $^3J_{C-P}$= 9.95 Hz), 28.2 (CH_2, cod), 29.4 (CH_2, cod), 31.2 (CH_2, cod), 31.2 (CH_3, ^{t}Bu), 31.3 (CH_3, ^{t}Bu), 32.1 (CH_3, ^{t}Bu), 32.5 (CH_2, cod), 34.7 (C, ^{t}Bu), 34.8 (C, ^{t}Bu), 35.4 (C, ^{t}Bu), 35.6 (C, ^{t}Bu), 62.0 (CH=, cod), 67.5 (CH=, cod), 69.2 (CH-OP), 71.4 (CH-N), 79.4 (CH_2-O_{ox}), 103.9 (CH=, cod) 117.4-149.3 (aromatic carbons), 161.6 (q, C-B, BArF, $^1J_{C-B}$= 49.7 Hz), 174.4 (C=N). MS HR-ESI [found 930.4205, $C_{47}H_{64}IrNO_4P$ $(M\text{-}BAr_F)^+$ requires 930.4202].

[Ir(cod)(L13b)]BAr_F: Yield: 63 mg (94%); ^{31}P NMR (161.9 MHz, $CDCl_3$): δ = 107.2 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.48 (s, 9H, CH_3, $SiMe_3$), 0.51 (s, 9H, CH_3, $SiMe_3$), 1.62 (d, 3H, CH_3, $^3J_{H-H}$= 6.4 Hz), 1.63 (m, 2H, CH_2, cod), 1.72 (m, 1H, CH_2, cod), 1.92 (m, 2H, CH_2, cod), 2.05 (m, 1H, CH_2, cod), 2.17 (m, 1H, CH_2, cod), 2.34 (m, 1H, CH_2, cod), 3.14 (m, 1H, CH=, cod), 4.03 (m, 1H, CH=, cod), 4.44 (dd, 1H, CH-O_{ox}, $^2J_{H-H}$= 9.6 Hz; $^3J_{H-H}$= 4.8 Hz), 4.84 (m, 2H, CH-O_{ox}, CH=, cod), 5.20 (m, 1H, CH-OP), 5.38 (m, 1H, CH-N), 5.75 (m, 1H, CH=, cod), 6.98 (d, 1H, CH=, $^3J_{H-H}$= 8.4 Hz), 7.04 (d, 1H, CH=, $^3J_{H-H}$= 8.8 Hz), 7.11 (d, 2H, CH=, $^3J_{H-H}$= 8.4 Hz), 7.26 (t, 3H, CH=, $^3J_{H-H}$= 6.4 Hz), 7.44-7.52 (m, 8H, CH=), 7.71 (s, 8H, CH=), 7.93 (d, 1H, CH=, $^3J_{H-H}$= 8.0 Hz), 7.96 (d, 1H, CH=, $^3J_{H-H}$= 8.0 Hz), 8.10 (s, 1H, CH=), 8.13 (s, 1H, CH=). ^{13}C (100.6 MHz, $CDCl_3$): δ= 0.2 (CH_3, $SiMe_3$), 1.3 (CH_3, $SiMe_3$), 19.3 (d, CH_3, $^3J_{C-P}$= 6.84 Hz), 26.3 (CH_2, cod), 29.4 (CH_2, cod), 31.4 (CH_2, cod), 34.7 (CH_2, cod), 60.9 (CH=, cod), 66.4 (CH=, cod), 68.2 (CH-OP), 71.2 (CH-N), 78.4 (CH_2-O_{ox}), 101.8 (d, CH=, cod, J_{C-P}= 18.3 Hz), 106.7 (d, CH=, cod, J_{C-P}= 15.3 Hz), 117.4-150.3 (aromatic carbons), 161.6 (q, C-B, BArF, $^1J_{C-B}$= 50.5 Hz), 173.4 (d, C=N, $^3J_{C-P}$= 7.64 Hz). MS HR-ESI [found 950.2804, $C_{45}H_{52}IrNO_4PSi_2$ $(M\text{-}BAr_F)^+$ requires 950.2802].

[Ir(cod)(L13c)]BAr_F: Yield: 61 mg (92%); ^{31}P NMR (161.9 MHz, $CDCl_3$): δ = 109.1 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.50 (s, 9H, CH_3, $SiMe_3$), 0.64 (s, 9H, CH_3, $SiMe_3$), 1.66 (m, 1H, CH_2, cod), 1.73 (d, 3H, CH_3, $^3J_{H-H}$= 6.8 Hz), 1.81 (m, 1H, CH_2, cod), 1.92 (m, 5H, CH_2, cod, 2.06 (m, 1H, CH_2, cod), 3.05 (m, 1H, CH=, cod), 3.97 (m, 1H, CH=, cod), 4.60 (dd, 1H, CH-O_{ox}, $^2J_{H-H}$= 9.2 Hz; $^3J_{H-H}$= 4.0 Hz), 4.91 (m, 2H, CH-O_{ox}, CH=,

cod), 5.18 (m, 1H, CH=, cod), 5.28 (m, 1H, CH-N), 5.47 (m, 1H, CH-OP), 6.96 (d, 1H, CH=, $^3J_{H-H}$= 8.8 Hz), 7.03 (d, 1H, CH=, $^3J_{H-H}$= 8.4 Hz), 7.18 (m, 2H, CH=), 7.25 (m, 2H, CH=), 7.46-7.52 (m, 6H, CH=), 7.72 (s, 9H, CH=), 7.95 (d, 1H, CH=, $^3J_{H-H}$= 8.0 Hz), 7.97 (d, 1H, CH=, $^3J_{H-H}$= 8.0 Hz), 8.13 (s, 1H, CH=), 8.18 (s, 1H, CH=). ^{13}C (100.6 MHz, $CDCl_3$): δ= 0.0 (CH_3, $SiMe_3$), 1.2 (CH_3, $SiMe_3$), 18.2 (d, CH_3, $^3J_{C-P}$= 7.64 Hz), 27.5 (CH_2, cod), 29.7 (CH_2, cod), 29.8 (CH_2, cod), 33.2 (CH_2, cod), 60.7 (CH=, cod), 69.2 (CH=, cod), 69.8 (CH-OP), 71.3 (CH-N), 79.2 (CH_2-O_{ox}), 104.6 (d, CH=, cod, J_{C-P}= 17.5 Hz), 105.7 (d, CH=, cod, J_{C-P}= 14.4 Hz), 117.4-150.6 (aromatic carbons), 161.6 (q, C-B, BArF, $^1J_{C-B}$= 49.7 Hz), 174.2 (C=N). MS HR-ESI [found 950.2805, $C_{45}H_{52}IrNO_4PSi_2$ (M-BAr_F)$^+$ requires 950.2802].

[Ir(cod)(L14a)]BAr_F: Yield: 65 mg (96%); ^{31}P NMR (161.9 MHz, $CDCl_3$): δ = 104.1 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.57 (d, 3H, CH_3, ^{i}Pr, $^3J_{H-H}$= 6.8 Hz), 0.89 (d, 3H, CH_3, ^{i}Pr, $^3J_{H-H}$= 6.8 Hz), 1.35 (s, 18H, CH_3, ^{t}Bu), 1.59 (s, 9H, CH_3, ^{t}Bu), 1.67 (s, 9H, CH_3, ^{t}Bu), 1.70 (m, 3H, CH_2, cod) 1.89 (m, 1H, CH_2, cod), 2.17 (m, 3H, CH_2, cod), 2.30 (m, 1H, CH_2, cod), 2.40 (m, 1H, CH, ^{i}Pr), 3.97 (m, 2H, CH=, cod), 4.48 (dd, 1H, CH-O_{ox}, $^2J_{H-H}$= 8.8 Hz, $^3J_{H-H}$= 4.4 Hz), 4.63 (m, 1H, CH=, cod), 4.84 (pt, 1H, CH-O_{ox}, J_{H-H}= 9.6 Hz), 4.90 (m, 1H, CH-OP), 5.34 (dd, 1H, CH-N, $^2J_{H-H}$= 9.6 Hz, $^3J_{H-H}$= 4.4 Hz), 5.65 (m, 1H, CH=, cod), 7.14-7.25 (m, 3H, CH=), 7.405-7.52 (m, 9H, CH=), 7.71 (s, 8H, CH=).^{13}C (100.6 MHz, $CDCl_3$): δ= 15.8 (CH_3, ^{i}Pr), 17.6 (CH_3, ^{i}Pr), 26.1 (CH_2, cod), 29.4 (CH_2, cod), 31.1 (CH_2, cod), 31.2 (CH_3, ^{t}Bu), 31.3 (CH_3, ^{t}Bu), 31.4 (CH_3, ^{t}Bu), 34.5 (CH_2, cod), 34.6 (CH, ^{i}Pr), 34.7 (C, ^{t}Bu), 34.8 (C, ^{t}Bu), 35.3 (C, ^{t}Bu), 35.6 (C, ^{t}Bu), 63.9 (CH=, cod), 64.0 (CH=, cod), 70.4 (CH-N), 75.9 (CH-OP), 78.9 (CH_2-O_{ox}), 101.4 (d, CH=, cod, J_{C-P}= 18.3 Hz), 105.4 (d, CH=, cod, J_{C-P}= 14.4 Hz), 117.4-149.1 (aromatic carbons), 161.6 (q, C-B, BArF, $^1J_{C-B}$= 50.5 Hz), 173.0 (C=N). MS HR-ESI [found 958.4518, $C_{49}H_{68}IrNO_4P$ (M-BAr_F)$^+$ requires 958.4515].

[Ir(cod)(L14b)]BAr_F: Yield: 64 mg (95%); ^{31}P NMR (161.9 MHz, $CDCl_3$): δ = 108.8 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.28 (d, 3H, CH_3, ^{i}Pr, $^3J_{H-H}$= 6.8 Hz), 0.55 (s, 18H, CH_3, $SiMe_3$), 0.84 (d, 3H, CH_3, ^{i}Pr, $^3J_{H-H}$= 7.2 Hz), 1.64 (m, 4H, CH_2, cod), 2.08 (m, 2H, CH_2, cod), 2.20 (m, 1H, CH_2, cod), 2.35 (m, 1H, CH_2, cod), 2.40 (m, 1H, CH, ^{i}Pr), 3.52 (m, 1H, CH=, cod), 4.08 (m, 1H, CH=, cod), 4.47 (dd, 1H, CH-O_{ox}, $^2J_{H-H}$= 9.2 Hz; $^3J_{H-H}$= 4.4 Hz), 4.75 (m, 1H, CH=, cod), 4.87 (m, 2H, CH-O_{ox}, CH-OP), 5.38 (m, 1H, CH-N), 5.85 (m, 1H, CH=, cod), 6.98 (t, 2H, CH=, $^3J_{H-H}$= 9.2 Hz), 7.11 (m, 2H, CH=), 7.25 (m, 3H, CH=), 7.45-7.52 (m, 8H, CH=), 7.71 (s, 8H, CH=), 7.94 (m, 2H, CH=), 8.11 (s, 1H, CH=), 8.14 (s, 1H, CH=). ^{13}C (100.6 MHz, $CDCl_3$): δ= 0.1 (CH_3, $SiMe_3$), 1.0 (CH_3, $SiMe_3$), 15.8 (CH_3, ^{i}Pr), 17.8 (CH_3, ^{i}Pr), 25.9 (CH_2, cod), 29.2 (CH_2, cod), 30.6 (d, CH, ^{i}Pr, $^3J_{C-P}$= 6.84 Hz), 31.7 (CH_2, cod), 35.0 (CH_2, cod), 61.2 (CH=, cod), 65.5 (CH=, cod), 70.5 (CH-N), 75.2 (CH-OP), 78.4 (CH_2-O_{ox}), 101.7 (d, CH=, cod, J_{C-P}= 19.1 Hz), 106.7 (d, CH=, cod, J_{C-P}= 13.6 Hz), 117.4-151.1 (aromatic carbons),

161.6 (q, C-B, BArF, $^{1}J_{C-B}$= 50.4 Hz), 173.4 (C=N). MS HR-ESI [found 978.3119, $C_{47}H_{56}IrNO_4PSi_2$ $(M\text{-}BAr_F)^+$ requires 978.3115].

[Ir(cod)(L14c)]BAr$_F$: Yield: 63 mg (93%); ^{31}P NMR (161.9 MHz, $CDCl_3$): δ = 108.9 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.51 (s, 9H, CH_3, $SiMe_3$), 0.64 (s, 9H, CH_3, $SiMe_3$), 0.95 (d, 3H, CH_3, ^{i}Pr, $^{3}J_{H-H}$= 6.4 Hz), 1.00 (d, 3H, CH_3, ^{i}Pr, $^{3}J_{H-H}$= 6.4 Hz), 1.85 (m, 5H, CH_2, cod), 2.00 (m, 2H, CH_2, cod), 2.14 (m, 1H, CH_2, cod), 2.45 (m, 1H, CH, ^{i}Pr), 3.33 (m, 1H, CH=, cod), 4.02 (m, 1H, CH=, cod), 4.62 (dd, 1H, CH-O_{ox}, $^{2}J_{H-H}$= 9.2 Hz; $^{3}J_{H-H}$= 4.4 Hz), 4.92 (m, 3H, CH=, cod, CH-O_{ox}, CH-OP), 5.29 (m, 2H, CH-N, CH=, cod), 6.99 (m, 2H, CH=), 7.26 (m, 4H, CH=), 7.42-7.53 (m, 9H, CH=), 7.73 (s, 8H, CH=), 7.96 (m, 2H, CH=), 8.13 (s, 1H, CH=), 8.16 (s, 1H, CH=). ^{13}C (100.6 MHz, $CDCl_3$): δ= 0.1 (CH_3, $SiMe_3$), 1.0 (CH_3, $SiMe_3$), 18.3 (CH_3, ^{i}Pr), 18.3 (CH_3, ^{i}Pr), 28.1 (CH_2, cod), 29.3 (CH_2, cod), 31.4 (CH_2, cod), 32.2 (d, CH, ^{i}Pr, $^{3}J_{C-P}$= 6.13 Hz), 32.6 (CH_2, cod), 60.6 (CH=, cod), 69.1 (CH=, cod), 71.0 (CH-N), 78.2 (CH_2-O_{ox}), 78.6 (CH-OP), 104.6 (d, CH=, cod, J_{C-P}= 16.9 Hz), 105.4 (d, CH=, cod, J_{C-P}= 14.6 Hz), 117.4-150.2 (aromatic carbons), 161.6 (q, C-B, BArF, $^{1}J_{C-B}$= 49.7 Hz), 173.6 (d, C=N, $^{3}J_{C-P}$= 6.13 Hz). MS HR-ESI [found 978.3118, $C_{47}H_{56}IrNO_4PSi_2$ $(M\text{-}BAr_F)^+$ requires 978.3115].

5.3.4.5. Typical procedure for the hydrogenation of olefins.

The alkene (0.5 mmol) and Ir complex (2 mol %) were dissolved in CH_2Cl_2 (2 mL) and 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 1H NMR. The enantiomeric excesses of hydrogenated products from **S1**-**S52**[8,9,10] and products derived from cyclic β-enamides **S31**-**S37**[15] were determined using the conditions previously described.

5.3.5. References

1 a) Balser, H.-U., Federsel, H.-J., Eds; *Asymmetric Catalysis in Industrial Scale: Challenges, Approaches and Solutions*, 2nd Ed; Wiley: Weinheim, **2010**. b) Ojima, I., Ed; *Catalytic Asymmetric Synthesis*, 3rd Ed; John Wiley & Sons, Inc.: Hoboken, **2010**. c) Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds; *Comprehensive Asymmetric Catalysis*; Springer-Verlag: Berlin, **1999**.

2 a) Brown, J. M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds; Springer-Verlag: Berlin, **1999**; Vol. I, pp 121. b) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, **1994**. c) Wang, D.-S.;

Chen, Q.-A.; Lu, S.-M.; Zhou, Y.-G. *Chem. Rev.* **2012**, *112*, 2557. d) Knowles, W. S.; Noyori, R. *Acc. Chem. Res*. **2007**, *40*, 1238.

[3] a) Geneˆt, J. P. In *Modern Reduction Methods*; Andersson, P. G., Munslow, I. J., Eds.; Wiley-VCH: Weinheim, **2008**. b) Chi, Y., Tang, W., Zhang, X. In *Modern Rhodium-Catalyzed Organic Reactions*; Evans, P. A. Eds.; Wiley-VCH: Weinheim, **2005**. c) Kitamura, M., Noyori, R. in *Ruthenium in Organic Synthesis*; Murahashi, S.-I., Ed.; Wiley-VCH: Weinheim, **2004**. d) Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029. e) Johnson, N. B.; Lennon, I. C.; Moran, P. H.; Ramsden, J. A. *Acc. Chem. Res.* **2007**, *40*, 1291. f) Weiner, B.; Szymanski, W.; Janssen, D. B.; Minnaard, A. J.; Feringa, B. L. *Chem. Soc. Rev.* **2010**, *39*, 1656.

[4] For reviews, see: a) Cui, X.; Burgess, K. *Chem. Rev.* **2005**, *105*, 3272. b) Källström, K.; Munslow, I.; Andersson, P. G. *Chem. Eur. J.* **2006**, *12*, 3194. c) Roseblade, S. J.; Pfaltz, A. *Acc. Chem. Res.* **2007**, *40*, 1402. d) Church, T. L.; Andersson, P. G. *Coord. Chem. Rev.* **2008**, *252*, 513. e) Pàmies, O.; Andersson, P. G.; Diéguez, M. *Chem. Eur. J.* **2010**, *16*, 14232. f) Woodmansee, D. H.; Pfaltz, A. *Chem. Commun.* **2011**, *47*, 7912. g) Zhu, Y.; Burgess, K. *Acc. Chem. Res.* **2012**, *45*, 1623. h) Verendel, J. J.; Pàmies, O.; Diéguez, M.; Andersson, P. G. *Chem. Rev.* **2014**, *114*, 2130.

[5] a) Crabtree, R. H.; Felkin, H.; Morris, G. E. *J. Organomet. Chem.* **1977**, *141*, 205. b) Crabtree, R. H. *Acc. Chem. Res.* **1979**, *12*, 331.

[6] Schnider, P.; Koch, G.; Prétôt, R.; Wang, G.; Bohnen, F. M.; Krüger, C.; Pfaltz, A. *Chem. Eur. J.* **1997**, *3*, 887.

[7] Lightfoot, A.; Schnider, P.; Pfaltz, A. *Angew. Chem. Int. Ed.* **1998**, *37*, 2897.

[8] See, for instance: a) Blankenstein, J.; Pfaltz, A. *Angew. Chem. Int. Ed.* **2001**, *40*, 4445. b) Hou, D.-R.; Reibenspies, J. H.; Colacot, T. J.; Burgess, K. *Chem. Eur. J.* **2001**, *7*, 5391. c) Menges, F.; Pfaltz, A. *Adv. Synth. Catal.* **2002**, *344*, 40. d) Perry, M. C.; Cui, X.; Powell, M. T.; Hou, D.-R.; Reibenspies, J. H.; Burgess, K. *J. Am. Chem. Soc.* **2003**, *125*, 113. e) Tang, W.; Wang, W.; Zhang, X. *Angew. Chem. Int. Ed.* **2003**, *42*, 943. f) Liu, D.; Tang, W.; Zhang, X. *Org. Lett.* **2004**, *6*, 513. g) McIntyre, S.; Hörmann, E.; Menges, F.; Smidt, S. P.; Pfaltz, A. *Adv. Synth. Catal.* **2005**, *347*, 282. h) Trifonova, A.; Diesen, J. S.; Andersson, P. G. *Chem. Eur. J.* **2006**, *12*, 2318. i) Lu, S.-M.; Bolm, C. *Angew. Chem. Int. Ed.* **2008**, *47*, 8920. j) Engman, M.; Cheruku, P.; Tolstoy, P.; Bergquist, J.; Völker, S. F.; Andersson, P. G. *Adv. Synth. Catal.* **2009**, *351*, 375. k) Zhao, J.; Burgess, K. *J. Am. Chem. Soc.* **2009**, *131*, 13236. l) Lu, W.-J.; Chen, Y.-W.; Hou, X.-L. *Adv. Synth. Catal.* **2010**, *352*, 103. m) Zhang, Y.; Han, Z.; Li, F.; Ding, K.; Zhang, A. *Chem. Commun.* **2010**, *46*, 156. n) Verendel, J. J.; Zhou, T.; Li, J.-Q.; Paptchikhine, A.; Lebedev, O.; Andersson, P. G. *J. Am. Chem. Soc*. **2010**, *132*, 8880. o) Franzke, A.; Pfaltz, A. *Chem. Eur. J.* **2011**, *17*, 4131. p) Shang, J.; Han, Z.; Li, Y.; Wang, X.; Ding, K. *Chem. Commun.* **2012**, *48*, 5172. q) Wang, X.; Han, Z.; Wang, Z.; Ding, K. *Angew. Chem. Int. Ed.* **2012**, *51*, 936. r) Verendel, J. J.; Li, J.-Q.; Quan, X.; Peters, B.; Zhou, T.; Gautun, O. R.; Govender, T.; Andersson, P. G. *Chem. Eur. J.* **2012**, *18*, 6507. s) Mazuela, J.; Pàmies, O.; Diéguez, M. *Eur. J. Org. Chem.* **2013**, 2139. t) Khumsubdee, S.; Fan, Y.; Burgess, K. *J. Org. Chem*. **2013**, *78*, 9969. u) Zhu, Y.; Burgess, K. *RSC*

Advances **2012**, *2*, 4728. v) Müller, M.-A.; Pfaltz, A. *Angew. Chem Int. Ed.* **2014**, *53*, 8668.

[9] a) Diéguez, M.; Mazuela, J., Pàmies, O., Verendel, J. J., Andersson, P. G. *J. Am. Chem. Soc.* **2008**, *130*, 7208. b) Diéguez, M.; Pàmies, O.; Verendel, J. J.; Andersson, P. G. *Chem. Commun.* **2008**, 3888.

[10] a) Mazuela, J.; Verendel, J. J.; Coll, M.; Schäffner, B.; Börner, A.; Andersson, P. G.; Pàmies, O.; Diéguez, M. *J. Am. Chem. Soc.* **2009**, *131*, 12344. b) Mazuela, J.; Paptchikhine, A.; Pàmies, O.; Andersson, P. G.; Diéguez, M. *Chem. Eur. J.* **2010**, 16, 4567. c) Mazuela, J.; Norrby, P.-O.; Andersson, P. G.; Pàmies, O.; Diéguez, M. *J. Am. Chem. Soc.* **2011**, *133*, 13634. d) Mazuela, J.; Pàmies, O.; Diéguez, M. *Adv. Synth. Catal.* **2013**, *355*, 2569. e) Mazuela, J.; Pàmies, O.; Diéguez, M. *ChemCatChem* **2013**, *5*, 2410.

[11] The ligand design has also been extended to include phosphite-thioethers, see for example: a) Coll, M.; Pàmies, O.; Diéguez, M. *Chem. Commun.* **2011**, *47*, 9215. b) Coll, M.; Pàmies, O.; Diéguez, M. *Adv. Synth. Catal.* **2013**, *355*, 143. c) Margalef, J.; Caldentey, X.; Karlsson, E. A.; Coll, M.; Mazuela, J.; Pàmies, O.; Diéguez, M.; Pericàs, M. A. *Chem. Eur. J.* **2014**, *20*, 12201. d) Biosca, M.; Coll, M.; Lagarde, F.; Brémond, E.; Routaboul, L.; Manoury, E.; Pàmies, O.; Poli, R.; Diéguez, M. *Tetrahedron* **2015**, http://dx.doi.org/10.1016/j.tet.2015.01.047. e) Borràs, C. ; Biosca, M. ; Pàmies, O. ; Diéguez, M. *Organometallics* **2015**, *34*, 5321.

[12] a) Lu, W.-J.; Chen, Y.-W.; Hou, X.-L. *Angew. Chem., Int. Ed.* **2008**, *47*, 10133. b) Maurer, F.; Huch, V.; Ullrich, A.; Kazmaier, U. *J. Org. Chem.* **2012**, *77*, 5139. c) ref 8i. d) ref 8q. e) ref 8r.

[13] For successful application, see: (a) Lu, W.-J.; Hou, X.-L. *Adv. Synth. Catal.* **2009**, *351*, 1224. b) ref 8p.

[14] For successful applications, see: (a) Ganić, A.; Pfaltz, A. *Chem. Eur. J.* **2012**, *18*, 6724. b) ref 8c. (c) Paptchikhine, A.; Cheruku, P.; Engman, M.; Andersson, P. G. *Chem. Commun.* **2009**, 5996.

[15] See for instance: a) Jiang, X.-B.; Lefort, L.; Goudriaan, P. L.; de Vries, A. H. M.; van Leeuwen, P. W. N. M. de Vries, J. G.; Reek, J. N. H. *Angew. Chem. Int. Ed.* **2006**, *45*, 1223. b) Wu, Z.; Ayad, T.; Ratevelomanana-Vidal, V. *Org. Lett.* **2011**, *13*, 3782. c) Revés, M.; Ferre, C.; León, T.; Doran, S.; Etayo, P.; Vidal-Ferran, A.; Riera, A.; Verdaguer, X. *Angew. Chem. Int. Ed.* **2010**, *49*, 9452. d) Liu, G.; Liu, X.; Cai, Z.; Jiao, G.; Xu, G.; Tang, W. *Angew. Chem. Int. Ed.* **2013**, *52*, 4235.

[16] Pharm, D. Q.; Nogid, A. *Clin. Ther.* **2008**, *30*, 813.

[17] Ross, S. B.; Thorberg, S.-O.; Jerning, E.; Mohell, N.; Stenfors, C.;Wallsten, C.; Milchert, I. G.; Ojteg, G. A. *CNS Drug Rev.* **1999***,* 5, 213

[18] Only three catalytic systems have provided high enantioselectivities, see: a) Cheruku, P.; Gohil, S.; Andersson, P. G. *Org. Lett.* **2007**, *9*, 1659 (ee's up to 95%). b) Mazuela, J.; Paptchikhine, A.; Pàmies, O.; Andersson, P. G.; Diéguez, M. *Chem. Eur. J.* **2010**, *16*, 4567 (ee's up to 82%). c) M. Biosca, A. Paptchikhine, O. Pàmies, P. G. Andersson, M. Diéguez, *Chem. Eur. J.* **2015**, *21*, 3455 (ee's up to 97%).

[19] Buisman, G. J. H.; Kamer, P. C. J.; van Leeuwen, P. W. M. N. *Tetrahedron: Asymmetry* **1993**, *4*, 1625.

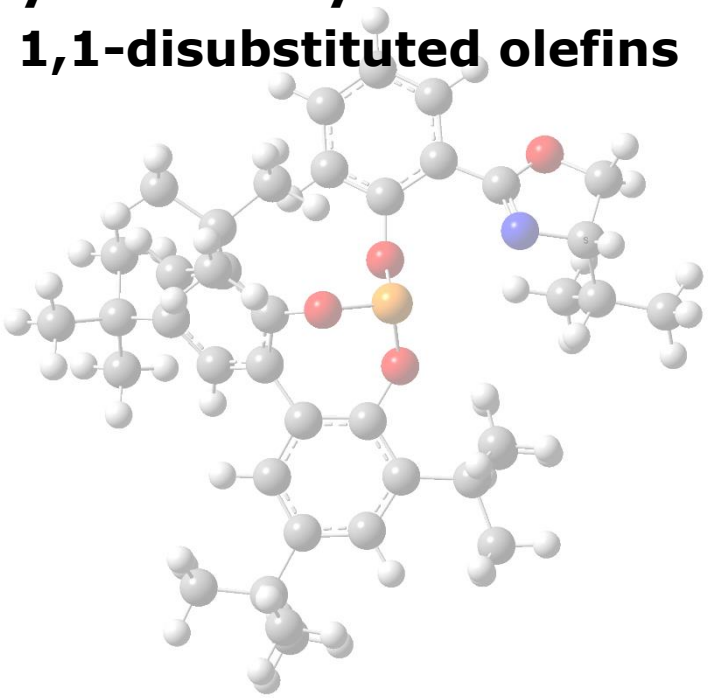
[20] a) Randy, M.; Duhaime, D. A.; Lombardo, I. A.; Alan, C. W. *J. Org. Chem.* **1985**, *50*, 873. b) Prepared by stereoselective Horner-Wadsworth-Emmons olefination: Paterson, I.; Yeung, K.-S.; Smaill, J. B. *Synlett* **1993**, 774; followed by reduction of the α,β-unsaturated ester: c) Corey, E. J.; Kirst, H. A.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1970**, *92*, 6314. For the synthesis of α,β-Unsaturated Carbonyl Compounds, see: d) Tian, F.; Yao, D.; Liu, Y.; Xie, F.; Zhang, W. *Adv. Synth. Catal.* **2010**, *352*, 1841.

[21] a) Pautigny, C.; Debouit, C.; Vayron, P.; Ayad, T.; Ratovelomanana-Vidal, V. *Tetrahedron Asymmetry* **2010**, *21*, 1382. b) Wu, Z.; Ayad, T.; Ratovelomanana-Vidal, V. *Org. Lett.* **2011**, *13*, 3782. c) Arribas, I.; Rubio, M.; Kleman, P.; Pizzano, A. *J. Org. Chem.* **2013**, *78*, 3997. d) Liu, G.; Liu, X.; Cai, Z.; Jiao, G.; Xu, G.; Tang, W. *Angew. Chem. Int. Ed.* **2013**, *52*, 4235.

[22] Lo Fiego, M. J.; Lockhart, M. T.; Chopa, A. B. *J. Organomet. Chem.* **2009**, *694*, 3674.

Chapter 6

Asymmetric hydroboration of 1,1-disubstituted olefins



UNIVERSITAT ROVIRA I VIRGILI
DESIGN OF TAILOR-MADE CHIRAL LIGAND LIBRARIES FOR C-X BOND FORMING REACTIONS. STUDY OF THE KEY INTERMEDIATES BY NMR AND DFT
Marc Magre Rosich

6. Asymmetric hydroboration of 1,1-disubstituted olefins

6.1. Background

Metal-catalyzed hydroboration of olefins has become an useful synthetic tool for organic chemists. Methods for transformation of the newly introduced carbon-boron bond with retention of stereoselectivity are crucial. The major advantage they offer is that the C-B formed bond can be derivatized to a consecutive carbon-oxygen, carbon-carbon, carbon-nitrogen. The organoboranes produced are important intermediates in many natural product and drug synthesis.

Mostly all hydroborations of olefins undergo catalyzed by Rh-based catalyst, being styrene derivatives the most used benchmark substrates.

Regarding 1,1-disubstituted olefins, the examples of their hydroboration is rarely existing. Whether the process mediated or catalyzed, in most asymmetric transformations involving olefins as prochiral reagents, 1,1-disubstituted olefins stand out as a particularly more challenging substrates. This can be attributed to the difficulty of a chiral auxiliary or chiral catalyst to discriminate between two relatively similar substituents at a germinal position and therefore, discriminate between the two faces of the olefin. For that reason, enantioselectivities for these substrates are usually lower than those obtained for the corresponding 1,2-disubstituted, trisubstituted or even tetrasubstituted analogues.

The first successful hydroboration of 1,1-disubstituted olefins was carried out by Soderquits *et al.* who designed chiral variants of 9-borabicyclononane (9-BBN) that mediated the hydroboration of four different terminal olefins, displaying an unprecedented enantioselectivities for the most biased substrates.

Subsequently, two important breakthroughs in asymmetric hydroboration of 1,1-disubstituted olefins were reported. They both included metal-catalyzed processes instead of expensive and sacrificial stoichiometric chiral auxiliaries.

The first breakthrough in metal-catalyzed hydroboration of 1,1-disubstitued olefins has been carried out by Hoveyda *et al.* They reported a NHC-Cu-catalyzed enantioselective hydroboration of acyclic and exocyclic 1,1-disubstituted alkenes. They were able to hydroborate different kind of sterically and electronically different 1,1-disubstituted alkenes providing organoboranes in high conversions and excellent enantioselectivities using NHC-Cu catalysts. The drawback of that transformation is the requirement of high catalyst loading (7.5 mol%), long reaction times (48 h), low temperature (ranging from -15 ºC to -50 ºC) and the presence of an almost equimolar amount of base.

The second breakthrough on metal-catalyzed hydroboration of 1,1-disubstituted olefins was carried out by Mazet *et al*. They presented a highly regio- and enantioselective catalytic hydroboration of α-substituted styrene derivatives, using phosphine-oxazoline

(PHOX) Ir-catalyst to afford high regioselectivities towards β-borylated product as well as high enantioselectivities for unhindered 1,1-disubstituted olefins. In that work, only high enantioselectivities could be achieved when small substituent (such as methyl) was present in α-position of the olefin. Moreover, the enantioselectivity was strongly affected by the electronic substituent on the aryl group, decreasing dramatically when electronrich substituent were present. However, it has the advantage that it can be performed under mild conditions and with low catalyst loading.

Taking into account all the drawbacks and advantages that these metal-catalyzed transformation presents, and also the similarity with the hydrogenation of 1,1-disubstituted olefins, where our phosphite-oxazoline have been successfully applied (See Section 5.2), we decided to test our privileged PHOX-based phosphite-oxazoline to the Ir-catalyzed asymmetric hydroboration of 1,1-disubstituted olefins. Herein, in Section 6.2, we present the application of PHOX-based phosphite-oxazoline ligands **L1**-**L4a**, **d**-**e**. A wide range of electronic and sterically different α-substituted styrene derivatives have been hydroborated to test the influence of replacing phosphine of PHOX ligand by a phosphite moiety. Our purpose is to achieve total regioselectivities towards β-borylated products and high enantioselectivities for a broader range of substrates.

6.2. Filling the gaps in the challenging asymmetric hydroboration of 1,1-disubstituted alkenes with simple phosphite-based phosphinooxazoline iridium catalysts

Magre, M.; Biosca, M.; Pàmies, O.; Diéguez, M. *ChemCatChem*, **2015**, *7*, 114.

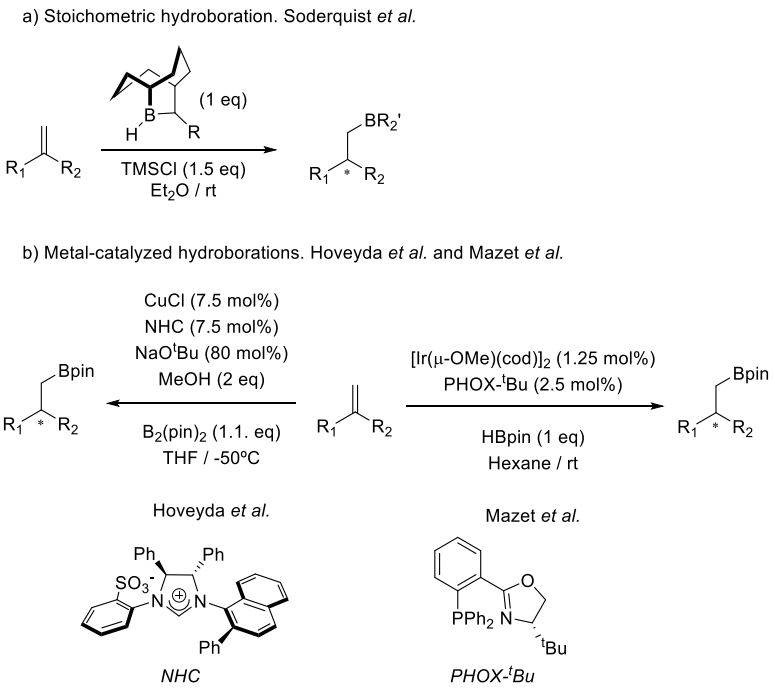
Abstract: *We have identified a readily accessible phosphinooxazoline-based phosphite-oxazoline catalytic system, (S)-4-isopropyl-2-{2-[(3,3',5,5'-tetra-tert-butyl-1,1'-biphenyl-2,2'-diyl) phosphite] phenyl}-2-oxazoline* ***L1a****, that can hydroborate a range of 1,1-disubstituted aryl olefins with high enantioselectivity (up to 94 %), excellent yields and perfect regioselectivity. The new phosphite-oxazoline ligands efficiently hydroborate a broader range of olefins than previous phosphinooxazoline PHOX ligands. In particular, a wide range of* α*-tert-butylstyrenes can be hydroborated that bear aryl substituents with different electronic and steric properties, which complements previous results with N-heterocyclic copper catalysts, the only other system reported to date that has achieved these reactions.*

6.2.1. Introduction

Many of today's pharmaceutical, fragrance and agrochemical compounds, and the chemicals used in functional materials are required as pure enantiomers.[1] As a result, the industrial production of enantiopure chiral compounds is gaining importance and synthetic procedures are constantly evolving towards high selectivity and productivity, atom economy, operational simplicity, cost efficiency, environmental friendliness, and low energy consumption. In comparison to other synthetic approaches, asymmetric catalysis is a smart strategy. A small amount of catalyst can produce large quantities of the desired chiral compound with only a few reaction steps and synthetic operations, thus bringing down the overall production cost, and decreasing the amount of byproducts. Chiral organoboron compounds have received a great deal of attention lately.[2] They are valuable organic intermediates because the C-B bond can be readily transformed to chiral C-N, C-O and C-C bonds.[2c,3] The synthesis of these compounds by transition-metal catalyzed asymmetric hydroboration is attracting considerable interest. However, whereas the asymmetric hydroboration of monosubstituted olefins (*i.e.* styrenes) and internal 1,2-disubstituted olefins (*i.e.* norbornadiene) has been successfully studied, the hydroboration of 1,1-disusbtituted olefins is still a challenge.[2,4] This is because the chiral transition metal catalyst has difficulty in controlling not only the specific boration at the desired terminal β-position rather than at the more substituted α-position (most catalysts favor the Markovnikov regioselectivity),[5] but also the face selectivity coordination (due to the presence of the two relatively similar substituents at the geminal position). To date high regio- and enantioselectivities have been reported in only three publications but the substrate scope is limited (Scheme 6.2.1).[6] In 2008 Soderquist *et*

al. reported the hydroboration of 1,1-disubstituted alkenes using stoichiometric quantities of chiral boranes with ee's between 28-92% (Scheme 6.2.1a).[6a] The highest enantioselectivity was observed only with 2,3,3-trimethylbut-1-ene.

Subsequently, two important breakthroughs in the asymmetric hydroboration of 1,1-disubstituted olefins were reported (Scheme 6.2.1b). They both included metal-catalyzed hydroboration processes instead of expensive and sacrificial stoichiometric chiral auxiliaries.



Scheme 6.2.1. State-of-the-art in the asymmetric hydroboration of challenging 1,1-disubstituted olefins.

One of them, reported by Hoveyda *et al.*, showed the asymmetric hydroboration of 1,1-disubstituted aryl-alkyl olefins with chiral Cu-based bidentate N-heterocyclic carbene catalysts.[6b] A range of α-methylstyrenes, and some aryl olefins with alkyl substituents other than the typical methyl unit and exocyclic alkenes, were hydroborated with high regioselectivities and enantioselectivities in the range 61-92% ee. Despite this important advance, high catalyst loading (7.5%), long reaction times (48h), low temperature (ranging from -15 ºC to -50 ºC) and the presence of an almost equimolar amount of base were required (Scheme 6.2.1b). Mazet *et al.* also reported the hydroboration of a range of 1,1-disubstituted aryl-alkyl olefins with excellent yields and regioselectivities (with exclusive attack at the desired β-position) but with the Ir-catalyst modified with the readily accessible phosphine-oxazoline PHOX-^{t}Bu ligand (Scheme 6.2.1b).[6c]

Enantioselectivity (up to 92%), however, was only high in the hydroboration of α-methylstyrene **S1**. The introduction of substituents at the aryl ring or the increase of the steric requirements at the alkyl substituent of the substrate decreased the enantioselectivity considerably. Although fewer substrates were successfully hydroborated than for the Cu-NHC based catalysts, the Ir-PHOX catalysts allow this transformation to take place under milder reaction conditions and with lower catalyst loading (Scheme 6.2.1b) which is more advantageous as a sustainable industrial process. Because of the limited substrate scope of the three advances mentioned, new developments in this field are still needed.

In most asymmetric transformations involving olefins as prochiral reagents (*i.e.* epoxidation, hydrogenation, etc.), 1,1-disubstituted olefins are systematically challenging substrates,[7] mainly due to face selectivity issues (as in the hydroboration reaction).

We recently showed that the highest reported enantioselectivities in the Ir-catalyzed hydrogenation of a very large range of simple 1,1-disubstituted olefins can be achieved by introducing a biaryl phosphite moiety into the ligand.[7c-d,8] Inspired by the work of Prof. Mazet[6c] and the similarities of the elementary steps involved in the hydroboration and hydrogenation, we studied here whether the introduction of a biaryl phosphite moiety into the ligand is also beneficial for the Ir-catalyzed hydroboration.

To this end, we took the previously successful PHOX ligand family and replaced the phosphine group with biaryl-phosphite moieties (ligands **L1**-**L4a**,**d**-**e**, Figure 6.2.1).

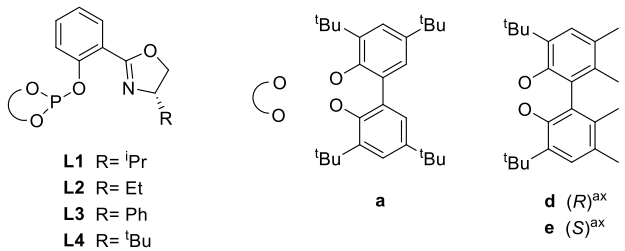


Figure 6.2.1. Phosphite-oxazoline PHOX-based ligands **L1**-**L4a**, **d**-**e**.

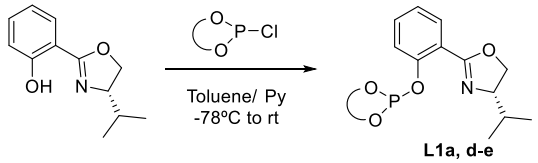
In this paper we present the application of these phosphite-oxazoline ligands **L1**-**L4a**,**d**-**e** in the asymmetric Ir-catalyzed hydroboration of 1,1-disubstituted olefins. These ligands incorporate the advantages of biaryl phosphites such as higher resistance to oxidation than phosphines, facile synthesis from readily available chiral alcohols and a straightforward modular construction.[9]

We investigated the catalytic performance by systematically varying the electronic and steric properties of the oxazoline substituents (**L1**-**L4**) and different substituents/configurations in the biaryl phosphite group (**a**, **d**-**e**).

6.2.2. Results and Discussion

6.2.2.1. Ligand synthesis

The phosphite-oxazoline PHOX-based ligands **L1a, d-e** can be straightforwardly synthesized by following the procedure previously described[10] in Section 5.2 (Scheme 6.2.2).



Scheme 6.2.2. Synthetic route for the synthesis of new phosphite-oxazoline PHOX-based ligands **L1a, d-e**.

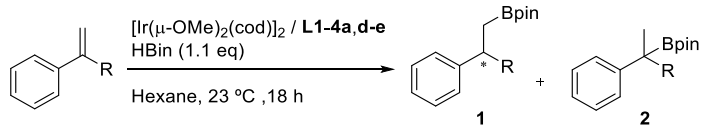
6.2.2.2. Initial screening experiments of phosphite-oxazoline PHOX-based ligands

As previously mentioned, the effectiveness of the catalyst in transferring the chiral information to the hydroborated product mainly depends on its ability to sterically differentiate between the two geminal substituents of the olefin. In order to assess the potential of the phosphite-oxazoline PHOX-based ligands **L1**-**L4a**, **d**-**e** in the hydroboration of substrates with different steric requirements, we initially evaluated them in the asymmetric Ir-catalyzed hydroboration of model substrate **S1**[2,6] and the hydroboration of more demanding **S2** (Table 6.2.1).

For purposes of comparison, we first tested **L1**-**L4a**, **d**-**e** using the same optimal reaction conditions found in the previous study of Mazet *et al.* with related Ir-PHOX catalytic systems.[6c] Reactions were therefore performed at room temperature, using 2.5 mol% of *in situ* generated catalyst ($[Ir(\mu\text{-OMe})(cod)]_2$/**L**) and hexane as solvent.[6c] The results are collected in Table 6.2.1.

All ligands favored the attack at the β-position, and the desired primary (pinacolato)boron adduct **1** was achieved with perfect regiocontrol (**1**/**2** ratio >99). Although enantioselectivities were moderate for α-methylstyrene **S1**, an unprecedentedly high enantioselectivity was achieved for the more challenging α-*tert*-butylstyrene **S2** (ee's up to 88%). It should be pointed out that the hydroboration of **S2** using the related phosphine-oxazoline PHOX-^{t}Bu ligand provided no conversion under the same reaction conditions (Table 6.2.1, entry 7). These important results indicate that both PHOX-based ligand families are complementary so we can successfully hydroborate both substrate types by correctly combining substrate and ligand type (phosphine-N or phosphite-N).

Table 6.2.1. Asymmetric hydroboration of α-methylstyrene **S1** and α-*tert*-butylstyrene **S2**.[a]



		S1		S2	
Entry	L*	% Conv (**1a**:**2a**)[b]	%ee[c]	% Conv (**1b**:**2b**)[b]	%ee[c]
1	**L1a**	100 (>99:1)	44 (*S*)	100 (>99:1)	88 (*S*)
2	**L1d**	50 (>99:1)	7 (*S*)	46 (>99:1)	43 (*S*)
3	**L1e**	60 (>99:1)	41 (*S*)	59 (>99:1)	79 (*S*)
4	**L2a**	100 (>99:1)	17 (*S*)	100 (>99:1)	43 (*S*)
5	**L3a**	100 (>99:1)	42 (*S*)	100 (>99:1)	86 (*S*)
6	**L4a**	96 (>99:1)	43 (*S*)	84 (>99:1)	88 (*S*)
7	**PHOX-^{t}Bu**	100 (>99:1)	92 (*S*)[6c]	0	-

[a] All reactions carried out in duplicate using 1 mmol of substrate, 1.25 mol% of [Ir(μ-OMe)(cod)]$_2$, 2.5 mol% of ligand, hexane (2 mL). [b] % Conversion measured by ^{1}H NMR. In all cases regioselectivities >99% were. [c] Determined by HPLC after conversion to the corresponding alcohols.

As far as the effect of the ligand parameters on activities and enantioselectivities is concerned, we found that bulky *tert*-butyl groups are needed at the *ortho* and *para* positions of the biaryl phosphite moiety to achieve the highest activities and enantioselectivities (Table 6.2.1, entry 1 vs 2 and 3). We also found that ligands with an *S* biaryl phosphite group provided better enantioselectivities than ligands with an *R* biaryl phosphite group (Table 6.2.1, entry 2 vs 3). This is an advantage because it means that the inexpensive 3,3',5,5'-tetra-*tert*-butyl-[1,1'-biphenyl]-2,2'-diyl phosphite moiety (**a**) can be used. For the oxazoline substituent, the enantioselectivities are highest with bulky isopropyl and *tert*-butyl groups (ligands **L1a** and **L4a**, Table 6.2.1, entries 1 and 6), but the activities are best when the sterical demand on the oxazoline substituents is decreased. The tradeoff between activities and enantioselectivities is therefore best with ligand **L1a** (Table 6.2.1, entry 1).

This result contrasts with the one described by Mazet's group, which required the presence of a *tert*-butyl oxazoline substituent to achieve high enantioselectivity, and it has an economic advantage because **L1a** is derived from L-valinol, which is around eight times cheaper than the L-*tert*-leucinol required for the synthesis of the PHOX-^{t}Bu ligand. We next optimized the reaction conditions by evaluating a variety of solvents and catalyst precursors using ligand **L1a**, which had provided the best results (Table 6.2.2).

Table 6.2.2. Asymmetric hydroboration of α-*tert*-butylstyrene **S2**. Effect of the solvent and catalyst precursors[a]

S2 **1b** **2b**

Entry	Solvent	[Cat. precursor]	% Conv (**1b**:**2b**)[b]	%ee[c]
1	Hexane	$[Ir(\mu\text{-OMe})(cod)]_2$	100 (>99:1)	88 (*S*)
2	THF	$[Ir(\mu\text{-OMe})(cod)]_2$	88 (>99:1)	76 (*S*)
3	CH_2Cl_2	$[Ir(\mu\text{-OMe})(cod)]_2$	100 (>99:1)	80 (*S*)
4	Toluene	$[Ir(\mu\text{-OMe})(cod)]_2$	96 (>99:1)	83 (*S*)
5	Hexane	$[Ir(\mu\text{-Cl})(cod)]_2$	100 (>99:1)[d]	92 (*S*)
6	Hexane	[Ir(cod)**L1a**]BAr_F	61 (>99:1)	66 (*S*)

[a] All reactions carried out in duplicate using 1 mmol of substrate, 1.25 mol% of Ir-catalyst precursor, 2.5 mol% of **L1a**, solvent (2 mL). [b] Determined by ^{1}H NMR. [c] Determined by HPLC after conversion to the corresponding alcohol. [d] 91% of isolated yield.

Although in all cases regioselectivity towards the desired β-adduct **1** remained excellent, activity and enantioselectivity were highly dependent on the solvent and the nature of the catalyst precursor. The combination of hexane and $[Ir(\mu\text{-Cl})(cod)]_2$ as catalyst precursor was found to be optimal (Table 6.2.2, entry 5). Under these new reaction conditions, we were therefore able to increase the enantioselectivity to 92% while maintaining the excellent yield and regioselectivity of the desired β-compound **1**. To the best of our knowledge Ir-**L1a** is the first catalytic system that can hydroborate **S2** with perfect regioselectivity, excellent yield and high enantioselectivity.

6.2.2.3. Asymmetric hydroboration of other 1,1-disubstituted olefins: scope and limitations

The unprecedented results obtained up to this point with Ir-**L1a** catalyst in the hydroboration of **S2** encouraged us to test Ir-**L1a** in the hydroboration of other 1,1-disubstituted olefins (Table 6.2.3).

First, we studied the hydroboration of several phenyl/alkyl olefins bearing alkyl substituents with different steric demands (**S3**-**S5**; Table 6.2.3, entries 3-5). Excellent regioselectivities of the desired β-adduct **1** were achieved. Enantioselectivities were moderate regardless of the steric demands of the alkyl substituent (entries 3-5). However, enantioselectivities were not as low as those observed with related Ir-PHOX

catalysts when the steric hindrance on alkyl substituents was increased (*i.e.* ee's decreased from 92% to 31% when the Me was replaced by an Et substituent).[6c]

Table 6.2.3. Asymmetric hydroboration of 1,1-disubstituted olefins. Scope and limitations.[a]

Entry	Substrate	R^1	R^2	**1**:**2**	% Yield [b]	%ee[c]
1	**S1**	C_6H_5	Me	>99:1	93	50 (*S*)
2	**S2**	C_6H_5	^{t}Bu	>99:1	91	92 (S)
3	**S3**	C_6H_5	Et	>99:1	90	55 (S)
4	**S4**	C_6H_5	^{i}Bu	>99:1	88	56 (S)
5	**S5**	C_6H_5	^{i}Pr	>99:1	89	58 (S)
6	**S6**	4-Me-C_6H_4	^{t}Bu	>99:1	92	94 (S)
7	**S7**	4-OMe-C_6H_4	^{t}Bu	>99:1	91	93 (S)
8	**S8**	4-CF_3-C_6H_4	^{t}Bu	>99:1	94	90 (S)
9	**S9**	2-Naph	^{t}Bu	>99:1	89	87 (S)
10	**S10**	3-Me-C_6H_4	^{t}Bu	>99:1	90	92 (*S*)
11	**S11**	4-OMe-C_6H_4	CF_3	>99:1	88	18 (*S*)
12[d]	**S11**	4-OMe-C_6H_4	CF_3	-	0	nd

[a] All reactions carried out in duplicate using 1 mmol of substrate, 1.25 mol% of $[Ir(\mu\text{-Cl})(cod)]_2$, 2.5 mol% of **L1a**, hexane (2 mL). [b] Determined by ^{1}H NMR. [c] Determined by HPLC or GC after conversion to the corresponding alcohol. [d] Reaction carried out using the Ir PHOX-^{t}Bu catalyst. The hydrogenated product was isolated in 45% yield and 0% ee.

We next studied several α-*tert*-butylstyrenes that had aryl substituents with different electronic and steric properties (**S6**-**S10**; Table 6.2.3, entries 6-10). Advantageously, Ir-**L1a** is very tolerant to variations in the substituents of the aryl ring and can hydroborate a wide range of α-*tert*-butylstyrenes with comparable high enantioselectivities (up to 94%) and yields and perfect regioselectivity. Accordingly, our results using several *para*-substituted α-*tert*-butylstyrenes (**S6**-**S8**) indicated that enantioselectivity is relatively insensitive to the electronic effects in the aryl ring (ee's in the range 90-94%; entries 2, 6-8). Enantioselectivities were, however, highest in the hydroboration of electron-rich olefins **S6** and **S7** (entries 6-7). Enantioselectivities were also excellent in the hydroboration of *meta*-substituted olefins (**S9**-**S10**; entries 9-10). Again these results contrast with the ones described by Mazet *et al.* with related Ir-PHOX

catalysts where the introduction of any type of substituent at the aryl ring of the substrate had a negative effect on enantioselectivity.[6c]

We then looked into the hydroboration of aryl/trifluoromethyl olefins. Due to the unique properties of the fluorine, the efficient hydroboration of these substrates opens up an appealing route for obtaining organic intermediates for the preparation of drugs, agrochemicals, and materials. To the best of our knowledge only Hoveyda *et al.* have attempted the hydroboration of this substrate class with their Cu-NHC catalysts although they obtained undesired difluoroallylboronates.[6b] Here we have tested the new Ir-**L1a** and related Ir-PHOX catalysts in the hydroboration of the model 1-methoxy-4-(3,3,3-trifluoroprop-1-en-2-yl)benzene **S11** substrate (Table 6.2.3, entries 11 and 12). While Ir-PHOX-^{t}Bu was found to be inadequate, because it provided exclusively the hydrogenated product in racemic form, the Ir-**L1a** catalyst gave the desired hydroborated product with perfect regioselectivity and good yield, albeit with low enantiocontrol. This result opens up new possibilities for further research and it demonstrates once again that the behavior is not that observed with the Ir-phosphine-oxazoline PHOX catalysts.

6.2.3. Conclusions

We have identified a readily accessible Ir-phosphite/oxazoline PHOX-based catalytic system (**L1a**) that can hydroborate a range of 1,1-disubstituted aryl olefins with high enantioselectivity (up to 94%), excellent yields and perfect regioselectivity. The new phosphite-oxazoline PHOX-based ligands can efficiently hydroborate a broader range of olefins than previous phosphine-oxazoline PHOX ligands. Particularly, we were able to successfully hydroborate a wide range of α-*tert*-butylstyrenes, with aryl substituents that have different electronic and steric properties, thus complementing the results of Cu-NHC catalysts, the only other system reported to date that has attempted these reactions. In addition, the introduction of a biaryl phosphite moiety allows for the first time the highly regioselective hydroboration of aryl/trifluoromethyl olefins. Another advantage over previous PHOX ligands is that the new ligands are stable to air and therefore easier to handle and can be manipulated and stored in air. This contribution opens up the path for the synthesis of new Ir phosphite-based catalysts for the challenging hydroboration of 1,1-disubstituted olefins. Further studies on the design of new Ir/phosphite-based catalysts to further broaden the scope of this hydroboration reaction are currently underway.

6.2.4. Experimental Section

6.2.4.1. General considerations

All reactions were carried out using standard Schlenk techniques under an argon atmosphere. Solvents were purified and dried by standard procedures. Phosphorochloridites were easily prepared in one step from the corresponding binaphthols.[11] Intermediate compound (*S*)-2-(4-isopropyl-4,5-dihydrooxazol-2-yl)phenol,[12] ligands **L1**-**L4a**[10], ligands **L1d**-**e** (see Section 5.2) and substrates **S2**,[13] **S3**,[14] **S4**,[15] **S5**,[13] **S11**[7c] were prepared as previously reported. Substrates **S6**-**S10** were prepared using the Wittig olefination procedure.[16] ^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded using a 400 MHz spectrometer. Chemical shifts are relative to those of $SiMe_4$ (^{1}H and ^{13}C) as internal standard or H_3PO_4 (^{31}P) as external standard. ^{1}H, ^{13}C and ^{31}P assignments were made on the basis of ^{1}H-^{1}H gCOSY and ^{1}H-^{13}C gHSQC.

6.2.4.2. General procedure for the asymmetric hydroboration of 1,1-disubstituted substrates

The corresponding ligand ($2.5.10^{-2}$ mmol) and $[Ir(\mu\text{-}Cl)(cod)]_2$ (8.4 mg; $2.5.10^{-5}$ mmol) were dissolved in hexane (2 mL) and stirred for 10 minutes at room temperature. Then, the slightly turbid solution was cooled to 0°C and the desired 1,1-disubstituted olefin (1.0 mmol) was slowly added. After 5 minutes, pinacolborane (150 μL, 1.0 mmol) was added dropwise. The ice bath was then removed and the reaction was stirred at room temperature. After 18 hours, the volatiles were evaporated and the crude mixture was purified by column chromatography (SiO_2; Et_2O/hexane (1:9)) to give the hydroborated product as colorless oil.
Enantiomeric excesses were determined after oxidation of the pinacolborane derivatives to the corresponding alcohols. Pinacolborane derivative (0.25 mmol) were dissolved in Et_2O (2 mL) and cooled to 0°C. NaOH (3N, 2.0 mL) and H_2O_2 (30%, 1.5 mL) were then added. The resulting solution was stirred at room temperature for 2 h. Then, the solution was extracted twice with Et_2O (2 mL) and dried over $MgSO_4$, to yield the desired chiral primary alcohol.

4,4,5,5-Tetramethyl-2-(2-phenylpropyl)-1,3,2-dioxaborolane (1a). ^{1}H NMR ($CDCl_3$), δ: 1.08 (s, 12H, CH_3, Bpin), 1.09 (m, 2H, CH_2), 1.20 (d, $^{3}J_{H\text{-}H}$= 8 Hz, 3H, CH_3), 2.95 (m, 1H, CH), 7.0-7.2 (m, 5H, CH=). ^{13}C NMR ($CDCl_3$), δ: 24.6 (CH_3, Bpin), 24.7 (CH_3, Bpin), 24.9 (CH_3), 35.8 (CH), 82.9 (C, Bpin), 125.7 (CH=), 126.6 (CH=), 128.1 (CH=), 149.2 (C). HRMS calcd. for $C_{15}H_{23}BO_2$ (M+): 246.1791; found: 246.1794. Enantiomeric excesses determined after oxidation to phenylpropan-1-ol. ^{1}H NMR ($CDCl_3$), δ: 1.23 (d, $^{3}J_{H\text{-}H}$= 8 Hz, 3H, CH_3), 2.95 (m, 1H, CH), 3.71 (m, 2H, CH_2), 7.2-7.4 (m, 5H, CH=).^{13}C NMR ($CDCl_3$), δ: 17.5 (CH_3), 42.4 (CH), 68.7 (CH_2), 126.7 (CH=), 127.4 (CH=),

128.6 (CH=), 143.6 (C). HRMS calcd. for $C_9H_{12}O$ (M+): 136.0888; found: 136.0885. Ee determined by HPLC using Chiracel IA column (hexane/2-propanol=99/1, 0.5 mL/min, 254 nm). t_R 38.9 min (*R*); t_R 41.7 min (*S*).

2-(3,3-Dimethyl-2-phenylbutyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1b). ^{1}H NMR ($CDCl_3$), δ: 0.83 (s, 9H, CH_3, ^{t}Bu), 0.91 (s, 6H, CH_3, Bpin), 0.96 (s, 6H, CH_3, Bpin), 1.18 (m, 2H, CH_2), 2.67 (m, 1H, CH), 7.05-7.20 (m, 5H, CH=). ^{13}C NMR ($CDCl_3$), δ: 24.2 (CH_3, Bpin), 24.5 (CH_3, Bpin), 27.7 (CH_3, ^{t}Bu), 34.0 (C, ^{t}Bu), 51.6 (CH), 82.7 (C, Bpin), 125.6 (CH=), 127.1 (CH=), 129.7 (CH=), 144.3 (C). HRMS calcd. for $C_{18}H_{29}BO_2$ (M+): 288.2261; found: 288.2259. Enantiomeric excesses determined after oxidation to 3,3-dimethyl-2-phenylbutan-1-ol. ^{1}H NMR ($CDCl_3$), δ: 0.87 (s, 9H, CH_3, ^{t}Bu), 2.65 (m, 1H, CH), 4.01 (m, 2H, CH_2), 7.05-7.35 (m, 5H, CH=). ^{13}C NMR ($CDCl_3$), δ: 28.4 (CH_3, ^{t}Bu), 33.1 (C, ^{t}Bu), 58.9 (CH), 62.6 (CH_2), 125.6 (CH=), 126.8 (CH=), 127.1 (CH=), 128.2 (CH=), 140.2 (C). HRMS calcd. for $C_{12}H_{18}O$ (M+): 178.1358; found: 178.1357. Ee determined by HPLC using Chiracel IA column (hexane/2-propanol=98/2, 0.5 mL/min, 220 nm). t_R 23.0 min (*S*); t_R 25.2 min (*R*).

4,4,5,5-Tetramethyl-2-(2-phenylbutyl)-1,3,2-dioxaborolane (1c). ^{1}H NMR ($CDCl_3$), δ: 0.73 (t, $^3J_{H-H}$= 8.0 Hz, 3H, CH_3), 1.08 (s, 12H, CH_3, Bpin), 1.12 (m, 2H, CH_2), 1.59 (m, 2H, CH_2), 2.65 (m, 1H, CH), 7.0-7.2 (m, 5H, CH=). ^{13}C NMR ($CDCl_3$), δ: 12.2 (CH_3), 24.6 (CH_3, Bpin), 24.7 (CH_3, Bpin), 35.8 (CH), 43.3 (CH_2), 82.9 (C, Bpin), 125.7 (CH=), 127.4 (CH=), 128.0 (CH=), 147.2 (C). HRMS calcd. for $C_{16}H_{25}BO_2$ (M+): 260.1948; found: 260.1947. Enantiomeric excesses determined after oxidation to 2-phenylbutan-1-ol. ^{1}H NMR ($CDCl_3$), δ: 0.85 (t, $^3J_{H-H}$= 8.0 Hz, 3H, CH_3), 1.5-1.8 (m, 2H, CH_2), 2.65 (m, 1H; CH), 3.75 (m, 2H, CH_2), 7.20-7.35 (m, 5H, CH=). ^{13}C NMR ($CDCl_3$), δ: 12.5 (CH_3), 25.7 (CH_2), 50.5 (CH), 67.3 (CH_2), 126.7 (CH=), 128.1 (CH=), 128.6 (CH=), 142.2 (C). HRMS calcd. for $C_{10}H_{14}O$ (M+): 150.1045; found: 150.1043. Ee determined by GC using CP-Chirasil-Dex CB column (90 kPa H_2, 110 °C isotherm). t_R 8.8 min (*S*); t_R 9.2 min (*R*).

4,4,5,5-Tetramethyl-2-(4-methyl-2-phenylpentyl)-1,3,2-dioxaborolane (1d). ^{1}H NMR ($CDCl_3$), δ: 0.81 (d, $^3J_{H-H}$= 6.0 Hz, 3H, CH_3, ^{i}Bu), 0.85 (d, $^3J_{H-H}$= 8.0 Hz, 3H, CH_3, ^{i}Bu), 1.02 (s, 12H, CH_3, Bpin), 1.2-1.6 (m, 5H), 2.95 (m, 1H, CH), 7.1-7.3 (m, 5H, CH=) ^{13}C NMR ($CDCl_3$), δ: 22.0 (CH_3, ^{i}Bu), 23.4 (CH_3, ^{i}Bu), 24.6 (CH_3, Bpin), 24.7 (CH_3, Bpin), 29.6 (CH_2, ^{i}Bu), 39.2 (CH, ^{i}Bu), 49.0 (CH), 82.8 (C, Bpin), 125.6 (CH=), 127.4 (CH=), 128.0 (CH=), 147.6 (C). HRMS calcd. for $C_{18}H_{29}BO_2$ (M+): 288.2261; found: 288.2262. Enantiomeric excesses determined after oxidation to 4-methyl-2-phenylpentan-1-ol. ^{1}H NMR ($CDCl_3$), δ: 0.79 (m, 6H, CH_3, ^{i}Bu), 1.2-1.6 (m, 5H), 2.85 (m, 1H, CH), 3.62 (m, 2H, CH_2), 7.1-7.3 (m, 5H, CH=).^{13}C NMR ($CDCl_3$), δ: 21.8 (CH_3, ^{i}Bu), 23.5 (CH_3, ^{i}Bu), 25.3 (CH_2, ^{i}Bu), 41.1 (CH, ^{i}Bu), 46.4 (CH), 68.0 (CH_2), 126.7 (CH=), 128.1 (CH=), 128.6 (CH=), 142.4 (C). HRMS calcd. for $C_{12}H_{18}O$ (M+): 178.1358; found: 178.1356. Ee

determined by HPLC using Chiracel IA column (hexane/2-propanol=98/2, 0.5 mL/min, 220 nm). t_R 22.5 min (*S*); t_R 24.3 min (*R*).

4,4,5,5-Tetramethyl-2-(3-methyl-2-phenylbutyl)-1,3,2-dioxaborolane (1e). ^{1}H NMR ($CDCl_3$), δ: 0.65 (d, $^3J_{H-H}$= 8.0 Hz, 3H, CH_3, ^{i}Pr), 0.87 (d, $^3J_{H-H}$= 8.0 Hz, 3H, CH_3, ^{i}Pr), 1.02 (s, 12H, CH_3, Bpin), 1.04 (s, 12H, CH_3, Bpin), 1.0-1.2 (m, 2H, CH_2), 1.68 (m, 1H, CH, ^{i}Pr), 2.55 (m, 1H, CH), 7.0-7.2 (m, 5H, CH=).^{13}C NMR ($CDCl_3$), δ: 20.4 (CH_3, ^{i}Pr), 20.6 (CH_3, ^{i}Pr), 24.4 (CH_3, Bpin), 24.6 (CH_3, Bpin), 35.3 (CH, ^{i}Pr), 48.3 (CH), 82.7 (C, Bpin), 125.6 (CH=), 127.7 (CH=), 128.3 (CH=), 146.1 (C). HRMS calcd. for $C_{17}H_{27}BO_2$ (M+): 274.2104; found: 274.2102. Enantiomeric excesses determined after oxidation to 3-methyl-2-phenylbutan-1-ol. ^{1}H NMR ($CDCl_3$), δ: 0.75 (d, $^3J_{H-H}$= 8.0 Hz, 3H, CH_3, ^{i}Pr), 1.02 (d, $^3J_{H-H}$= 8.0 Hz, 3H, CH_3, ^{i}Pr), 1.93 (m, 1H, CH, ^{i}Pr), 2.55 (m, 1H, CH), 3.8-4.0 (m, 2H, CH_2), 7.2-7.4 (m, 5H, CH=). ^{13}C NMR ($CDCl_3$), δ: 21.0 (CH_3, ^{i}Pr), 21.1 (CH_3, ^{i}Pr), 30.1 (CH, ^{i}Pr), 55.8 (CH), 65.2 (CH_2), 126.7 (CH=), 128.5 (CH=), 128.7 (CH=), 141.6 (C). HRMS calcd. for $C_{11}H_{16}O$ (M+): 164.1201; found: 164.1202. Ee determined by HPLC using Chiracel IA column (hexane/2-propanol=98/2, 0.5 mL/min, 210 nm). t_R 25.2 min (*S*); t_R 26.5 min (*R*).

2-(3,3-Dimethyl-2-(p-tolyl)butyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1f). ^{1}H NMR ($CDCl_3$), δ: 0.85 (s, 9H, CH_3, ^{t}Bu), 0.94 (s, 6H, CH_3, Bpin), 0.97 (s, 6H, CH_3, Bpin), 1.21 (m, 2H, CH_2), 2.27 (s, 3H, CH_3), 2.67 (m, 1H, CH), 6.9-7.1 (m, 4H, CH=). ^{13}C NMR ($CDCl_3$), δ: 20.9 (CH_3), 24.2 (CH_3, Bpin), 24.5 (CH_3, Bpin), 27.7 (CH_3, ^{t}Bu), 34.0 (C, ^{t}Bu), 51.2 (CH), 82.7 (C, Bpin), 127.7 (CH=), 129.5 (CH=), 134.9 (C), 141.2 (C). HRMS calcd. for $C_{19}H_{31}BO_2$ (M+): 302.2417; found: 302.2415. Enantiomeric excesses determined after oxidation to 3,3-dimethyl-2-(p-tolyl)butan-1-ol. ^{1}H NMR ($CDCl_3$), δ: 0.88 (s, 9H, CH_3, ^{t}Bu), 2.33 (s, 3H, CH_3), 2.64 (m, 1H, CH), 4.0 (m, 2H, CH_2), 7.1-7.2 (m, 4H, CH=).^{13}C NMR ($CDCl_3$), δ: 21.0 (CH_3), 28.4 (CH_3, ^{t}Bu), 33.0 (C, ^{t}Bu), 58.9 (CH), 62.5 (CH_2), 128.9 (CH=), 129.6 (CH=), 136.3 (C), 136.7 (C) HRMS calcd. for $C_{13}H_{20}O$ (M+): 192.1514; found: 192.1511. Ee determined by GC using Chiradex B-DM column (77 kPa H_2, 110 °C isotherm). t_R 26.5 min (*S*); t_R 27.5 min (*R*).

2-(2-(4-Methoxyphenyl)-3,3-dimethylbutyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1g). ^{1}H NMR ($CDCl_3$), δ: 0.83 (s, 9H, CH_3, ^{t}Bu), 0.90 (s, 6H, CH_3, Bpin), 0.97 (s, 6H, CH_3, Bpin), 1.22 (m, 2H, CH_2), 2.65 (m, 1H, CH), 3.76 (s, 3H, OCH_3), 6.75 (d, 2H, $^3J_{H-H}$= 8.0 Hz, CH=), 7.07 (d, 2H, $^3J_{H-H}$= 8.0 Hz, CH=). ^{13}C NMR ($CDCl_3$), δ: 24.2 (CH_3, Bpin), 24.6 (CH_3, Bpin), 27.6 (CH_3, ^{t}Bu), 34.1 (C, ^{t}Bu), 50.7 (CH), 55.2 (OCH_3), 82.7 (C, Bpin), 112.5 (CH=), 130.4 (CH=), 136.6 (C), 157.7 (C). HRMS calcd. for $C_{19}H_{31}BO_3$ (M+): 318.2366; found: 318.2365. Enantiomeric excesses determined after oxidation to 2-(4-methoxyphenyl)-3,3-dimethylbutan-1-ol. ^{1}H NMR ($CDCl_3$), δ: 0.87 (s, 9H, CH_3, ^{t}Bu), 2.63 (m, 1H, CH), 3.82 (s, 3H, CH_3O), 3.97 (m, 2H, CH_2), 6.87 (d, 2H, $^3J_{H-H}$= 8.4 Hz, CH=), 7.14 (d, 2H, $^3J_{H-H}$= 8.4 Hz, CH=). ^{13}C NMR ($CDCl_3$), δ: 28.3 (CH_3, ^{t}Bu), 33.1 (C, ^{t}Bu), 55.2 (OCH_3), 58.1 (CH), 62.5 (CH_2), 113.6 (CH=), 130.6 (CH=),

131.6 (C), 158.4 (C). HRMS calcd. for $C_{13}H_{20}O_2$ (M+): 208.1463; found: 208.1460. Ee determined by GC using CP-Chirasil-Dex CB column (90 kPa H_2, 110 °C for 40 min, 5 °C/min until 150 °C, 20 °C/min until 170 °C). t_R 49.6 min (*S*); t_R 49.9 min (*R*).

2-(3,3-Dimethyl-2-(4-(trifluoromethyl)phenyl)butyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1h). ^{1}H NMR ($CDCl_3$), δ: 0.86 (s, 6H, CH_3, Bpin), 0.88 (s, 6H, CH_3, Bpin), 0.95 (s, 9H, CH_3, ^{t}Bu), 1.27 (m, 2H, CH_2) 2.77 (m, 1H, CH), 7.28 (d, 2H, $^3J_{H-H}$= 8.0 Hz, CH=), 7.47 (d, 2H, $^3J_{H-H}$= 8.0 Hz, CH=). ^{13}C NMR ($CDCl_3$), δ: 24.1 (CH_3, Bpin), 24.5 (CH_3, Bpin), 27.6 (CH_3, ^{t}Bu), 29.7 (C, ^{t}Bu), 51.6 (CH), 82.9 (C, Bpin), 124.1 (CH=), 132.2 (CH=), 128.9 (C), 152.3 (C). HRMS calcd. for $C_{19}H_{28}BF_3O_2$ (M+): 356.2134; found: 356.2133. Enantiomeric excesses determined after oxidation to 3,3-dimethyl-2-(4-(trifluoromethyl)phenyl)butan-1-ol. ^{1}H NMR ($CDCl_3$), δ: 0.87 (s, 9H, CH_3, ^{t}Bu), 2.76 (m, 1H, CH), 4.06 (m, 2H, CH_2), 7.34 (d, 2H, $^3J_{H-H}$= 7.6 Hz, CH=), 7.59 (d, 2H, $^3J_{H-H}$= 7.6 Hz, CH=). ^{13}C NMR ($CDCl_3$), δ: 28.3 (CH_3, ^{t}Bu), 32.1 (C, ^{t}Bu), 58.8 (CH), 62.5 (CH_2), 125.0 (CH=), 130.6 (CH=), 145.8 (C), 160.0 (C). HRMS calcd. for $C_{13}H_{17}BF_3O$ (M+): 246.1231; found: 246.1229. Ee determined by HPLC using Chiracel IA column (hexane/2-propanol=98/2, 0.5 mL/min, 220 nm). t_R 32.7 min (*S*); t_R 38.4 min (*R*).

2-(3,3-Dimethyl-2-(naphthalen-2-yl)butyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1i). ^{1}H NMR ($CDCl_3$), δ: 0.81 (s, 9H, CH_3, ^{t}Bu), 0.87 (s, 6H, CH_3, Bpin), 0.91 (s, 6H, CH_3, Bpin), 1.2-1.4 (m, 2H, CH_2), 2.89 (m, 1H, CH), 7.4-7.8 (m, 7H, CH=). ^{13}C NMR ($CDCl_3$), δ: 24.1 (CH_3, Bpin), 24.5 (CH_3, Bpin), 27.8 (CH_3, ^{t}Bu), 34.4 (C, ^{t}Bu), 51.7 (CH), 82.7 (C, Bpin), 124.4 (CH=), 125.4 (CH=), 126.3 (CH=), 127.3 (CH=), 127.7 (CH=), 132.2 (C), 133.0 (C). HRMS calcd. for $C_{22}H_{31}BO_2$ (M+): 338.2417; found: 338.2415. Enantiomeric excesses determined after oxidation to 3,3-dimethyl-2-(naphthalen-2-yl)butan-1-ol. ^{1}H NMR ($CDCl_3$), δ: 0.83 (s, 9H, ^{t}Bu), 2.79 (m, 1H, CH), 4.07 (m, 2H, CH_2), 7.30-7.77 (m, 7H, CH=) ^{13}C NMR ($CDCl_3$), δ: 28.5 (CH_3, ^{t}Bu), 33.7 (C, ^{t}Bu), 59.1 (CH), 62.6 (CH_2), 125.5 (CH=), 126.1 (CH=), 127.5 (CH=), 127.6 (CH=), 127.7 (CH=), 132.5 (C), 133.2 (C), 137.7 (C). HRMS calcd. for $C_{16}H_{20}O$ (M+): 228.1514; found: 228.1513. Ee determined by HPLC using Chiracel IA column (hexane/2-propanol=98/2, 0.5 mL/min, 220 nm). t_R 40.4 min (*S*); t_R 44.5 min (*R*).

2-(3,3-Dimethyl-2-(m-tolyl)butyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1j). ^{1}H NMR ($CDCl_3$), δ: 0.93 (s, 9H, CH_3, ^{t}Bu), 0.95 (s, 6H, CH_3, Bpin), 0.96 (s, 6H, CH_3, Bpin), 1.23 (m, 2H, CH_2), 2.29 (s, 3H, CH_3), 2.68 (m, 1H, CH), 6.9-7.1 (m, 5H, CH=). ^{13}C NMR ($CDCl_3$), δ: 21.4 (CH_3), 24.2 (CH_3, Bpin), 24.5 (CH_3, Bpin), 27.7 (CH_3, ^{t}Bu), 34.0 (C, ^{t}Bu), 51.5 (CH), 82.6 (C, Bpin), 126.2 (CH=), 127.0 (CH=), 136.3 (CH=), 138.0 (C), 144.3 (C). HRMS calcd. for $C_{19}H_{31}BO_2$ (M+): 302.2417; found: 302.2414. Enantiomeric excesses determined after oxidation to 3,3-dimethyl-2-(m-tolyl)butan-1-ol. ^{1}H NMR ($CDCl_3$), δ: 0.89 (s, 9H, CH_3, ^{t}Bu), 2.35 (s, 3H, CH_3), 2.65 (m, 1H, CH), 4.01 (m, 2H, CH_2), 7.05-7.2 (m, 5H, CH=). ^{13}C NMR ($CDCl_3$), δ: 21.6 (CH_3), 28.4 (CH_3, ^{t}Bu), 33.0 (C, ^{t}Bu), 58.9 (CH), 62.6 (CH_2), 126.8 (CH=), 128.05 (CH=), 137.7 (C). HRMS

calcd. for $C_{13}H_{20}O$ (M+): 192.1514; found: 192.1512. Ee determined by GC using CP-Chirasil-Dex CB column (90 kPa H_2, 110 °C isotherm). t_R 20.1 min (*S*); t_R 21.9 min (*R*).

4,4,5,5-Tetramethyl-2-(3,3,3-trifluoro-2-(4-methoxyphenyl)propyl)-1,3,2-dioxaborolane (1k). ^{1}H NMR ($CDCl_3$), δ: 1.03 (s, 6H, CH_3, Bpin), 1.09 (s, 6H, CH_3, Bpin), 1.40 (m, 2H, CH_2), 3.54 (m, 1H, CH), 3.79 (s, 3H, CH_3O), 6.84 (d, 2H, $^3J_{H-H}$= 8.4 Hz, CH=), 7.23 (d, 2H, $^3J_{H-H}$= 8.4 Hz, CH=). ^{13}C NMR ($CDCl_3$), δ: 24.3 (CH_3, Bpin), 24.4 (CH_3, Bpin), 44.8 (q, CH, $^3J_{H-F}$= 28.1 Hz), 55.2 (CH_3O), 83.0 (C, Bpin), 113.6 (CH=), 128.5 (d, C, J_{C-F} = 29.7 Hz), 128.7 (C), 130.0 (CH=), 159.2 (C). HRMS calcd. for $C_{16}H_{22}BF_3O_3$ (M+): 330.1614; found: 330.1612. Enantiomeric excesses determined after oxidation to 3,3,3-trifluoro-2-(4-methoxyphenyl)propan-1-ol. ^{1}H NMR ($CDCl_3$), δ: = 3.45 (m, 1H, CH), 3.8 (s, 3H, CH_3O), 3.98 (m, 1H, CH_2), 4.16 (m, 1H, CH_2), 6.92 (d, 2H, $^3J_{H-H}$= 8.4 Hz, CH=), 7.25 (d, 2H, $^3J_{H-H}$= 8.4 Hz, CH=). ^{13}C NMR ($CDCl_3$), δ: 51.5 (q, CH, J_{C-F} = 25.4 Hz), 55.2 (CH_3O), 61.2 (CH_2), 114.3 (CH=), 124.6 (d, C, J_{C-F} = 30.2 Hz), 130.2 (CH=), 159.7 (C). HRMS calcd. for $C_{10}H_{11}F_3O$ (M+): 220.0711; found: 220.0712. Ee determined by GC using CP-Chirasil-Dex CB column (90 kPa H_2, 110 °C isotherm). t_R 28.2 min (*S*); t_R 29.4 min (*R*).

6.2.5. References

1 a) *Comprehensive Asymmetric Catalysis*; Eds.: Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H.; Springer-Verlag: Berlin, **1999**. b) *Catalytic Asymmetric Synthesis*; 3rd Edition; Ed. Ojima, I; John Wiley & Sons, Inc.: Hoboken, **2010**. c) *Asymmetric Catalysis in Industrial Scale: Challenges, Approaches and Solutions*; 2nd Ed; Eds.: Blaser, H. U.; Federsel, H.-J.; Wiley: Weinheim, Germany, **2010**. d) *Asymmetric Catalysis in Organic Synthesis*; Ed.: Noyori, R.: Wiley: New York, **1994**. e) Busacca, C. A.; Fandrick, D. R.; Song, J. J.; Senanayakl, C. H. *Adv. Synth. Catal.* **2011**, *353*, 1825.

2 For reviews, see: a) Burgess, K.; Ohlmeyer, M. J. *Chem. Rev.* **1991**, *91*, 1179. b) Hayashi, T. in *Comprehensive Asymmetric Catalysis*; Eds.: Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H.; Springer-Verlag: Berlin, **1999**, vol. 1, pp. 351. c) Crudden, C. M.; Edwards, D. *Eur. J. Org. Chem*. **2003**, 4695. d) Carroll, A.-M.; OSullivan, T. P.; Guiry, P. J. *Adv. Synth. Catal.* **2005**, *347*, 609. e) Crudden, C. M.; Glasspoole, B. W.; Lata, C. J. *Chem. Commun.* **2009**, 6704. f) Fernández, E.; Guiry, P. J.; Connole, K. P. T.; Brown, J. M. *J. Org. Chem.* **2014**, *79*, 5391.

3 See for example: a) Matteson, D. S. *Chem. Rev.* **1989**, *89*, 1535. b) Hupe, E.; Marek, I.; Knochel, P. *Org. Lett.* **2002**, *4*, 2861. c) Imao, D.; Glasspoole, B.W.; Laberge, V. S.; Crudden, C. M. *J. Am. Chem. Soc.* **2009**, *131*, 5024.

4 Thomas, S. P.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2009**, *48*, 1896.

5 a) Sato, M.; Miyaura, N.; Suzuki, A. *Tetrahedron Lett.* **1990**, *31*, 231. b) Burgess, K.; Ohlmeyer, M. J. *J. Org. Chem.* **1988**, *53*, 5178. c) Burgess, K.; van der Donk, W. A.; Ohlmeyer, M. J. *Tetrahedron: Asymmetry* **1991**, *2*, 612. d) Hayashi, T.; Matsumoto, Y.; Ito, Y. *Tetrahedron: Asymmetry* **1991**, *2*, 601.

[6] a) Gonzalez, A. Z.; Román, J. G.; Gonzalez, E.; Martinez, J.; Medina, J. R.; Matos, K.; Soderquist, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 9218. b) Corberán, R; Mszar, N. W.; Hoveyda. A. H. *Angew. Chem. Int. Ed.* **2011**, *50*, 7079. c) Mazet, C.; Gérard, D. *Chem. Commun.* **2011**, *47*, 298.

[7] See for example: a) Wang, B.; Wong, O. A.; Zhao, M.-X.; Shi, Y. *J. Org. Chem.* **2008**, *73*, 9539 (epoxidation). b) Wang, X.; Zak, M.; Maddess, M.; O'Shea, P.; Tillyer, R.; Grabowski, E. J. J.; Reider, P. J. *Tetrahedron Lett.* **2000**, *41*, 4865 (dihydroxylation). c) Mazuela, J.; Verendel, J. J.; Coll, M.; Schäffner, B.; Börner, A.; Andersson, P. G.; Pàmies, O.; Diéguez, M. *J. Am. Chem. Soc.* **2009**, *131*, 12344 (hydrogenation). d) Pàmies, O.; Andersson, P. G.; Diéguez, M. *Chem. Eur. J.* **2010**, *16*, 14232 (hydrogenation).

[8] a) Diéguez, M.; Mazuela, J.; Pàmies, O.; Verendel, J. J.; Andersson, P. G. *J. Am. Chem. Soc.* **2008**, *130*, 7208. b) Diéguez, M.; Pàmies, O.; Verendel, J. J.; Andersson, P. G. *Chem. Commun.* **2008**, 3888. c) Mazuela, J.; Norrby, P.-O.; Andersson, P. G.; Pàmies, O.; Diéguez, M. *J. Am. Chem. Soc.* **2011**, *133*, 13634. d) Coll, M.; Pàmies, O.; Diéguez, M. *Chem. Commun.* **2011**, *47*, 9215. e) Mazuela, J.; Pàmies, O.; Diéguez, M. *Adv. Synth. Catal.* **2013**, *355*, 2569. f) Mazuela, J.; Pàmies, O.; Diéguez, M. *ChemCatChem* **2013**, *5*, 2410. g) Coll, M.; Pàmies, O.; Diéguez, M.*Adv. Synth. Catal.* **2013**, *355*, 143. h) Margalef, J.; Caldentey, X.; Karlsson, E. A.; Coll, M.; Mazuela, J.; Pàmies, O.; Diéguez, M.; Pericàs, M. A. *Chem. Eur. J.* **2014**, *20*, 1220.

[9] a) Claver, C.; Pàmies, O.; Diéguez, M. in *Phosphorus Ligands in Asymmetric Catalysis,* (Ed.: A. Börner), Wiley-VCH, Weinheim, **2008**, pp. 506. b) van Leeuwen, P. W. N.M.; Kamer, P. C. J.; Claver, C.; Pàmies, O.; Diéguez, M. *Chem. Rev.* **2011**, *111*, 2077.

[10] Pàmies, O.; Diéguez, M.; Claver, C. *J. Am. Chem. Soc.* **2005**, *127*, 3646.

[11] Buisman, G. J. H.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Tetrahedron: Asymmetry* **1993**, *4*, 1625.

[12] Gómez-Simón, M.; Jansat, S.; Muller, G.; Panyella, D.; Font-Bardía, M.; Solans, X. *J. Chem. Soc., Dalton Trans.* **1997**, 3755.

[13] Barlunega, J.; Fañanás, F. J.; Sanz, R.; Marcos, C.; Ignacio, J. M. *Chem. Comm.* **2005**, 933.

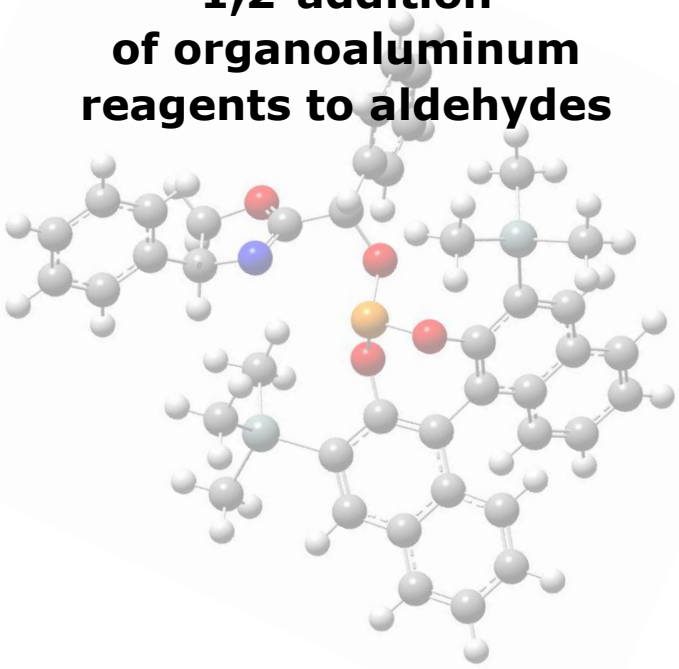
[14] Reitz, D. B.; Beak, P.; Farney, R. F.; Helmick, L. S. *J. Am. Chem. Soc.* **1978**, *100*, 5428.

[15] Nakamura, E.; Mori, S.; Nakamura, M.; Morokuma, K. *J. Am. Chem. Soc.* **1997**, *119*, 4887.

[16] Lo Fiego, Lockhart, M. T.; Chopa, A. B. *J. Organomet. Chem.* **2009**, *694*, 3674.

Chapter 7

Asymmetric Ni-catalyzed 1,2-addition of organoaluminum reagents to aldehydes



UNIVERSITAT ROVIRA I VIRGILI
DESIGN OF TAILOR-MADE CHIRAL LIGAND LIBRARIES FOR C-X BOND FORMING REACTIONS. STUDY OF THE KEY INTERMEDIATES BY NMR AND DFT
Marc Magre Rosich

7. Asymmetric Ni-catalyzed 1,2-addition of organoaluminum reagents to aldehydes

7.1. Background

The addition of carbon nucleophiles to carbonyl compounds such as aldehydes, is one of the most fundamental transformation for organic synthesis. The formed stereogenic secondary alcohols are interesting building blocks for fine chemistry. The use of lithium and magnesium organometallic species, which are too reactive and can react without the presence of the chiral catalyst, had led to low enantioselectivities. In contrast, diorganozinc reagents are less reactive and its addition to carbonyl compounds can be therefore asymmetrically catalyzed by a metal. Nevertheless, diorganozinc are quite expensive and in addition, important and valuable organozinc reagents, such as, $ZnMe_2$, are not very reactive. The reactivity of triorganoaluminum reagents is found between those two organometallic groups. They slowly react with carbonyl groups and they also show tolerance to diverse functional groups. Another advantage is the low price of unfunctionalized trialkylaluminum reagents (AlR_3, R= Me, Et, ^{n}Pr, ^{n}Bu,…), because they can be easily produced on an industrial scale by reaction of aluminum hydride and olefins. Despite these advantages, only few examples of 1,2-addition of organoaluminum compounds to carbonyls have been reported in the literature. In this respect, only Ti- and Ni-catalyst precursors have been successfully used for the 1,2-addition of triorganoaluminum reagents to aldehydes. Catalysts based on titanium complexes usually provide high enantioselectivities, but the high catalyst loadings (10-20 mol%) as well as the slow turnover rate, hamper their potential utility. These drawbacks can be overcome by using Ni-catalysts. In this context, the first breakthrough was presented in 2005 by Woodward *et al.* They applied binaphthyl-based phosphoramidites in the Ni-catalyzed 1,2-addition of trialkylaluminum reagents to aldehydes. Excellent conversions and enantioselectivities (81-95% ee) were obtained with either electron-rich or electron-deficient benzaldehyde derivatives.

Later, our group in collaboration with Woodward group disclosed that sugar-based phosphite ligands can also be used, providing high enantioselectivities (ee's up to 91%). Our group also showed that furanoside phosphite-phosphoramidite and diphosphoramidite ligands can be used in the Ni-1,2-addition to aldehydes, achieving enantioselectivities up to 84% using benzaldehyde.

For this purpose, in the following sections we present the application of PHOX-type ligands (**L3** and **L5**-**L7a**-**c**; Section 7.2) and second the generation of phosphite-oxazoline ligands (**L9**-**L14a**-**c**; Section 7.3) to the asymmetric Ni-catalyzed 1,2-addition of trialkylaluminum reagents to aryl aldehydes, with different electronic and steric properties. All results presented in Sections 7.2 and 7.3 are preliminary, demonstrating

the potential ability of those Ni-phosphite-oxazoline systems to catalyze the addition of different trialkylaluminum reagents ($AlMe_3$, $AlEt_3$ and DABAL-Me_3) to aldehydes enantioselectively.

7.2. First PHOX-based phosphite-oxazoline applied to asymmetric Ni-catalyzed 1,2-addition of triorganoaluminum to aldehydes

Magre, M.; Pàmies, O.; Diéguez, M. *Preliminary results*

Abstract: *PHOX-based phosphite-oxazoline ligands **L3** and **L5**-**L7a**-**c** have been tested in the enantioselective Ni-catalyzed 1,2-addition of triorganoaluminum reagents to aldehydes. Excellent yields (up to 93%) and moderate enantioselectivities (up to 62% ee) have been achieved with a range of benzaldehydes and several trialkylaluminum reagents.*

7.2.1. Introduction

The value of enantiopure alcohols lies mainly in their use as valuable building blocks for the synthesis of natural, pharmaceutical and agricultural products.[1] The catalytic asymmetric addition of organoaluminum reagents to aldehydes can provide a potencial synthetic tool for the preparation of these compounds.[1] Lithium and magnesium organometallic species are too reactive and its addition is very difficult to be stereocontrolled by a transition metal catalyst. On the other hand, diorganozinc are less reactive, and although they have been widely and successfully used, their high price makes them not very attractive from an industrial point of view.[2] The reactivity of triorganoaluminum reagents is found between those two organometallic groups explained above. Thus, not only trialkylaluminum reagents slowly react with carbonyl groups[3] but also they show a higher functional group tolerance than their magnesium and lithium analogues.[4] An additional advantage is the low price of unfunctionalized organoaluminum compounds (AlR_3, R= Me, Et, ^{n}Pr, ^{n}Bu,…), which can be easily produced.[5]

Despite all these advantages, only few examples of 1,2-addition of organoaluminum compounds to carbonyls have been reported in the literature.[6-10] In this respect, only Ti-[6] and Ni-based[7-10] catalysts have been used for the 1,2-addition of triorganoaluminum reagents to aldehydes.

In 2005, Woodward *et al.* discovered that nickel-based catalysts can allow high enantioselectivities at low catalyst loadings (0.05–1 mol%), thus overcoming the previously used Ti-catalysts' main drawback of requiring high catalyst loadings (10–20 mol %).[6] The new Ni-catalysts afforded excellent conversions and enantioselectivities (81-95% ee) for electron-rich and electron-deficient aryl-aldehydes.[7]

Later, our group in collaboration with Woodward group successfully applied monophosphite ligands derived from sugar scaffolds, achieving excellent enantioselectivities (ee's up to 91%).[8,9] Our group also reported the application of bidentate ligands containing phosphite and phosphoramidite moieties. That work represented the first application of bidentated ligands in the Ni-catalyzed asymmetric

1,2-addition of triorganoaluminum reagents to aldehydes, which opens the Ni-catalyzed 1,2-addition to the use of bidentated ligands.

Here we present the application of PHOX-based phosphite-oxazoline ligands **L3** and **L5**-**L7a**-**c** (Figure 7.2.1) which have been previously synthesized and successfully applied in several metal-catalyzed reactions (see Chapters 3, 5 and 6).[11]

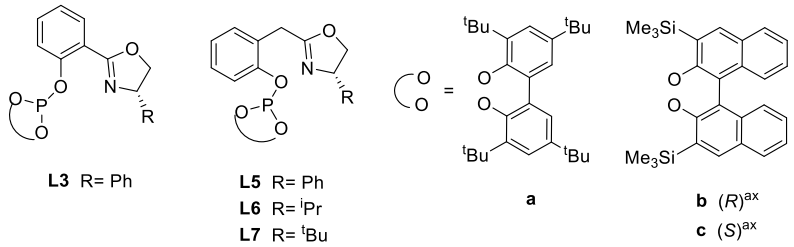


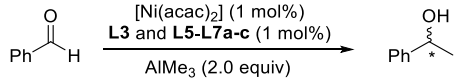
Figure 7.2.1. PHOX-based phosphite-oxazoline **L3** and **L5**-**L7a**-**c**.

7.2.2. Results and discussion

7.2.2.1. Asymmetric addition of $AlMe_3$ to benzaldehyde

First, we screened ligands **L3** and **L5-L7a**-**c** using benzaldehyde as benchmark substrate and $AlMe_3$ as alkylating agent following already reported conditions (Table 7.2.1).[8-10] Results showed that both enantioselectivities and yields are not dependent on ligand to metal ratio. Thus, using 0.5 eq or 2 eq of ligand neither yields nor enantioselectivities changed, suggesting that the phosphite-oxazoline ligands coordinates in a bidentate manner (entries 1 vs 2 and 3). Then, we evaluated the influence on the catalytic performance of replacing achiral biphenyl phosphite moiety (**a**) by a chiral binaphthyl moiety (**b** and **c**). Results showed that the presence of a chiral biaryl phosphite moiety has a positive effect on enantioselectivity (entry 4 and 5 *vs* 1). The results also indicated that the configuration of the product alcohols is controlled by the configuration of the biaryl phosphite. So, both enantiomers of the secondary alcohol are easily accessible in similar levels of enantioselectivities. After ligand evaluation, we found that ligands **L6b**-**c**, containing a methylene spacer between the oxazoline and the phenyl ring of the ligand and an isopropyl substituent in the oxazoline, provided the highest enantioselectivities, achieving both enantiomers in moderate enantioselectivities (up to 55% ee, entries 10 and 11).

Table 7.2.1. Screening of **L3** and **L5**-**L7a**-**c** in the asymmetric Ni-catalyzed 1,2-addition of $AlMe_3$ to benzaldehyde.



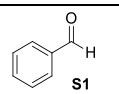
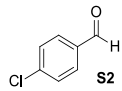
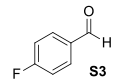
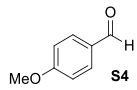
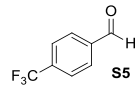
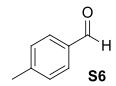
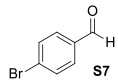
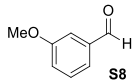
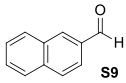
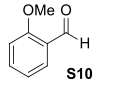
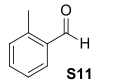
Entry[a]	Ligand	L/Ni	% Conv[b]	% Yield[c]	% ee[d]
1	**L3a**	1	100	91	4 (*R*)
2	**L3a**	0.5	100	89	4 (*R*)
3	**L3a**	2	100	90	4 (*R*)
4	**L3b**	1	99	89	28 (*S*)
5	**L3c**	1	70	62	33 (*R*)
6	**L5a**	1	100	93	8 (*R*)
7	**L5b**	1	100	91	24 (*S*)
8	**L5c**	1	100	92	24 (*R*)
9	**L6a**	1	100	94	1 (*R*)
10	**L6b**	1	100	91	50 (*S*)
11	**L6c**	1	99	93	55 (*R*)
12	**L7a**	1	100	90	2 (*S*)
13	**L7b**	1	100	91	37 (*S*)
14	**L7c**	1	100	88	27 (*R*)

[a] Reaction conditions: T= -20 ºC, [$Ni(acac)_2$] (1 mol%), $AlMe_3$ (2 equiv.), substrate (1 mmol), THF (8 mL). [b] % Conversion determined by GC after 3 hours. [c] Isolated yield. [d] Enantiomeric excess measured by GC using Cyclodex-B column.

7.2.2.2. Asymmetric addition of several aluminum reagents to a range of benzaldehyde-type aldehydes.

We, then decided to study the substrate scope with ligands **L6b** and **L6c**. The results are summarized in Table 7.2.2. The replacement of $AlMe_3$ by bulkier $AlEt_3$ had no effect on the catalytic performance, maintaining both conversions and enantioselectivities. In contrast, the use of air-stable DABAL-Me_3 showed slight lower conversions and enantioselectivities. The lower enantioselectivity when using DABAL-Me_3 can be explained because the reaction is carried out at higher temperature than with $AlMe_3$.
Then we studied if the electronic modification on the aryl group could have any influence on the reaction performance. We found that the introduction of an halide on the aryl substituent (**S2**-**S3** and **S7**; entries 2, 3 and 7) has no effect on both yield and enantioselectivities. Nevertheless, the presence of a strong donating group, such as a methoxy group (substrate **S4**), had a slight negative effect on enantioselectivity (from 53% ee for **S1** to 48% ee for **S4**; entry 1 *vs* 4). On the other hand, the reaction with substrate **S5**, containing electronwithdrawing *p*-CF_3 substituent, proceeded with higher enantioselectivities than **S1** (ee's up to 61%, entry 5).

Table 7.2.2. Substrate scope using **L6b** and **L6c** in the asymmetric Ni-catalyzed 1,2-addition of triorganoaluminum reagents to aldehydes.

			$AlMe_3$[a]		$AlEt_3$[a]		DABAL-Me_3[b]	
Entry	Substrate	L*	% Conv[c]	% ee[d]	% Conv[c]	% ee[d]	% Conv[c]	% ee[d]
1	 S1	**L6b**	100 (91)	50 (*S*)	100 (89)	51 (*S*)	94 (87)	44 (*S*)
		L6c	99 (93)	53 (*R*)	100 (87)	53 (*R*)	92 (86)	47 (*R*)
2	 S2	**L6b**	100 (88)	51 (*S*)	100 (87)	50 (*S*)	89 (82)	44 (*S*)
		L6c	100 (91)	52 (*R*)	100 (90)	54 (*R*)	90 (81)	46 (*R*)
3	 S3	**L6b**	100 (90)	50 (*S*)	100 (86)	50 (*S*)	84 (80)	43 (*S*)
		L6c	100 (91)	54 (*R*)	100 (88)	53 (*R*)	89 (83)	46 (*R*)
4	 S4	**L6b**	100 (90)	46 (*S*)	100 (89)	44 (*S*)	79 (74)	40 (*S*)
		L6c	100 (92)	48 (*R*)	100 (90)	47 (*R*)	84 (76)	42 (*R*)
5	 S5	**L6b**	100 (93)	53 (*S*)	100 (94)	54 (*S*)	89 (83)	48 (*S*)
		L6c	100 (91)	59 (*R*)	100 (93)	61 (*R*)	83 (77)	50 (*R*)
6	 S6	**L6b**	100 (93)	50 (*S*)	100 (94)	50 (*S*)	89 (83)	44 (*S*)
		L6c	100 (91)	52 (*R*)	100 (93)	52 (*R*)	83 (77)	46 (*R*)
7	 S7	**L6b**	100 (92)	51 (*S*)	100 (91)	52 (*S*)	88 (82)	43 (*S*)
		L6c	100 (91)	54 (*R*)	100 (90)	55 (*R*)	90 (85)	46 (*R*)
8	 S8	**L6b**	100 (89)	50 (*S*)	100 (90)	51 (*S*)	90 (86)	43 (*S*)
		L6c	100 (92)	55 (*R*)	100 (92)	53 (*R*)	92 (84)	47 (*R*)
9	 S9	**L6b**	100 (91)	55 (*S*)	100 (90)	57 (*S*)	88 (82)	49 (*S*)
		L6c	100 (89)	59 (*R*)	100 (89)	62 (*R*)	93 (87)	54 (*R*)
10	 S10	**L6b**	100 (87)	52 (*S*)	100 (92)	52 (*S*)	90 (82)	47 (*S*)
		L6c	100 (92)	56 (*R*)	100 (90)	55 (*R*)	88 (83)	49 (*R*)
11	 S11	**L6b**	100 (89)	53 (*S*)	100 (91)	54 (*S*)	89 (82)	44 (*S*)
		L6c	100 (88)	56 (*R*)	100 (88)	55 (*R*)	88 (84)	48 (*R*)

[a] Reaction conditions: T= -20 ºC, $[Ni(acac)_2]$ (1 mol%), AlR'_3 (2 equiv.), substrate (1 mmol), THF (8 mL). [b] Reaction conditions: T= 5 ºC, $[Ni(acac)_2]$ (1 mol%), DABAL-Me_3 (1.2 equiv.), substrate (1 mmol), THF (8 mL). [c] % Conversion determined by GC after 3 hours. In brackets are shown the yields determined by GC using dodecane as internal standard. [d] Enantiomeric excess measured by GC using Cyclodex-B column.

Sterics on the aryl moiety have shown no influence on the catalytic performance (entries 8-11). The use of substrates **S8** and **S9**, with *meta* substituents, and *ortho* substituted

substrates **S10** and **S11** provided therefore similar levels of enantioselectivity than **S1** (entries 8-11).

7.2.3. Conclusions

We have applied the PHOX-based phosphite-oxazoline ligands **L3** and **L5**-**L7a**-**c** in the asymmetric Ni-catalyzed 1,2-addition of triorganoaluminum reagents to aldehydes. We have found that enantioselectivity is mainly affected by the phosphite moiety. The use of chiral biaryl phosphite moiety not only has a positive effect on enantioselectivity but also it allows to achieve both enantiomers of the product by simply changing the configuration of the biaryl moiety. Enantioselectivities up to 62% ee were achieved using ligands **L6b** and **L6c**.

The results also indicate that the catalytic performance is hardly affected by either the triorganoaluminum source or the electronic and steric demand of the substrate. Thus, moderate enantioselectivities were achieved using a range of benzaldehydes and different trialkylaluminum reagents such as $AlMe_3$, $AlEt_3$ and air-stable DABAL-Me_3.

7.2.4. Experimental section

7.2.4.1. General Considerations

All syntheses were performed by using standard Schlenk techniques under an argon atmosphere. Solvents were purified by standard procedures. The synthesis of ligands **L3** and **L5**-**L7a**-**c** has been previously described in Section 3.3. All other reagents were used as commercially available.

7.2.4.2. Typical procedure for the Ni-catalyzed enantioselective 1,2- addition of trialkylaluminum reagents to aldehydes

$[Ni(acac)_2]$ (2.4 mg, 9.32 μmol, 1 mol %) and the corresponding ligand (9.32 μmol, 1 mol %) were stirred in dry THF (8 mL) under an argon atmosphere at -20 ºC for 10 min. Neat aldehyde (1 mmol) was then added and trialkylaluminum (2 mmol) was added dropwise over 10 min. After the desired reaction time, the reaction was quenched with 2 M HCl (8 mL). Then, dodecane (80 μL) was added, the mixture was extracted with Et_2O (10 mL) and the organic layer was dried over $MgSO_4$. Conversions and enantioselectivities were measured by GC.[7a]

7.2.4.3. Typical procedure for the Ni-catalyzed enantioselective 1,2-addition of DABAL-Me_3 to aldehydes

[$Ni(acac)_2$] (2.4 mg, 9.32 μmol, 1 mol %) and the corresponding ligand (9.32 μmol, 1 mol %) were stirred in dry THF (8 mL) under an argon atmosphere at 5 ºC for 10 min. Neat aldehyde (1 mmol) was then added and DABAL-Me_3 (336 mg, 1.3 mmol, 1.3 equiv) was added over 10 min. After the desired reaction time, the reaction was quenched with 2 M HCl (8 mL). Then, dodecane (80 μL) was added, the mixture was extracted with Et_2O (10 mL) and the organic layer was dried over $MgSO_4$. Conversions and enantioselectivities were measured by GC.[7a]

7.2.5. References

1 a) Soai, K.; Shibata, T. *Alkylation of carbonyl groups. In: Comprehensive asymmetric catalysis.* Eds. Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. **2000**, Vol II, Springer, Berlin. b) Pu, L.; Yu, H.-B. *Chem. Rev.* **2001**, *101*, 757. c) Luderer, M. R.; Bailey, W. F.; Fair, J. D.; Sommer, M. B. *Tetrahedron: Asymmetry* **2009**, *20*, 981. d) Trost, B. M.; Weiss, A. H. *Adv. Synth. Catal.* **2009**, *351*, 963. e) Kolb, A.; Von Zezschwitz, P. *Organoaluminum Couplings to Carbonyls, Imines and Halides.* In *Top. Organomet. Chem.* **2013**, *41*, 245. Eds. Woodward, S.; Dagone, S. Springer-Verlag Berlin Heidelberg.

2 a) Kitamura, M.; Okada, S.; Suga, S.; Noyori, R. *J. Am. Chem. Soc.* **1989**, *111*, 4028. b) Boezio, A. A.; Pytkowicz, J.; Cöté, A.; Charette, A. B. *J. Am. Chem. Soc.* **2003**, *125*, 14260.

3 Oishi, M. *Triorganoaluminum compounds.* Ed. Yamamoto, H. *Science of Synthesis*, **2004**, vol 7. Thieme, Stuttgart.

4 a) Andrus, M. B.; Meredith, E. L.; Hicken, E. J.; Simmons, B. L.; Glancey, R. R.; Ma, W. *J. Org. Chem.* **2003**, *68*, 8162. b) Liu, B.; Zhou, W.-S. *Org. Lett.* **2004**, *6*, 71. c) Chanu, A.; Safir, I.; Basak, P.; Chiaroni, A.; Arseniyadis, S. *Org. Lett.* **2007**, *9*, 1351.

5 Cotton, F. A.; Wilkinson, G. *Advanced Inorganic Chemistry*, 5th ed. Wiley, New York, **1988**, 224.

6 a) Chan, A. S. C.; Zhang, F.-Y.; Yip, C.-W.; *J. Am. Chem. Soc.* **1997**, *119*, 4080. b) Pagenkopf, B. L.; Carreira, E. M. *Tetrahedron Lett.* **1998**, *39*, 9593. c) Lu, J.-F.; You, J.-S.; Gau, H.-M.; *Tetrahedron: Asymmetry* **2000**, *11*, 2531. d) You, J.-S.; Hseih, S.-H.; Gau, H.-M.; *Chem. Commun.* **2001**, 1546. e) Fernández-Mateos, E.; Maciá, B.; Yus, M. *Tetrahedron; Asymmetry* **2012**, *23*, 789.

7 a) Biswas, K.; Prieto, O.; Goldsmith, P. J.; Woodward, S. *Angew. Chem. Int. Ed.* **2005**, *44*, 2232. b) Biswas, K.; Chapron, A.; Copper, T.; Fraser, P. K.; Novak, A.; Prieto, O.; Woodward, S. *Pure Appl. Chem.* **2006**, *78*, 511.

8 a) Mata, Y.; Diéguez, M.; Pàmies, O.; Woodward, S. *J. Org. Chem.* **2006**, *71*, 8159. b) Mata, Y.; Diéguez, M.; Pàmies, O.; Woodward, S. *Inorg. Chim. Acta.* **2008**, *361*, 1381.

[9] Alegre, S.; Diéguez, M.; Pàmies, O. *Tetrahedron: Asymmetry* **2011**, *22*, 834.

[10] a) Raluy, E.; Diéguez, M.; Pàmies, O. *Tetrahedron Lett.* **2009**, *50*, 4495. b) Raluy, E.; Diéguez, M.; Pàmies, O. *Tetrahedron: Asymmetry* **2009**, *20,* 1575.

[11] a) Pàmies, O.; Diéguez, M.; Claver, C. *J. Am. Chem. Soc.* **2005**, 127, 3646. b) Mazuela, J.; Pàmies, O.; Diéguez, M. *Chem. Eur. J.* **2010**, 16, 3434. c) Magre, M.; Biosca, M.; Pàmies, O.; Diéguez, M. *ChemCatChem* **2015**, 7, 114. d) Bellini, R.; Magre, M.; Biosca, M.; Norrby, P.-O.; Pàmies, O.; Diéguez, M.; Moberg, C. *ACS Catal*. **2016**, *6*, 1701.

7.3. Phosphite-oxazoline ligands containing an alkyl backbone chain for Ni-catalyzed enantioselective 1,2-addition of triorganoaluminum reagents to aldehydes.

Magre, M.; Pàmies, O.; Diéguez, M. *Preliminary results*

Abstract: *Herein we report the application of a new family of phosphite-oxazoline ligands* ***L9-L14a-c*** *to the asymmetric Ni-catalyzed 1,2-addition of trialkylaluminum reagents to aldehydes. Excellent yields (up to 93%) and moderate enantioselectivities (up to 64% ee) were achieved using a wide range of trialkylaluminum reagents and aryl aldehydes.*

7.3.1. Introduction

1,2-Addition of organometallic reagents to carbonyl compounds constitutes one of the most fundamental operations in organic synthesis for the formation of chiral secondary alcohols.[1] Since many chiral alcohols are highly valuable intermediates for preparing chiral pharmaceutical and agricultural products, in this context, catalytic addition of dialkylzincs to aldehydes has attracted much attention.[2] Nevertheless, the use of trialkylaluminum compounds[3] is more interesting than the use of diorganozinc reagents because they are economically available in industrial scale from aluminum hydride and olefins.[4] Moreover, they also show a higher functional group tolerance.[5] Despite all these advantages, only few examples of 1,2-addition of organoaluminum compounds to carbonyls have been reported in the literature.[6-10] The mostly used transition metal complexes are those based on titanium. They usually afford high enantioselectivities, but the high catalyst loadings (10-20 mol%) and the slow turnover rate hamper their potential utility.[6] More recently, the use of Ni-based catalyst has emerged as an alternative to those Ti-catalysts. They provide enantioselectivities similar to those using titanium complexes but with low catalyst loadings (1 mol%).[7] In this respect, the first breakthrough in Ni-1,2 addition of triorganoaluminum reagents to aldehydes was presented in 2005 by Woodward *et al.* with the use of binaphthyl-based phosphoramidites. Using benzaldehyde as standard substrate, they determined that using either AlR_3 or the air stable analogue DABAL-Me_3, enantioselectivities were hardly changed (88% ee for $AlMe_3$ and 92% for DABAL-Me_3 adduct), but yields were, in some cases, lower using non-stable triorganoaluminum reagents. Excellent conversions and enantioselectivities (81-95% ee) were obtained either with electron-rich or electron-deficient benzaldehyde derivatives.

In 2006, our group in collaboration with Woodward group found that the application of sugar-based phosphite ligands provided high enantioselectivity (ee's up to 91%).[8a] Our group also demonstrated that bidentate phosphite-phosphoramidite and diphosphoramidite ligands can also be applied in this transformation, achieving

enantioselectivities up to 84% for benzaldehyde.[10] In the last section, we have shown that bidentated P,N-ligands can be also used in this transformation, albeit with moderate enantioselectivities.

In this section, we present the application of previously reported phosphite-oxazoline **L9**-**L14a**-**c** (Figure 7.3.1) with the purpose of improving the catalytic performance for this transformation.

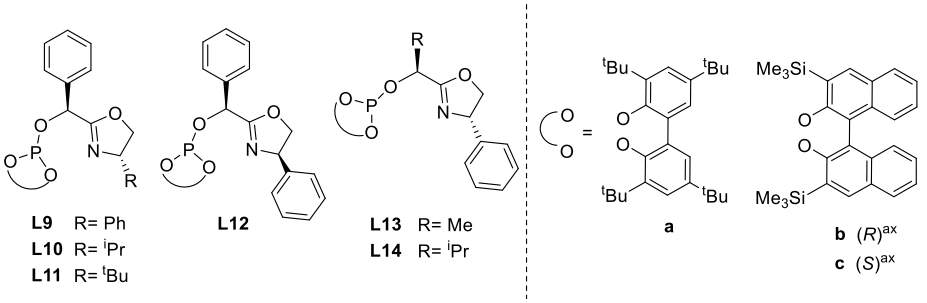


Figure 7.3.1. Phosphite-oxazoline ligands **L9**-**L14a-c** applied to Ni-catalyzed enantioselective 1,2-addition of triorganoaluminum reagents to aldehydes.

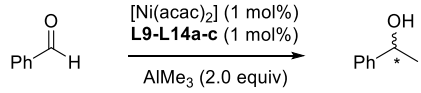
7.3.2. Results and discussion

7.3.2.1. Asymmetric addition of $AlMe_3$ to benzaldehyde

In a first set of experiments, we screened ligands **L9**-**L14a**-**c** using benzaldehyde as benchmark substrate and $AlMe_3$ as alkylating agent following conditions which have been already reported by our group (Table 7.3.1).[8-10]

As we obtained previously using PHOX-type phosphite-oxazolines (Section 7.2), both enantioselectivity and yield are not dependent on the ligand-to-metal ratio (Table 7.3.1, entries 2 vs 3 and 4). The results using a full set of ligands indicated that ligands containing an enantiopure biaryl phosphite moiety (**b** and **c**) provide higher enantioselectivities than those with an achiral biaryl phosphite group (**a**). Substituents on the oxazoline have a slight effect on the enantioselectivity, achieving higher levels of enantioselectivity with ligands containing less bulky Ph-oxazoline substituent. Interestingly, both enantiomers of the secondary alcohol can be obtained using diastereoisomeric ligands **L9b** and **L12c** (ee's up to 58%; Table 7.3.1, entries 2 and 13). Regarding the substituent on the alkyl chain (Ph, Me and ^{i}Pr), we found that it had no influence on the catalytic performance (entries 4-5 vs 14-17).

Table 7.3.1. Screening of **L9**-**L14a**-**c** in the asymmetric Ni-catalyzed 1,2-addition of $AlMe_3$ to benzaldehyde.



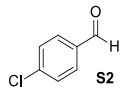
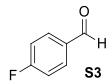
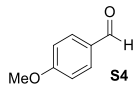
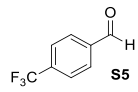
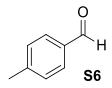
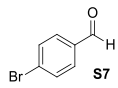
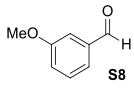
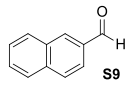
Entry[a]	Ligand	L/Ni	% Conv[b]	% Yield[c]	% ee[d]
1	**L9a**	1	100	94	2 (*R*)
2	**L9b**	1	100	92	58 (*S*)
3	**L9b**	0.5	100	91	57 (*S*)
4	**L9b**	2	100	90	58 (*S*)
5	**L9c**	1	100	93	47 (*R*)
6	**L10a**	1	95	89	2 (*R*)
7	**L10b**	1	100	94	46 (*S*)
8	**L10c**	1	100	90	48 (*R*)
9	**L11b**	1	100	89	39 (*S*)
10	**L11c**	1	100	92	38 (*R*)
11	**L12a**	1	100	92	14 (*R*)
12	**L12b**	1	100	89	47 (*S*)
13	**L12c**	1	100	91	58 (*R*)
14	**L13b**	1	100	89	56 (*S*)
15	**L13c**	1	100	92	48 (*R*)
16	**L14b**	1	100	88	57 (*S*)
17	**L14c**	1	100	90	46 (*R*)

[a] Reaction conditions: T= -20 ºC, $[Ni(acac)_2]$ (1 mol%), $AlMe_3$ (2 equiv.), substrate (1 mmol), THF (8 mL). [b] % Conversion determined by GC after 3 hours. [c] Isolated yield. [d] Enantiomeric excess measured by GC using Cyclodex-B column.

7.3.2.2. Asymmetric addition of several aluminum reagents to a range of benzaldehyde-type aldehydes.

We then applied ligands **L9b** and **L12c** using other aldehydes and aluminum reagents. The results are summarized in Table 7.3.2. As in previous Section 7.2.2.2, the replacement of $AlMe_3$ by bulkier $AlEt_3$ had no effect on the catalytic performance, maintaining both conversions and enantioselectivities (table 7.3.2, entry 1), and the use of air-stable DABAL-Me_3 showed slightly lower conversions and enantioselectivities.

Table 7.3.2. Substrate scope using **L9b** and **L12c** in the asymmetric Ni-catalyzed 1,2-addition of triorganoaluminum reagents to aldehydes.

			$AlMe_3$[a]		$AlEt_3$[a]		DABAL-Me_3[b]	
Entry	Substrate	L*	% Conv[c]	% ee[d]	% Conv[c]	% ee[d]	% Conv[c]	% ee[d]
1	 S1	**L9b**	100 (90)	58 (*S*)	100 (89)	59 (*S*)	100 (87)	51 (*S*)
		L12c	100 (91)	58 (*R*)	100 (90)	58 (*R*)	100 (86)	50 (*R*)
2	 S2	**L9b**	100 (92)	58 (*S*)	100 (90)	57 (*S*)	100 (87)	50 (*S*)
		L12c	100 (93)	58 (*R*)	100 (92)	58 (*R*)	100 (84)	50 (*R*)
3	 S3	**L9b**	100 (93)	58 (*S*)	100 (91)	58 (*S*)	100 (87)	51 (*S*)
		L12c	100 (93)	58 (*R*)	100 (90)	58 (*R*)	99 (84)	50 (*R*)
4	 S4	**L9b**	100 (90)	52 (*S*)	100 (89)	52 (*S*)	100 (90)	47 (*S*)
		L12c	100 (91)	51 (*R*)	100 (91)	50 (*R*)	100 (91)	46 (*R*)
5	 S5	**L9b**	100 (90)	62 (*S*)	100 (88)	61 (*S*)	100 (88)	54 (*S*)
		L12c	100 (90)	63 (*R*)	100 (89)	62 (*R*)	100 (86)	56 (*R*)
6	 S6	**L9b**	100 (92)	58 (*S*)	100 (89)	59 (*S*)	100 (88)	50 (*S*)
		L12c	100 (91)	58 (*R*)	100 (90)	59 (*R*)	100 (87)	50 (*R*)
7	 S7	**L9b**	100 (89)	57 (*S*)	100 (88)	58 (*S*)	100 (86)	49 (*S*)
		L12c	100 (91)	58 (*R*)	100 (89)	58 (*R*)	100 (89)	50 (*R*)
8	 S8	**L9b**	100 (92)	60 (*S*)	100 (91)	60 (*S*)	100 (85)	53 (*S*)
		L12c	100 (93)	59 (*R*)	100 (89)	60 (*R*)	100 (87)	53 (*R*)
9	 S9	**L9b**	100 (91)	64 (*S*)	100 (90)	63 (*S*)	100 (84)	55 (*S*)
		L12c	100 (93)	63 (*R*)	100 (88)	63 (*R*)	100 (86)	55 (*R*)
10	 S10	**L9b**	100 (89)	60 (*S*)	100 (89)	59 (*S*)	100 (81)	53 (*S*)
		L12c	100 (90)	61 (*R*)	100 (88)	59 (*R*)	100 (86)	52 (*R*)
11	 S11	**L9b**	100 (91)	60 (*S*)	100 (88)	59 (*S*)	100 (87)	51 (*S*)
		L12c	100 (92)	60 (*R*)	100 (87)	59 (*R*)	99 (86)	52 (*R*)

[a] Reaction conditions: T= -20 °C, $[Ni(acac)_2]$ (1 mol%), AlR'_3 (2 equiv.), substrate (1 mmol), THF (8 mL). [b] Reaction conditions: T= 5 °C, $[Ni(acac)_2]$ (1 mol%), DABAL-Me_3 (1.2 equiv.), substrate (1 mmol), THF (8 mL). [c] % Conversion determined by GC after 3 hours. In brackets are shown the yields determined by GC using dodecane as internal standard. [d] Enantiomeric excess measured by GC using Cyclodex-B column.

Then we studied if the electronic modification on the aryl group in the substrate could have any influence on the reaction performance. We found that the introduction of an

halide on the aryl substituent (**S2**-**S3** and **S7**; entries 2, 3 and 7) has no effect on both yield and enantioselectivity. Nevertheless, the presence of a strong donating group, such as a methoxy group (substrate **S4**), had a slight negative effect on the enantioselectivities (ee's decreased from 53% ee for **S1** to 48% ee for **S4**; entry 1 *vs* 4). On the other hand, the reaction with substrate **S5**, containing electronwithdrawing *p*-CF_3 substituent, proceeded with higher enantioselectivities than **S1**.
Sterics on the aryl moiety have shown no influence on the catalytic performance (entries 8-11). The use of substrates **S8** and **S9** with *meta* substituents and *ortho* substituted substrates **S10** and **S11** provided similar levels of enantioselectivity than **S1** (entries 8-11).

7.3.3. Conclusions

We have applied phosphite-oxazoline ligands **L9**-**L14a-c** in the asymmetric Ni-catalyzed 1,2-addition of triorganoaluminum reagents to aldehydes. We have found that enantioselectivity is mainly affected by the phosphite moiety. The use of chiral biaryl phosphite moiety has a positive effect on enantioselectivity. Just by using diastereoisomeric ligands **L9b** and **L12c**, both enantiomers of the secondary alcohol can be obtained, albeit in moderate enantioselectivity (ee's up to 63%)
The results also indicate that the catalytic performance is hardly affected by either the triorganoaluminum source or the electronic and steric demand of the substrate. Thus, moderate enantioselectivities were achieved using a range of benzaldehydes and different trialkylaluminum reagents such as $AlMe_3$, $AlEt_3$ and air-stable DABAL-Me_3.
Comparing the previously described PHOX-based phosphite-oxazoline **L6b** and **L6c** (Section 7.2) with phosphite-oxazoline ligands **L9b** and **L12c** we found that replacing the *ortho*-phenylene tether by a chiral alkyl chain on the ligand backbone, do not improve enantioselectivities.

7.3.4. Experimental section

7.3.4.1. General Considerations

All syntheses were performed by using standard Schlenk techniques under an argon atmosphere. Solvents were purified by standard procedures. The synthesis of ligands **L9**-**L14a**-**c** has been previously described in Section 3.4. All other reagents were used as commercially available.

7.3.4.2. Typical procedure for the Ni-catalyzed enantioselective 1,2- addition of trialkylaluminum reagents to aldehydes

[Ni(acac)$_2$] (2.4 mg, 9.32 μmol, 1 mol %) and the corresponding ligand (9.32 μmol, 1 mol %) were stirred in dry THF (8 mL) under an argon atmosphere at -20 ºC for 10 min. Neat aldehyde (1 mmol) was then added and trialkylaluminum (2 mmol) was added dropwise over 10 min. After the desired reaction time, the reaction was quenched with 2 M HCl (8 mL). Then, dodecane (80 μL) was added, the mixture was extracted with Et_2O (10 mL) and the organic layer was dried over $MgSO_4$. Conversions and enantioselectivities were measured by GC.[7a]

7.3.4.3. Typical procedure for the Ni-catalyzed enantioselective 1,2-addition of DABAL-Me$_3$ to aldehydes

[Ni(acac)$_2$] (2.4 mg, 9.32 μmol, 1 mol %) and the corresponding ligand (9.32 μmol, 1 mol %) were stirred in dry THF (8 mL) under an argon atmosphere at 5 ºC for 10 min. Neat aldehyde (1 mmol) was then added and DABAL-Me$_3$ (336 mg, 1.3 mmol, 1.3 equiv) was added over 10 min. After the desired reaction time, the reaction was quenched with 2 M HCl (8 mL). Then, dodecane (80 μL) was added, the mixture was extracted with Et_2O (10 mL) and the organic layer was dried over $MgSO_4$. Conversions and enantioselectivities were measured by GC.[7a]

7.3.5. References

1 a) Soai, K.; Shibata, T. *Alkylation of carbonyl groups. In: Comprehensive asymmetric catalysis.* Eds. Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. **2000**, Vol II, Springer, Berlin. b) Pu, L.; Yu, H.-B. *Chem. Rev.* **2001**, *101*, 757. c) Luderer, M. R.; Bailey, W. F.; Fair, J. D.; Sommer, M. B. *Tetrahedron: Asymmetry* **2009**, *20*, 981. d) Trost, B. M.; Weiss, A. H. *Adv. Synth. Catal.* **2009**, *351*, 963. e) Binder, V. M.; Singaram, B. *Org. Prep. Proced. Int.* **2011**, *43*, 139. f) Kolb, A.; Von Zezschwitz, P. *Organoaluminum Couplings to Carbonyls, Imines and Halides.* In *Top. Organomet. Chem.* **2013**, *41*, 245. Eds. Woodward, S.; Dagone, S. Springer-Verlag Berlin Heidelberg.

2 a) Kitamura, M.; Okada, S.; Suga, S.; Noyori, R. *J. Am. Chem. Soc.* **1989**, *111*, 4028. b) Boezio, A. A.; Pytkowicz, J.; Cöté, A.; Charette, A. B. *J. Am. Chem. Soc.* **2003**, *125*, 14260.

3 Oishi, M. *Triorganoaluminum compounds.* Ed. Yamamoto, H. *Science of Synthesis*, **2004**, vol 7. Thieme, Stuttgart.

4 Cotton, F. A.; Wilkinson, G. *Advanced Inorganic Chemistry*, 5th ed. Wiley, New York, **1988**, 224.

[5] a) Andrus, M. B.; Meredith, E. L.; Hicken, E. J.; Simmons, B. L.; Glancey, R. R.; Ma, W. *J. Org. Chem.* **2003**, *68*, 8162. b) Liu, B.; Zhou, W.-S. *Org. Lett.* **2004**, *6*, 71. c) Chanu, A.; Safir, I.; Basak, P.; Chiaroni, A.; Arseniyadis, S. *Org. Lett.* **2007**, *9*, 1351.

[6] a) Chan, A. S. C.; Zhang, F.-Y.; Yip, C.-W.; *J. Am. Chem. Soc.* **1997**, *119*, 4080. b) Pagenkopf, B. L.; Carreira, E. M. *Tetrahedron Lett.* **1998**, *39*, 9593. c) Lu, J.-F.; You, J.-S.; Gau, H.-M.; *Tetrahedron: Asymmetry* **2000**, *11*, 2531. d) You, J.-S.; Hseih, S.-H.; Gau, H.-M.; *Chem. Commun.* **2001**, 1546. e) Fernández-Mateos, E.; Maciá, B.; Yus, M. *Tetrahedron; Asymmetry* **2012**, *23*, 789.

[7] a) Biswas, K.; Prieto, O.; Goldsmith, P. J.; Woodward, S. *Angew. Chem. Int. Ed.* **2005**, *44*, 2232. b) Biswas, K.; Chapron, A.; Copper, T.; Fraser, P. K.; Novak, A.; Prieto, O.; Woodward, S. *Pure Appl. Chem.* **2006**, *78*, 511.

[8] a) Mata, Y.; Diéguez, M.; Pàmies, O.; Woodward, S. *J. Org. Chem.* **2006**, *71*, 8159. b) Mata, Y.; Diéguez, M.; Pàmies, O.; Woodward, S. *Inorg. Chim. Acta.* **2008**, *361*, 1381.

[9] Alegre, S.; Diéguez, M.; Pàmies, O. *Tetrahedron: Asymmetry* **2011**, *22*, 834.

[10] a) Raluy, E.; Diéguez, M.; Pàmies, O. *Tetrahedron Lett.* **2009**, *50*, 4495. b) Raluy, E.; Diéguez, M.; Pàmies, O. *Tetrahedron: Asymmetry* **2009**, *20,* 1575.

Chapter 8

Conclusions

UNIVERSITAT ROVIRA I VIRGILI
DESIGN OF TAILOR-MADE CHIRAL LIGAND LIBRARIES FOR C-X BOND FORMING REACTIONS. STUDY OF THE KEY INTERMEDIATES BY NMR AND DFT
Marc Magre Rosich

8. Conclusions

1. Chapter 3. *Asymmetric allylic substitution reactions.* The conclusion of this chapter can be summarized as follows:

Four different families of phosphite-nitrogen ligands have been synthesized and applied to the Pd-catalyzed asymmetric allylic substitution reaction. Moreover, furanoside-based phosphite-phosphoramidite ligand library have been applied to the Cu-catalyzed asymmetric allylic alkylation.

- In Section 3.2, PHOX-based phosphite-oxazoline ligands **L1a**, **L1f**-**g** have been applied to the Pd-catalyzed asymmetric allylic substitution. We have expanded the substrate as well as the nucleophile scope for this reaction, based on the previously reported work. Moreover, NMR (Nuclear Magnetic Resonance) and DFT (Density Functional Theory) have been carried out to fully understand the catalytic behavior of those privileged phosphite-oxazoline ligands. Excellent activities, regio- and enantioselectivities (up to >99%) have been achieved in several substrate and with a wide range of nucleophiles.
- In Section 3.3, we report a reduced but structurally valuable phosphite-oxazoline ligand library **L5**-**L7a**-**c** for the Pd-catalyzed allylic substitution of several substrate types. These ligands, which are easily accessible in three steps, differ from previous phosphite-based PHOX ligands **L1** in the presence of a methylene spacer between the oxazoline group and the phenyl ring. With these ligands we also studied the effect of varying the oxazoline substituent and the biaryl phosphite group. By suitable tuning the ligand parameters we have been able to achieve high activities (TOF > 4000 mol substrate×(mol Pd×h)$^{-1}$) and excellent enantioselectivities for a range of hindered substrates using a wide range of nucleophiles. We have found that he introduction of a methylene spacer has been positive in terms of nucleophile scope. Thus, in contrast to the phosphite-based PHOX ligands **L1a**, **L1f**-**g**, a range of aliphatic alcohols with different electronic properties could be successfully used as nucleophiles. Nevertheless, although good enantioselectivities were also achieved when using unhindered substrates, ee's were lower than with previous PHOX-based ligands **L1a**, **L1f**-**g**. As in Section 3.2, the DFT calculations agree with an early TS.
- In Section 3.4, we report a third generation of phosphite-oxazoline PHOX-based ligand library **L8**-**L14a**-**c** for the Pd-catalyzed allylic substitution of several substrate and nucleophile types. These ligands allow us to study the influence of a second stereocentre on the ligand backbone, the substituents/configurations on the oxazoline group as well as the variation of the biaryl phosphite group, which showed to be crucial in terms of enantioselectivity. By suitable tuning the ligand parameters we have been able to achieve high activities (TOF > 8000 mol substrate×(mol Pd×h)$^{-1}$) and excellent enantioselectivities (ee's up to 99%) for a range of hindered and unhindered substrates

using a wide range of C, N- and O-nucleophiles. The results compare favorably with ligands **L1a, L1f-g** (Section 3.2). The effect of the substituent at the alkyl chain was studied, achieving the highest enantioselectivities with ligands **L8** and **L13** (ee's up to 99%) containing two or one methyl group at the alkyl backbone chain, respectively. As in previous Sections 3.2 and 3.3, the DFT calculations agree with an early TS and the enantioselectivities can be therefore explained by both the population of the Pd-η^3-allyl intermediates and the relative electrophilicity of the allylic carbon atoms.

- In Section 3.5, amino-phosphite ligands **L15**-**L20a**-**g** have been successfully applied in the Pd-catalyzed asymmetric allylic substitution. We have demonstrated that replacing oxazoline by a more robust N-donor group such as amine, excellent conversions and enantioselectivities (up to 99%) can be achieved with several substrates and nucleophiles. Using DFT calculations we have been able to fully understand the influence of the ligand in the enantioselectivity, and therefore synthesizing the simplest and most efficient amino-phosphite ligand.
- In Section 3.6, furanoside phosphite-phosphoramidite and diphosphoramidite ligands **L20**-**L25a**-**f** have been applied to Cu-catalyzed asymmetric allylic alkylation using non-stabilized nucleophiles such as Grignard and diorganozinc reagents. Excellent regioselectivity was achieved (98% towards branched product) as well as good enantioselectivities (up to 78%) for a wide range of cinammyl-type substrates and non-stabilized nucleophiles.

2. Chapter 4. *Enantioselective synthesis of α-aryl oxindoles via decarboxylative protonation.* The conclusions of this chapter can be summarized as follows:

We have developed the first catalytic asymmetric preparation of tertiary sterically hindered α-aryl oxindoles via enantioselective Pd-catalyzed decarboxylative protonation of the corresponding α-aryl-β-amido allyl esters. The method utilizes readily accessible α-aryl-β-amido allyl esters and commercially available Meldrum's acid as the proton donor. The reaction occurs under very mild conditions and in short reaction times, providing excellent yields and promising enantioselectivities (ee's up to 78%). In contrast to the Pd-decarboxylative protonation for synthesizing chiral isoflavanones and α-aryl cyclic ketones, phosphine-oxazoline PHOX-based ligands have provided low selectivity. After the screening of three large series of phosphite-N (N=oxazoline and pyridine) ligand families **L1**-**L4a** and **L26**-**L37a**-**e** we found that the best results were obtained with a readily accessible phosphite-pyridine ligand library **L30**-**L37**. The introduction of an enantiopure biaryl phosphite moiety played an essential role in increasing the enantioselectivity of the Pd-catalytic systems. An important advantage over PHOX based-ligands is that these phosphite-pyridine ligands are stable to air and therefore easier to handle, manipulate and store. As far as the substrates is concerning, for enantioselectivities to be high, the aryl group of the substrate must contain

substituents in *ortho* and *para*-positions, that are, at the same time, strongly electron donating. In this study we have been therefore able to identify a readily accessible phosphite-pyridine palladium catalytic system (Pd–**30c**) that can be used in the preparation of hindered and electronrich α-aryl onxindole with excellent yields (up to 96%) and promising enantioselectivities (ee's up to 78%). Using DFT calculations, we have been able to see that the most stable transition state is that in which the protonation occurs from the *re*-face of the prochiral Pd-enolate (TS_{re}-**B**), providing the *S*-product.

3. Chapter 5. *Asymmetric hydrogenation of olefins.* The conclusion of this chapter can be summarized as follows:

Two different phosphite-oxazoline ligand families have been synthesized and applied to the Ir-catalyzed asymmetric hydrogenation of olefins.

- In Section 5.2, we have successfully applied new Ir(I)-catalyst precursors ([Ir(cod)(**L1**-**L7a**-**g**)]BAr_F), modified with easily accessible PHOX-based phosphite-oxazoline ligands previously described in Chapter 3, for the asymmetric hydrogenation of demanding minimally functionalized alkenes and cyclic β-enamides. The catalytic results indicated that enantioselectivity is highly affected by the ligand parameters as well as the substrate. The new Ir-PHOX-based phosphite-oxazoline catalysts have been able to efficiently hydrogenate not only minimally functionalized model olefins, but also a wide range of challenging olefins that have recently received a great deal of attention because the resulting hydrogenated compounds can be easily stereoselectively transformed into high-value organic compounds. The results are among the best reported so far. On the other hand, it should be noted the excellent enantioselectivities achieved in the hydrogenation of β-aryl enamides, which gave access to 2-aminotetralines and 3-aminochromanes in enantioselectivities up to 99%.
- In Section 5.3, we have successfully applied new Ir(I)-catalyst precursors ([Ir(cod)(**L8**-**L14a**-**g**)]BAr_F), modified with easily accessible phosphite/phosphinite-oxazoline ligands, for the asymmetric hydrogenation of several substrate types. The ligands used differ from previously phosphite-oxazoline PHOX ligands presented in Section 5.2 in the presence of an alkyl chain instead of the flat *ortho*-phenylene tether. The catalytic results indicated that enantioselectivity is highly affected by the ligand parameters as well as the substrate. By suitable choosing the ligands parameters, however, we have been able to achieve high enantioselectivities (typically ee's>95%) not only for a wide range of minimally functionalized tri- and disubstituted olefins, with examples containing poorly coordinative groups (i.e. α,β-unsaturated ketones, amides and esters, alkenylboronic esters, enol phosphinates, …); but also in the hydrogenation of challenging functionalized olefins such as the β-aryl enamides, which provide easy access to 2-aminotetralines and 3-aminochromanes.

4. Chapter 6. *Asymmetric hydroboration of 1,1-disubstituted olefins.* The conclusions of this chapter can be summarized as follows:

We have identified that privileged phosphite-oxazoline PHOX ligands **L1**-**L4a**, **d**-**e** can be successfully extended to Ir-hydroboration of olefins. A readily accessible Ir-phosphite/oxazoline PHOX-based catalytic system can hydroborate a range of 1,1-disubstituted aryl olefins with high enantioselectivity (up to 94%), excellent yields and perfect regioselectivity. The new phosphite-oxazoline PHOX-based ligands can efficiently hydroborate a broader range of olefins than previous Ir-PHOX catalytic system developed by Mazet *et al*. In particular, we were able to successfully hydroborate a wide range of α-*tert*-butylstyrenes, with aryl substituents that have different electronic and steric properties, thus complementing the results of Cu-NHC catalysts developed by Hoveyda *et al.*, the only other system reported to date that has attempted these reactions. Moreover, the introduction of a biaryl phosphite moiety allows for the first time the highly regioselective hydroboration of aryl/trifluoromethyl olefins. Another advantage over previous PHOX ligands is that the new ligands are stable to air and therefore easier to handle and can be manipulated and stored in air. This contribution opens up the path for the synthesis of new Ir phosphite-based catalysts for the challenging hydroboration of 1,1-disubstituted olefins.

5. Chapter 7. *Asymmetric Ni-catalyzed 1,2-addition of organoaluminum reagents to aldehydes.* The conclusions of this chapter can be summarized as follows:

In Chapter 7, we have applied two families of phosphite-oxazolines to the enantioselective Ni-catalyzed 1,2-addition of trialkylaluminum to benzaldehyde-type aldehydes. All work in this chapter is presented as preliminary results.

- In Section 7.2, for the first time, PHOX-based phosphite-oxazoline **L3**, **L5-L7a**-**c** have been applied to Ni-catalyzed 1,2-addition of trialkylaluminum to aldehydes. Three different aluminum sources ($AlMe_3$, $AlEt_3$ and DABAL-Me_3) have been studied and successfully applied to sterically and electronically different benzaldehyde-type aldehydes in high yields and moderate enantioselectivities (94% yield, 62% ee).
- In Section 7.3. we present the application of the previously described phosphite-oxazoline ligand families **L9**-**L14a**-**c** to enantioselective Ni-catalyzed 1,2-addition of triorganoaluminum reagents to aldehydes. As in Section 7.2, three different aluminum sources ($AlMe_3$, $AlEt_3$ and DABAL-Me_3) have been studied and applied to different benzaldehyde-type aldehydes in high yields and moderate enantioselectivities (93% yield, 63% ee).

Chapter 9

Resum (Summary)

UNIVERSITAT ROVIRA I VIRGILI
DESIGN OF TAILOR-MADE CHIRAL LIGAND LIBRARIES FOR C-X BOND FORMING REACTIONS. STUDY OF THE KEY INTERMEDIATES BY NMR AND DFT
Marc Magre Rosich

9. Resum (Summary)

El desenvolupament de metodologies per a l'obtenció de compostos enantiomèricament purs ha incrementat en les últimes dècades, ja que aquests productes quirals tenen un gran impacte en la societat actual perquè són la base de fàrmacs, insecticides, perfums i productes naturals, entre altres. En aquest context, la catàlisi asimètrica ha esdevingut una eina útil per a l'obtenció d'aquests compostos. Més concretament, la catàlisi asimètrica en la que el catalitzador està basat en un centre metàl·lic i un lligand coordinat al metall ha estat la tècnica més emprada en els últims anys. Aquests complexos organometàl·lics ofereixen propietats molt concretes, com per exemple la seva gran selectivitat en els processos enantioselectius i altes activitats per a reaccions específiques. La modificació del lligand serà clau per a poder obtenir grans nivells de selectivitat i altes activitats; per això els lligands han de ser modulables, la qual cosa permetria poder realitzar canvis estructurals del lligand i poder estudiar la seva influencia en la reacció, i així saber l'estructura idònia del lligand que aporti millors resultats en la catàlisi asimètrica. A part de ser modulable, un lligand també ha de ser fàcil de sintetitzar, per donar-li un valor afegit.

El nostre grup de recerca s'ha especialitzat en la síntesi de lligands fosfit, altament actius en diferents reaccions asimètriques catalitzades per metalls de transició. A diferència de les fosfines, els lligands fosfit presenten un major caràcter π-acceptor i més resistència a la oxidació i són fàcilment sintetitzables a partir d'alcohols quirals que es troben a la natura, com per exemple aminoalcohols. Un inconvenient dels fosfits és que són fàcilment hidrolitzables, però en el nostre grup s'ha vist que aquest factor es pot minimitzar introduint grups biaril molt voluminosos.

En aquest context, aquesta tesi es centra en la síntesi de varies famílies de lligands π-acceptors quirals, que compleixin els requisits esmentats anteriorment, i la seva aplicació a reaccions asimètriques d'alt valor industrial i acadèmic: substitució al·lílica catalitzada per pal·ladi o coure, reacció de protonació descarboxilativa d'oxindoles catalitzada per pal·ladi, hidrogenació d'olefines poc funcionalitzades catalitzada i β-enamides cíclques per iridi; hidroboració d'olefines catalitzada per iridi i addició de compostos organoaluminats a aldehids catalitzada per níquel. Més concretament, s'han sintetitzat i aplicat diferents famílies de fosfit-oxazolina, fosfit-amina, fosfit-fosforamidit i fosfit-piridina. A més a més, en alguns casos s'han realitzat processos de càlcul teòrics DFT per a poder realitzar una millor optimització estructural dels lligands aplicats.

Després de la introducció (Capítol 1) i dels objectius (Capítol 2), es presenten 5 capítols basats en 5 reaccions asimètriques catalitzades per metalls de transició.

En el capítol 3, es presenta la síntesi i l'aplicació de 5 famílies de lligands fosfit diferents i la seva aplicació a reaccions de substitució al·lílica catalitzada per pal·ladi o coure.

El primer apartat d'aquest capítol 3 inclou el manuscrit "*Conformational preferences of a tropos biphenyl phosphinooxazoline- A ligand with wide substrate scope",* on es descriu l'aplicació de lligands fosfit-oxazolina PHOX en la reacció de substitució al·lílica asimètrica catalitzada per pal·ladi. S'han obtingut elevades activitats i enantioselectivitats per un gran ventall de substrats i nucleòfils (>99% ee). A més a més, gràcies a estudis computacionals (*DFT*) han permès estudiar l'espècie responsable de l'origen d'aquesta alta enantioselectivitat.

En el segon apartat del capítol 3 s'inclou el manuscrit "*Asymmetric Pd-catalyzed allylic substitution using phosphite-oxazoline PHOX-based ligands containing a methylene linker",* on es descriu la síntesi i l'aplicació de lligands fosfit-oxazolina basats en modificacions dels lligands aplicats a l'apartat anterior. Amb aquesta modificació, s'ha pogut estudiar la influència en l'activiat i la selectivitat que té introduir un grup metilè com a espaiador entre el fosfit i l'oxazolina. Aquesta modificació, ha permès augmentar el nombre de nucleòfils utilitzats, mantenint els grans valor d'enantioselectivitat en molts casos.

En el tercer apartat s'inclou el manuscrit "*Phosphite-oxazoline PHOX-based ligands containing an alkyl backbone chain for asymmetric Pd-catalyzed allylic substitution reactions. Study of the key Pd-intermediates"*, on es descriu la síntesi i l'aplicació de una segona generació de lligands fosfit-oxazolina, en la qual s'ha introduït un segon centre quiral a la molècula en comparació a la PHOX fosfit-oxazolina explicada a la Secció 3.2. Un gran nombre de substrats i nucleòfils han estat cribats en èxit, obtenint excel·lents enantioselectivitats. A més a més, s'han realitzat estudis computacionals mitjançant càlculs *DFT* i estudis de Ressonància Magnètica Nuclear (RMN) els quals han estat claus per estudiar l'origen de les enantioselectivitats obtingudes.

En el quart apartat del capítol 3 s'inclou el manuscrit "*Alternating theoretical and experimental optimization of a new amino-phosphite ligand library for asymmetric Pd-catalyzed allylic substitution",* on es descriu la síntesi i aplicació de lligands fosfit-amina. Aquests nous lligands, són altament estables degut a la major robustesa del grup amina respecte al grup oxazolina utilitzats en els apartats anteriors. Gràcies a alternar la química computacional i els assajos experimentals s'ha pogut optimitzar l'estructura del lligand que ofereix més elevades activitats i enantioselectivitats per un ampli ventall de substrats i nucleòfils. A més a més, gràcies a estudis de RMN, hem pogut analitzar els intermedis Pd-π-al·lil i la seves reactivitats, els responsables de les altes enantioselectivitats obtingudes.

Per últim, a l'apartat 5 del capítol 3 s'inclou el manuscrit "*Furanoside phosphite-phosphoramidite and diphosphoramidite ligans applied to asymmetric Cu-catalyzed allylic substitution reactions",* on s'inclou l'aplicació de lligands bidentats amb esquelet furanosa a la reacció de substitució al·lílica asimètrica catalitzada per coure. Aquests lligands fosfit-fosforamidit basats en esquelet furanosa han proporcionat elevades

regioselectivitats (98:2 cap al regioisòmer desitjat) i enantioselectivitats moderades (76% d'excés enantiomèric) en un ventall de substrats tipus cinamil i diferents nucleòfils com organomagnesians i diorganozincs.

En el quart capítol es presenten els resultats d'una col·laboració entre el nostre grup de recerca i el grup del Prof. Patrick J. Guiry a Dublín, mitjançant una estada de doctorat de 3 mesos. En aquest capítol s'inclou el manuscrit *"First catalytic asymmetric synthesis of sterically hindred tertiary α-aryl oxindoles via Pd-catalyzed decarboxylative protonation",* on es descriu la aplicació de lligands fosfit-nitrogen, prèviament sintetitzats i aplicats en el nostre grup, en la protonació descarboxilativa asimètrica catalitzada per pal·ladi. Aquesta reacció s'aplica en substrats del tipus α-aril-β-amido al·lil esters, i s'estudia l'influencia de diferents grups aril en la enantioselectivitat del procés. S'han obtingut enantioselectivitats prometedores (excessos enantiomèrics fins al 78%) per a onxindoles que contenen grups aril molt impedits estèricament i rics en densitat electrònica. A més a més, s'han realitzat estudis de càlcul computacional per a poder entendre millor l'origen de la enantioselectivitat, ja que hi ha un buit de coneixement en aquest camp. Aquest és el primer cas de síntesi enantioselectiva de α-aril oxindoles a la bibliografia.

En el cinquè capítol es presenta l'aplicació de lligands fosfit-oxazolina, sintetitzats i aplicats anteriorment en substitució al·lílica catalitzada per Pd (en el capítol 3), en la hidrogenació asimètrica d'olefines catalitzada per iridi.

En el primer apartat s'inclou el manuscrit *"Ir-Catalyzed asymmetric hydrogenation of olefins using PHOX-based phosphite-oxazoline ligands"*, on es descriu l'aplicació dels lligands PHOX fosfit-oxazolina, descrits en els apartats anteriors, en la hidrogenació d'una gran varietat d'olefines, aconseguint enantioselectivititats molt elevades (fins a un excés enantiomeric del 99%) tant en olefines mínimament funcionalitzades com en β-enamides cícliques.

En el segon apartat s'inclou el manuscrit *"Asymmetric Ir-catalyzed hydrogenation of challenging olefins using phosphite/phosphinite-oxazoline PHOX-based ligands containing an alkyl backbone chain",* on es descriu l'aplicació de lligands fosfit-oxazolina, prèviament aplicats en substitució al·lílica (Secció 4.4) en la hidrogenació d'un gran ventall d'olefines mínimament funcionalitzades. S'han aconseguit excessos enantiomèrics elevats de fins al 99% per una gran varietat de substrats.

En el sisè capítol es presenta el manuscrit *"Filling the gaps in the challenging asymmetric hydroboration of 1,1-disubstituted alkenes with simple phosphite-based phosphinooxazoline iridium catalysts"* on es descriu l'aplicació de lligands PHOX fosfit-oxazolina ja descrits en la Secció 3.2 i 5.2, en la hidroboració asimètrica d'olefines 1,1-disubstitutides catalitzada per iridi. S'han obtingut grans resultats en termes de regio- (>99% cap a la posició β) i enantioselectivitat (excessos enantiomèrics fins al 94%),

sobretot en la hidroboració d'olefines que contenen un grup voluminós *tert*-butil en la posició 1. Anteriorment ja s'havia aplicat lligands fósfor-nitrogen en la hidroboració d'olefines 1,1-disubtituides, però el lligand utilitzat (PHOX phosphina-oxazolina) només proporcionava elevades enantioselectivitats quan grups poc voluminosos, com per exemple un grup metil, en a la posició 1 de l' olefina.

Finalment en el setè capítol, basat en resultats preliminars, es presenta l'aplicació de lligands basats en l'estructura PHOX fosfit-oxazolina i la família de lligands fosfit-oxazolina resultant de la seva modificació en la addició asimètrica de compostos organoaluminats a aldehids catalitzada per níquel.

La primera part inclou el manuscrit "*First PHOX-based phosphite-oxazoline applied to asymmetric Ni-catalyzed 1,2-addition of triorganoaluminum to aldehydes",* en la que es descriu l'aplicació de lligands PHOX fosfit-oxazolina en la addició de compostos organoaluminats, com per exemple $AlMe_3$, $AlEt_3$ i DABAL-Me_3, a aldehids del tipus benzaldehid i derivats electrònics i estèrics d'aquest. S'han obtingut moderades enantioselectivitats (62% d'excés enantiomèric), essent uns resultats prometedors, degut a l'escassa aplicació del lligands bidentats fòsfor-nitrogen en aquesta transformació.

La segona part inclou el manuscrit "*Phosphite-oxazoline ligands containing an alkyl backbone chain for Ni-catalyzed enantioselective 1,2-addition of triorganoaluminum reagents to aldehydes",* en la que es descriu l'aplicació de lligands fosfit-oxazolina que contenen una cadena alquílica (prèviament descrits a la Secció 3.4 i 5.3). Com en l'apartat anterior, s'ha estudiat l'addició de diferents compostos alquilalumini a un ampli rang d'aldehids, obtenint excessos enantiomèrics de fins al 64%.

Chapter 10

Appendix

UNIVERSITAT ROVIRA I VIRGILI
DESIGN OF TAILOR-MADE CHIRAL LIGAND LIBRARIES FOR C-X BOND FORMING REACTIONS. STUDY OF THE KEY INTERMEDIATES BY NMR AND DFT
Marc Magre Rosich

10. Appendix

10.1. List of papers

1. Magre, M.; Pàmies, O.; Diéguez, M. *PHOX-Based Phosphite-Oxazoline Ligands for the Enantioselective Ir-Catalyzed Hydrogenation of Cyclic β-Enamides*. *ACS Catalysis.* **2016.** *Accepted manuscript*
2. Pàmies, O.; Magre, M.; Diéguez, M. *Extending the Substrate Scope for the Iridium-Catalyzed Hydrogenation of Minimally Functionalized Olefins by Using Biaryl Phosphite-Based Modular Ligand Libraries. Chem. Rec.* **2016**. DOI: 10.1002/tcr.201600024. **Review**
3. Magre, M.[+]; Bellini, R.[+]; Biosca, M.; Norrby, P.-O.; Pàmies, O.; Diéguez, M.; Moberg, C. *Conformational Preferences of a Tropos Phospinoozaxoline- A Ligand with Wide Substrate Scope. ACS Catalysis* **2016**, *6*, 1701. [+]Both authors contributed equally to this work.
4. Magre, M.; Biosca, M.; Norrby,P.-O.; Pàmies, O.; Diéguez, M. *Theoretical and experimental optimization of a new amino phosphite ligand library for asymmetric palladium-catalyzed allylic substitution. ChemCatChem* **2015**, *7*, 4091.
5. Magre, M.; Biosca, M.; Pàmies, O.; Diéguez, M. *Filling the Gaps in the Challenging Asymmetric Hydroboration of 1,1-Disubstituted Alkenes with Simple Phosphite-Based Phosphinooxazoline Iridium Catalysts. ChemCatChem* **2015**, *7*, 114. **Back Cover Article**
6. Andrews, P.; Latham, C.M.; Magre, M.; Willcox, D.; Woodward, S. *$ZrCl_2(\eta\text{-}C_5Me_5)_2$-$AlHCl_2{\cdot}(THF)_2$: efficient hydroalumination of terminal alkynes and cross-coupling of the derived alanes. Chem. Commun.* **2013**, *49*, 1488. **Front Cover Article**
7. Magre, M.; Mazuela, J.; Diéguez, M.; Pàmies, O.; Alexakis, A. *Furanoside phosphite-phosphoramidite and diphosphoramidite ligands applied to asymmetric Cu-catalyzed allylic substitution reactions. Tetrahedron Asymmetry* **2012**, *23*, 67.

10.2. Meeting contributions

1. Authors: Magre, M.; Biosca, M., Pàmies, O.; Diéguez, M.
   Title: Asymmetric hydroboration of 1,1-disubstituted alkenes with simple phosphite-based PHOX iridium catalysts
   Contribution: Poster
   Congress: OMCOS 18 – Organometallic Chemistry Directed Towards Organic Synthesis

Place: Sitges, Spain
Date: 28th June-2nd July 2015

2. Authors: Magre, M.; Pàmies, O.; Diéguez, M.
Contribution: Organization and attendance.
Congress: COST-CARISMA- Catalytic Routines For Small Molecules Activation
Place: Tarragona, Spain.
Date: 18th-20th March 2015

3. Authors: Magre, M.; Pàmies, O.; Diéguez, M.
Title: SIMPLE phosphite-amine ligands for asymmetric Pd-catalyzed allylic substitutuion reactions
Contribution: Poster
Congress: GEQOXXXII – Grupo Especializado Química Organometálica (RSEQ)
Place: Tarragona, Spain
Date: 17th-19th September 2014

4. Authors: Magre, M., Guiry, P. J.
Contribution: Attendance
Congress: 20th ICPC – International Conference on Phosphorus Chemistry.
Place: Dublin, Ireland
Date: 28th June- 2nd July 2014

5. Authors: Magre, M.; Mazuela, J.; Diéguez, M.; Pàmies, O.; Alexakis, A.
Title: Sugar phosphoroamidite-based ligands for asymmetric Cu-catalyzed allylic substitution reactions
Contribution: Poster
Congress: 18th International Symposium in Homogeneous Catalysis (ISHC)
Place: Toulouse, France
Date: 9th – 13th July 2012

10.3. PhD research abroad

1. University College Dublin, Ireland.
Under the supervision of Prof. Patrick J. Guiry
May-July 2014

2. University of Nottingham, United Kingdom (UK)
Under the supervision of Prof. Simon Woodward
June-July 2015