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PhD-Thesis

Supervised by Dr. Montserrat Diéguez
and Dr. Oscar Pàmies

Departament
de Química Física i Inorgànica

UNIVERSITAT ROVIRA I VIRGILI
TARRAGONA
2009

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MONTSERRAT DIÉGUEZ FERNÁNDEZ i OSCAR PÀMIES OLLÉ, Professora Titular d'Universitat i Professor Agregat del Departament de Química Física i Inorgànica.

CERTIFIQUEN:

Que la present memòria que duu per títol: "SCREENING OF MODULAR PHOSPHOROAMIDITE AND PHOSPHITE-CONTAINING LIGAND LIBRARIES IN ASYMMETRIC METAL-CATALYZED REACTIONS" per a l'obtenció del títol de Doctor, ha estat realitzada per EVA RALUY GONZÁLEZ sota la nostra direcció a l'Àrea de Química Inorgànica del Departament de Química Física i Inorgànica d'aquesta Universitat i que acompleix els requeriments per poder optar a Menció Europea.

Tarragona, setembre de 2009

Dra. Montserrat Diéguez Fernández / Dr. Oscar Pàmies Ollé

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Una vegada escrita la tesi, arribe el moment de fer memòria i agrair a tota la gent que directa i indirectament ha participat en la realització d'aquesta.

En primer lloc als meus directors: la Montse, per confiar en mi, donar-me l'oportunitat de treballar en el seu grup i ensenyar-me a "quadrar" en el laboratori; i a l'Òscar per tot el que he aprés d'ell.

A tota la resta de professores del departament i de l'àrea: l'Anna, per introduir-me en el mon dels fosfits; la Yolanda, pel seu suport en el primer any de doctorat; la Carmen, por sus cenas y comidas multiculturales; l'Aurora, l'Elena, la Pilar, la Núria i la Mar. Ha estat un plaer compartir aquest temps amb vosaltres.

A la gent que s'encarregue de fer-nos el dia a dia més fàcil: l'Arantxa, por su extremada paciencia con las ISO, los papeleos, disolventes,...; a la Maria José, con la que pasé mis primeros días en un laboratorio de investigación; al Jordi, a les secretàries del departament, a la gent de recursos científics, especialment al Ramon, sempre disposat a ajudar i no perdre mai, però mai, la paciència; i com no als companys i professors del departament d'orgànica per estar sempre disposats a ajudar i trobar sempre aquell producte que et fa falta.

A una de les parts més importants, els companys, sense la qual no hagués pogut tirar endavant aquesta tesi, ni poder recordar ara tants bons moments com hem passat.

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Als doctors del grup: l'Aitor, moltes gràcies pels teus consells i recolzament, Cyril, Nicola, Olivier, Henry i Ali, por estar siempre dispuesto a ayudar اشكرك جزيل الشكر. Ese lab 2.17: la Mercè, per tots els mails que me vas escriure, que no van ser pocs i per tots els bons moments que hem passat tant dins com fora del labo; el Javi, por el lanzamiento de corcho como deporte olímpico; a la Sabina, molta sort i ànims; i l'Angélica, por tu llegada al labo, por tu apoyo, todos los días de trabajo compartidos y todas esas noches de guayabo. A l'Amadeu, quins labos que hem passat!; a l'Oriol, per portar el compte dels dies que mancaven...; a la Cris, perque ets la pera. A la Isa, por su visita a esos mundos de niebla y lluvia; la Tati, te deseo mucha suerte y paciencia. Com no, a la resta de les Maries per tots els bons moments que hem passat al seminari: la Dolores, por compartir todas esas mañanas, esos nervios y buenos momentos que espero sean muchos más; i a la Cris, per la teva alegria, optimisme i per ser com ets. A tota la gent que ha passat d'estància: Gwaine, Kara, Vanesa, Norbert, Ben, Lourdes i Doris, ... Bueno i a tu Ari, perque amb tu he aprés a mirar una mica millor aquestes maquinotes que en diuen ordinadors, per la teva paciència, per tots els riures, per la teva amistat i per estar allí sempre que feie falta.

I would like to thank Prof. Alexakis to accept me in his group and specially to Stephane Rosset, for his extremely patience.
També agrair al Xavi i la Montse, per fer-me sentir com a casa, per deixar-me compartir tants bons moments amb ells i per les seves

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excursionetes. No us oblidaré mai. And Sirinporn, ขอบคุณมากสำหรับมิตรภาพที่ดีของคุณโชค.

I per últim agrair a les persones més importants: a l'Hugo, per compartir la teva vida amb mi; i als meus pares, per haver-me donat tot sense demanar res a canvi, perque sense vosaltres no seria qui soc ni estaria on estic. Moltes gràcies a tots.

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a small drop of water

in an immense ocean

Isaac Newton

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Structure of the thesis

This thesis is based on eight papers published in international journals. These papers have been reedited to provide a uniform format throughout the thesis.

The thesis is divided into eight chapters.

- Chapter 1. *Introduction*. This chapter first presents the importance of metal asymmetric catalysis in the synthesis of enantiomerically pure compounds. An important step in this synthesis is the design and preparation of chiral ligands. Among them, new chiral ligands derived from carbohydrate are presented. These ligands are applied to four asymmetric catalytic reactions, which are reviewed in detail in this chapter. For each reaction, the antecedents, performance and main achievements are discussed, with emphasis on the application of carbohydrate ligands. The state-of-the-art and current needs in this field justify the objectives of the thesis.

- Chapter 2. *Objectives*. Based on the aspects discussed in chapter 1, this chapter presents the objectives of the thesis. These involve the synthesis and application of carbohydrate ligands in asymmetric catalysis.

- Chapter 3. *Asymmetric Pd-catalyzed allylic substitution*. This chapter contains two sections on the development and application of new phosphite-phosphoroamidite and diphosphoroamidite ligand libraries in the asymmetric Pd-catalyzed allylic substitution reactions. The first section, *Modular furanoside phosphite-phosphoroamidite, a readily available ligand library for asymmetric Pd-catalyzed allylic substitution reactions. Origin of enantioselectivity*, describes the synthesis and application of a phosphite-phosphoroamidite ligand library in the

asymmetric Pd-catalyzed allylic substitution of several substrates with different electronic and steric properties. This paper also discusses the synthesis and characterization of the Pd-π-allyl intermediates to provide greater insight into the origin of the enantioselectivity. The second section, *Sugar-based diphosphoroamidite as a promising new class of ligands in the Pd-catalyzed asymmetric allylic alkylation reactions*, includes the development and application of a new diphosphoroamidite ligand library in asymmetric allylic substitution.

- Chapter 4. *Asymmetric Cu-catalyzed allylic alkylation.* This chapter contains one section, *Furanoside phosphite-phosphoroamidite, di- and monophosphoroamidite ligands for asymmetric Cu-catalyzed allylic alkylations*, which discusses the preliminary results in the application phosphite-phosphoroamidite, diphosphoroamidite (both ligand libraries developed in Chapter 3) and monophosphororamidite ligands in the asymmetric Cu-catalyzed allylic alkylation reactions. It also describes the synthesis of a new monophosphoroamidite ligand library.

- Chapter 5. *Asymmetric Cu-catalyzed 1,4-conjugate addition.* This chapter contains two sections on the application of the phosphite-phosphoroamidite and diphosphoroamidite (developed in Chapter 3), and monophosphoroamidite (developed in Chapter 4) and phosphite ligand libraries in the asymmetric Cu-catalyzed 1,4-addition reactions. The first one, *Furanoside phosphite-phosphoroamidite and diphosphoroamidite ligands for Cu-catalyzed asymmetric 1,4-conjugate addition reactions*, reports the investigations of the Cu-catalyzed 1,4-conjugate addition of organometallic reagents to enones using the phosphite-phosphoroamidite and diphosphoroamidite ligand libraries. The second section, *Sugar-based phosphite and phosphoroamidite ligands for the Cu-catalyzed asymmetric*

1,4-conjugate addition to enones, includes the application of the sugar-based monophosphoroamidite and monophosphite ligand libraries in the Cu-catalyzed 1,4-conjugate addition of organometallic reagents to cyclic and linear enones.

- Chapter 6. *Asymmetric Ni-catalyzed 1,2-addition.* This chapter contains two sections on the application of the phosphite-phosphoroamidite and diphosphoroamidite (developed in Chapter 3) and monophosphoroamidite (developed in Chapter 4) ligand libraries in the asymmetric Ni-catalyzed 1,2-addition reactions. The first one, *Furanoside phosphite-phosphoroamidite and diphsophoroamidite: new ligand classes for the asymmetric nickel-catalyzed trialkylaluminum addition to aldehydes,* reports the investigations of the Ni-catalyzed trialkylaluminium 1,2-addition to aldehydes using the phosphite-phosphoroamidite and diphosphoroamidite ligand libraries. The second section, *Screening of a modular sugar-based phosphoroamidite ligand library in the asymmetric nickel-catalyzed trialkylaluminum addition to aldehydes,* includes the application of the carbohydrate-based monophosphoroamidite ligand library in the Ni-catalyzed trialkylaluminium 1,2-addition to several aldehydes types.

- Chapter 7. *Conclusions*. This chapter presents the conclusions of the work presented in this thesis.

- The *Appendix* contains the list of papers and meeting presentations given by the author during the period of development of this thesis.

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Chapter 1

Introduction

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1. Introduction

The preparation of enantiomerically enriched compounds plays currently a pivotal role in several important areas such as pharmaceuticals, agrochemicals, fine chemicals and natural product chemistry. One of the main methods for producing enantiopure compounds is enantioselective homogeneous metal catalysis. 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.[1]

To obtain the highest levels of reactivity and selectivity in catalytic enantioselective reactions, several parameters must be optimized. Among them, the selection and design of the chiral ligand is perhaps the most crucial step. One of the simplest ways to obtain chiral ligands is to transform or derivatize natural chiral compounds. The structural diversity of carbohydrates and the high density of functional groups offer a wide variety of opportunities for derivatization and tailoring of synthetic tools in the search of the right ligand for each particular reaction.[2] One limitation with natural compounds from the chiral pool is that generally only one enantiomer is easily accessible and, indeed, the L-enantiomers of most naturally occurring D-carbohydrates are either prohibitively expensive or unavailable. However, this problem can often be solved by the use of pseudo-enantiomers that can also be prepared from the D-series.

In this context, this thesis focuses on the development of new chiral ligand libraries derived from carbohydrates and their application in the enantioselective Pd- and Cu-catalyzed allylic substitution reactions,

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Cu-catalyzed asymmetric 1,4-conjugate addition to α,β-unsaturated substrates and Ni-catalyzed asymmetric addition of trialkylaluminum to aldehydes. In next section, we collect the most important carbohydrate-derivative ligand families developed for asymmetric metal-catalyzed reactions. The following sections describe the background of each asymmetric catalytic reactions studied in this thesis.

1.1. Carbohydrate ligands' background in asymmetric catalysis

In recent decades, several types of carbohydrate ligands have been prepared thanks to the high diversity of backbone structures and the fact that they can be easily functionalized and modified. Nowadays, many type of carbohydrate ligands have been successfully applied in several catalytic asymmetric reactions (mainly in asymmetric hydrogenation). A review of the research into carbohydrate ligands highlighted four main carbohydrate derivative ligand families applied in asymmetric catalysis:

- The first important family is the pyranoside diphosphinite ligands **1** derived from D-glucose (Figure 1) mainly developed by the groups of Selke and Rajanbabu. These ligands were the first successful application of diphosphinite ligands in asymmetric catalysis. They were applied with excellent enantioselectivities in the Rh-catalyzed asymmetric hydrogenation of dehydroaminoacids (ee's up to 99%)[3] and in the Ni-catalyzed asymmetric hydrocyanation of vinylarenes (ee's up to 91%).[4]

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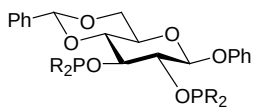
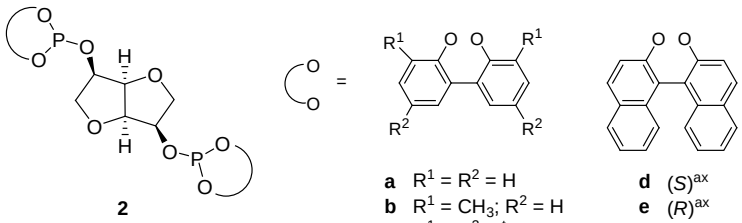


1

Figure 1. Pyranoside diphosphinite ligands **1**.

- The second family is the C_2-diphosphite ligands **2** derived from D-mannitol. These ligands, developed by Reetz and co-workers, were successfully applied in the asymmetric hydrogenation of dehydroaminoacid derivatives (ee's up to 98%).[5]



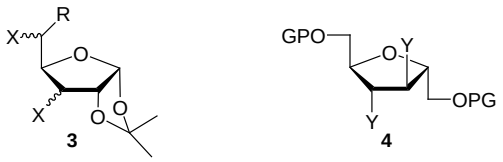
2

a $R^1 = R^2 = H$
b $R^1 = CH_3$; $R^2 = H$
c $R^1 = R^2 = {}^tBu$

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

Figure 2. Diphosphite ligands **2**.

- The third important series of carbohydrate derivative ligands in asymmetric catalysis is the furanoses derived from D-(+)-xylose, D-(+)-glucose and D-glucosamine (Figure 3). These ligands were successfully applied in several asymmetric catalytic processes, such as hydrogenation, hydroformylation and allylic substitution reactions.[6]



3 **4**

X = PPh_2, OPR_2, $OP(OR)_2$
R = Me, H

Y = OPR_2, $OP(OR)_2$
PG = Protecting group

Figure 3. Furanoside ligands **3** and **4**.

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- The last important family of carbohydrate ligands are the phospholane ligands derived from D-mannitol (Figure 4). In the last few years, these compounds have mainly emerged as a powerful new class of ligands for asymmetric hydrogenation (ee's up to 99%)[7] and for asymmetric allylic substitution (ee's up to 99%)[8] reactions.

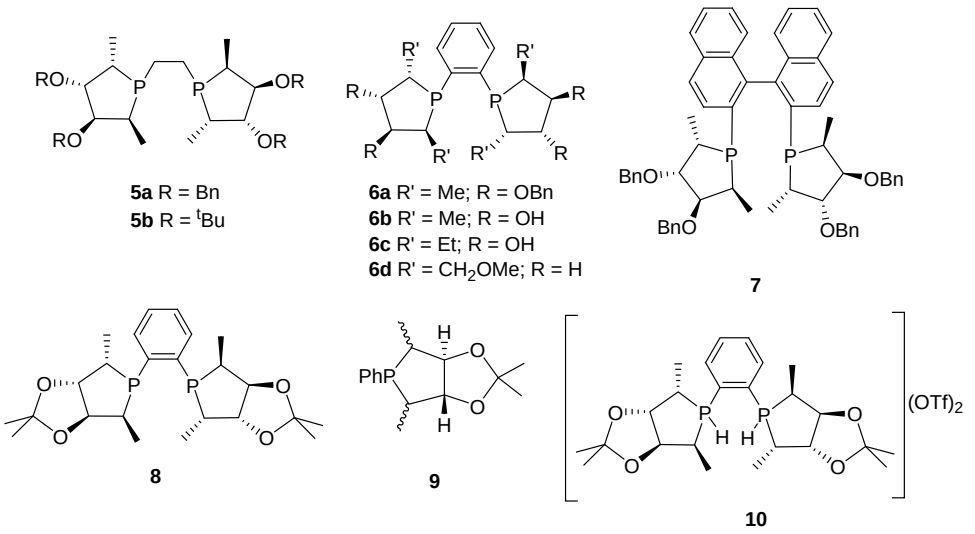

Figure 4. Phospholane ligands derived from D-mannitol.

1.2. Asymmetric Pd-catalyzed allylic substitution

Enantioselective Pd-catalyzed allylic substitutions represent a synthetically valuable strategy for the construction of asymmetric carbon-carbon and carbon-heteroatom bonds. The mild reaction conditions and the compatibility with many functional groups make this method attractive for the application in the synthesis of drugs and natural products.[9]

In this process, an allylic racemic substrate which contains a leaving group (LG), normally an acetate or carbonate, is attacked by a

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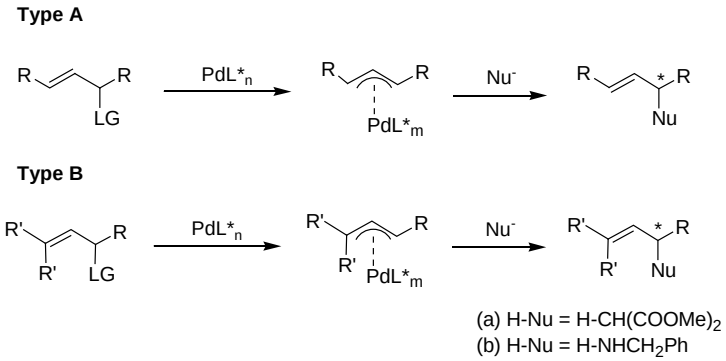
nucleophile (typically a carbon or nitrogen nucleophile). Scheme 1 shows two important classes of allylic substitutions that can be carried out enantioselectively with chiral catalysts. Type A reactions start from a racemic substrate (linear or cyclic) and proceed via symmetrical allyl systems. In this case, the enantioselectivity is determined by the regioselectivity of nucleophilic attack and therefore depends on the ability of the chiral ligand to differentiate between the two allylic termini. In type B reactions, racemic or prochiral substrates possessing two identical geminal substituents at one of the allylic termini react via π-allyl intermediate which can isomerize via the well-established π-σ-π mechanism. In this case, enantioselection can occur either in the ionization step, leading to the allyl intermediate, or in the nucleophilic addition step. For these latter substrates, not only does the enantioselectivity of the process need to be controlled, but the regioselectivity is also a problem because a mixture of regioisomers may be obtained.



Scheme 1. Two classes of asymmetric allylic substitution reactions.

The range of substrates (linear and cyclic) tested is quite wide (Figure 5). However, *rac*-1,3-diphenylprop-2-enyl (**S1**) is widely used as

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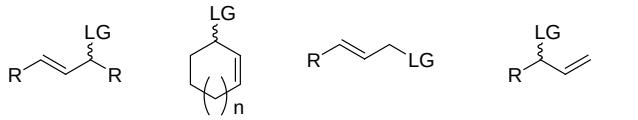
a model substrate for testing a new ligand. With regard to the metal source, a variety of transition metal complexes derived from Pd, Ni, Ru, Rh, Ir, Mo, W and other elements are known to catalyze allylic substitutions.[1d] However, the most widely used catalysts are palladium complexes. A wide range of carbon and heteroatom stabilized 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 new catalysts, many other stabilized carbanions bearing carbonyl, sulfone, nitrile or nitro groups have also been used. There are only a few examples of enantioselective reactions with non-stabilized nucleophiles such as diorganozinc or Grignard reagents.[9]



S1 R = Ph
S2 R = Me
S3 n = 1
S4 n = 2
S5 R = 1-Naphtyl
S6 R = 1-Naphtyl

Figure 5. The most common substrates for the enantioselective allylic substitution.

1.2.1. Mechanism

The catalytic cycle for Pd-catalyzed allylic substitution reactions with stabilized nucleophiles is well established and involves four main steps (Figure 6).[9]

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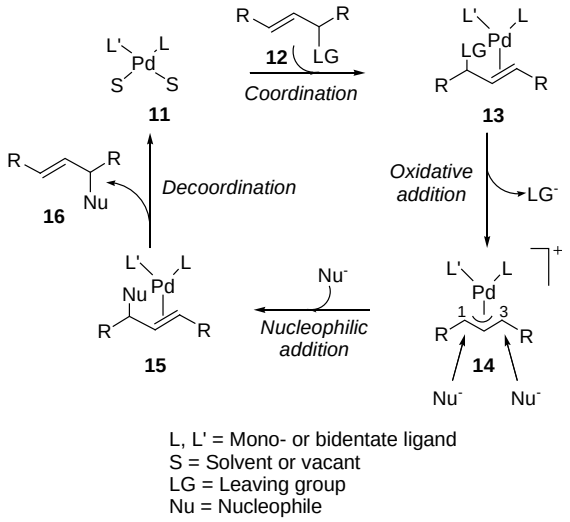

Figure 6. Catalytic cycle for the Pd-catalyzed allylic substitution reaction with stabilized nucleophiles.

The first step of the catalytic cycle is the coordination of an allylic substrate **12** to the catalyst precursor **11**, which enters the cycle at the Pd(0) oxidation level. Both Pd(0) and Pd(II) complexes can be used as precatalysts due to Pd(II) is easily reduced *in situ* by the nucleophile to the Pd(0) form. The most widely used precursors are $Pd_2(dba)_3 \cdot dba$, (dba = dibenzylidenacetone), $Pd(OAc)_2$ and $[Pd(\eta^3\text{-}C_3H_5)(\mu\text{-}Cl)]_2$. Next step is the oxidative addition of complex **13** to form the π-allyl intermediate **14**, which is usually the rate-determining step of the reaction. The product of this oxidative addition has two susceptible positions for receiving nucleophilic attack (C-1 and C-3). After nucleophilic addition, an unstable Pd(0)-olefin complex **15** is produced, which readily releases the final product **16**.

It is accepted, that the enantioselectivity of the process is controlled by the external nucleophilic attack on the most electrophilic allylic carbon terminus of the π-allyl intermediate **14**.[9] Therefore, the π-

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allyl intermediate **14** plays an important role in the catalytic cycle and it is recognized as the intermediate which controls regio- and enantioselectivity. This intermediate can be isolated in the absence of nucleophiles. It is known, that allyl complex type-**14** can show a dynamic behaviour in solution, which results in a mixture of isomers (Figure 7).

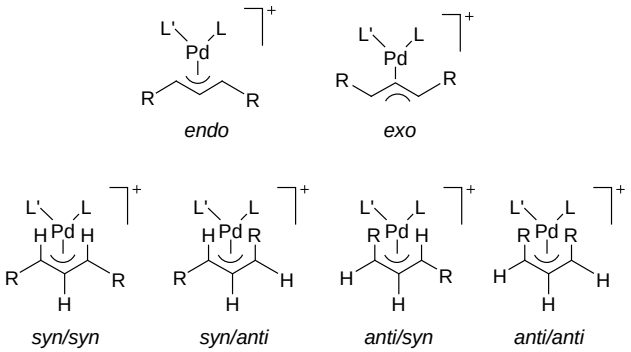

Figure 7. Possible isomers adopted by the Pd-allyl complex **14**.

To achieve high enantioselectivities, the formation of a single isomer is necessary, if we assume that the reaction rates are similar for all possible isomers. Both the oxidative addition and the nucleophilic attack usually occur stereoselectively with inversion of configuration. Therefore, if the intermediate allyl complex does not undergo any isomerization that changes its configuration, the overall process **11** to **16** proceeds with the retention of configuration, i.e. the nucleophile is introduced at the same side of the allyl plane that was occupied by the leaving group LG.

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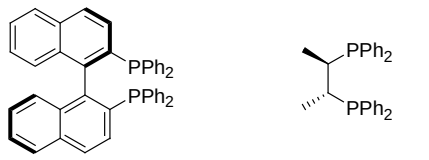
1.2.2. Ligands

Since the first enantioselective catalytic process described by Trost in 1977, with moderate enantioselectivity,[10] many catalytic systems have been tested. These have provided excellent enantiomeric excesses.[9]

Unlike asymmetric hydrogenation process, few diphosphines have provided good enantioselectivities in allylic substitutions. Though high ee's could be obtained in certain cases for instance, with BINAP and CHIRAPHOS (Figure 8), the scope of standard diphosphines in this process seems limited.



BINAP **CHIRAPHOS**

Figure 8. BINAP and CHIRAPHOS ligands.

However, one of the most versatile ligands for this process is a diphosphine **17** developed by Trost (Figure 9).[9b,11] The remarkable properties of this ligand are related to the bite angle, which is larger than in unstrained Pd-diphosphine complexes. Consequently, the P-aryl groups generated a chiral cavity, in which the allyl system is embedded, that provides high ee's for several sterically undemanding substrates. For diphosphines and other homodonor systems, the chiral discrimination is therefore induced by the C_2 or C_1 backbone of the ligand.

The selection of chiral ligands for highly enantioselective allylic substitution has mainly focused on the use of mixed bidentate donor ligands such as phosphorus-nitrogen, phosphorus-sulfur and sulfur-

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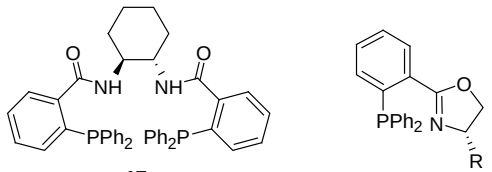
nitrogen. In this context, the phosphine-oxazoline PHOX ligands represent, together with Trost's ligand, one of the most representative ligands developed for this process (Figure 9).[9e] The efficiency of this type of hard-soft heterodonor ligands has been mainly attributed to the different electronic effects of the donor atoms that predominantly produced the nuclephilic attack at one of the allyl carbon atoms (the one located *trans* to the best π-acceptor).

Other ligands, such as bidentate nitrogen and sulfur, have also exhibited very good catalytic behavior.[9b,f,h]



17

Trost's ligand PHOX ligands

Figure 9. Two of the most representative ligands developed for the Pd-catalyzed allylic substitution reactions.

Carbohydrate ligands have only recently shown their huge potential as a source of highly effective chiral ligands in this process. Several types of ligands, mainly heterodonors, have been developed for this process and some of the results are among the best ever reported.

In the next section, we summarize some of the most relevant results obtained for the Pd-catalyzed allylic substitution reactions with carbohydrate ligands.

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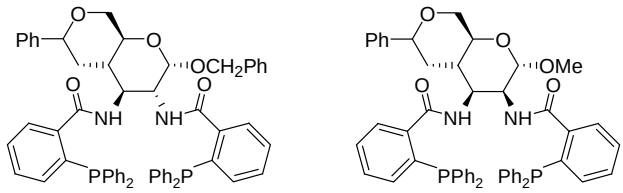
1.2.2.1. P-donor ligands

Phosphine ligands

One of the best results obtained in the allylic substitution using phosphine ligands have been achieved with the family independently developed by RajanBabu and Zhang. These authors reported the use of monophospholanes **9** and diphospholanes **6**-**8** ligands, derived from D-mannitol, in the Pd-catalyzed allylic alkylation of substrate **S1** (Figure 4),[8a-c] with high enantioselectivities (ee's up to 99%). It is also observed that the sense of the asymmetric induction is controled by the absolute stereochemistry of the P-carrying carbons. Both enantiomers of the product can therefore be obtained.

In 2006, Ruffo and co-workers developed a modification of the Trost-bis(phosphinoamides) ligands using diamines based on glucose and mannose as chiral auxiliaries (Figure 10, ligands **18** and **19**) for the highly enantioselective Pd-catalyzed desymmetrization of meso-cyclopenten-2-ene-1,4-diol biscarbamate (ee's up to 97%). Interestingly, both enantiomers of the product can be obtained in high enantioselectivities by switching from glucose (**18**) to mannose (**19**) derivative ligands. [12]



18 **19**

Figure 10. Bis(phosphinylamides) ligands **18** and **19** developed by Ruffo and co-workers.

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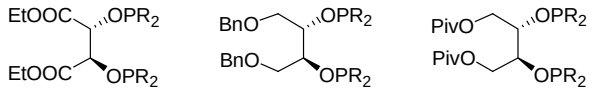
Phosphinite ligands

The most successful family of phosphinite ligands were reported by RajanBabu and co-workers. These authors reported the use of diphosphinite ligands **20**-**22**, derived from tartaric acid, in the allylic alkylation of substrate **S1** with enantioselectivities up to 77% (Figure 11).[13]



20 (73% (*R*)) **21** (31% (*S*)) **22** (77% (*R*))

Figure 11. Diphosphinite ligands **20**-**22**. The enantioselectivities obtained in the allylic alkylation of substrate **S1** are also shown.

Phosphite ligands

In 2001, it has been reported the first diphosphite ligand family (**23-29**) applied to Pd-catalyzed asymmetric allylic substitution reactions (Figure 12).[6e,14] The highly modular construction of these ligands allows sufficient flexibility to fine-tune (a) the various configurations of the carbohydrate backbone, (b) the substituents on C-5 of the carbohydrate backbone (R = H, Me, OTBDPS) and (c) the steric and electronic properties of the diphosphite substituents (**a**-**h**). The many combinations they provide are the key to finding the most suitable ligands for each particular substrate. Therefore, this set of ligands has been successfully applied in the Pd-catalyzed allylic substitution of dimethyl malonate and benzylamine to several acyclic and cyclic allylic esters (Figure 13).

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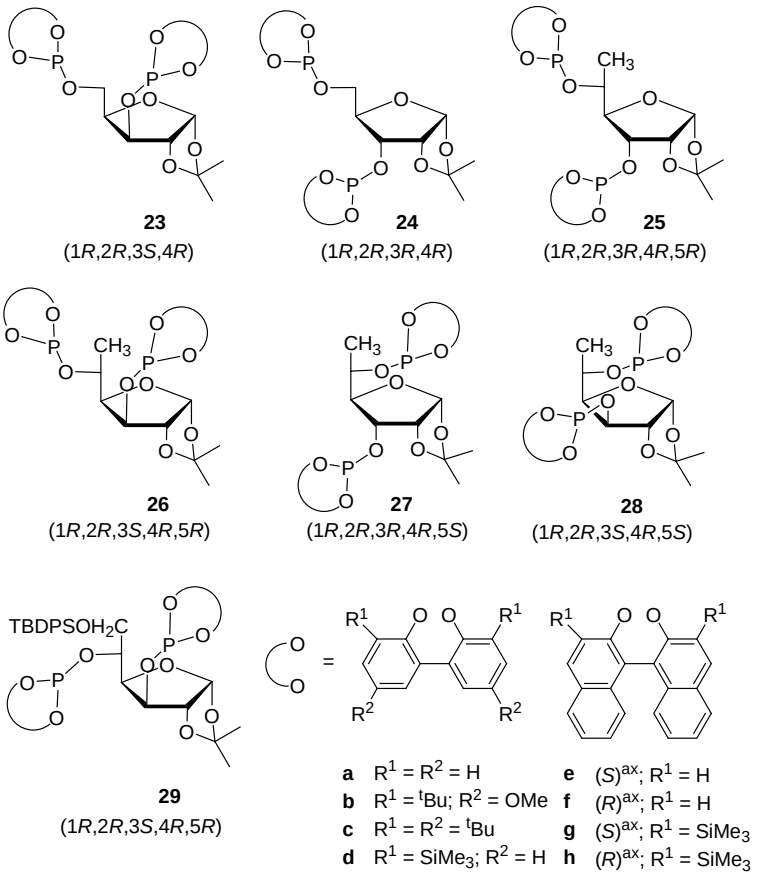

Figure 12. Furanoside diphosphite ligands **23-29**. (TBDPS = *tert*-butyldiphenylsilyl).

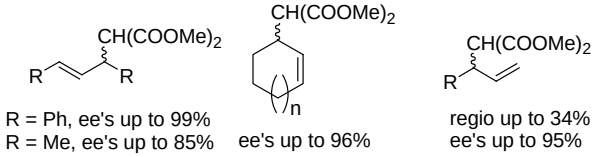

Figure 13. Acyclic and cyclic allylic esters tested with ligands **23-29**.

Results indicated that activities were best when the substituent at C-5 was Me and when the ligand contained bulky substituents at the *ortho* positions and electrodonating substituents at the *para* positions of the

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biphenyl moieties (i.e., **b** ~ **c** > **d** > **a**). Enantioselectivities were affected by the substituent at C-5, the phosphite moieties, the configuration of carbon atoms C-3 and C-5 and the configurations of the biaryl moieties. Enantioselectivities were best with ligand **26c**, which has a glucofuranoside backbone and bulky *tert*-butyl substitutents at both *ortho* and *para* positions of the biphenyl moieties. The results also indicated that the nucleophilic attack takes place *trans* to the carbon atom C-5. Ligand **23c** was also used to stabilize Pd-nanoparticles. These nanoparticles catalyzed the allylic alkylation of **S1** with dimethyl malonate leading to an almost total conversion of the (*R*) enantiomer and almost no reaction with the (*S*). This gives rise to 97% ee for the alkylation product and a kinetic resolution of the substrate recovered with ca. 90% ee.[15]

Recently, furanoside diphosphite ligands with C_2 symmetry **30** and **31** (Figure 14), systematically modified at positions C-2 and C-5 and in the biaryl phosphite moieties and prepared from D-glucosamine and D-glucitol, were successfully applied in the Pd-catalyzed allylic substitution reaction of **S1**. Ligand **30** provided excellent activities and enantioselectivities (ee's up to 99%).[6g]

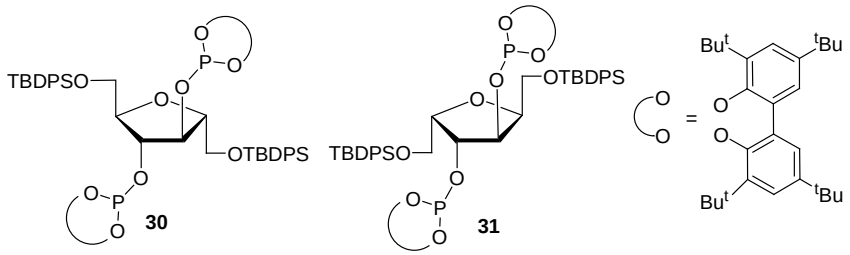

Figure 14. Diphosphite ligands **30** and **31**.

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1.2.2.2. S-donor ligands

Sulfur donor ligands have been used much less than phosphorus ligands in this process because a mixture of diastereomers can be obtained upon coordination of the thioether ligand to the metal, which can lead to a decrease in stereoselection if the relative rates of the intermediates are similar. Despite this, high enantiomeric excesses have been achieved.[9f,h] In this context, Khiar and co-workers used a combinatorial approach to find the best dithioether ligand **32** from a library of 64 potential ligands (four linkers x four carbohydrate residues x four protective groups) (Figures 15 and 16) for the Pd-catalyzed allylic alkylation of dimethyl malonate to **S1** (ee's up to 90%).[16a] In the search for both enantiomers of the alkylation product, the authors successfully prepared pseudo-enantiomers **33** and **34** derived from D-galactose and D-arabinose, respectively (Figure 16).[16b]

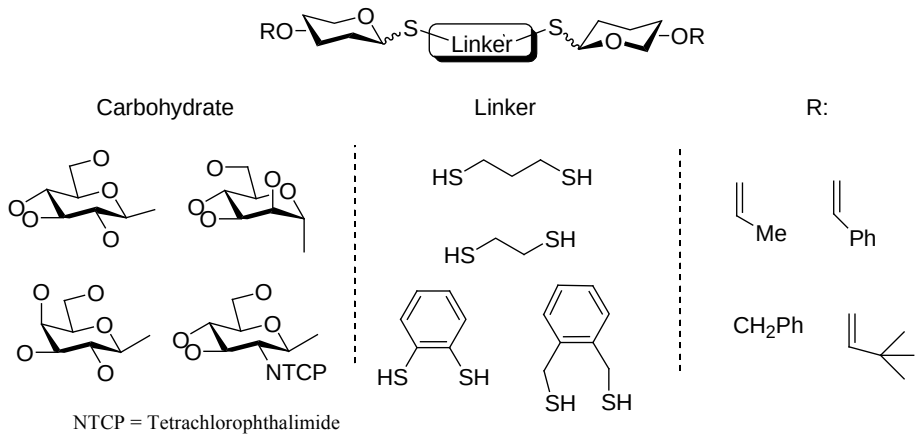

Figure 15. Scheme of the dithioether ligand library studied by Khiar and co-workers.

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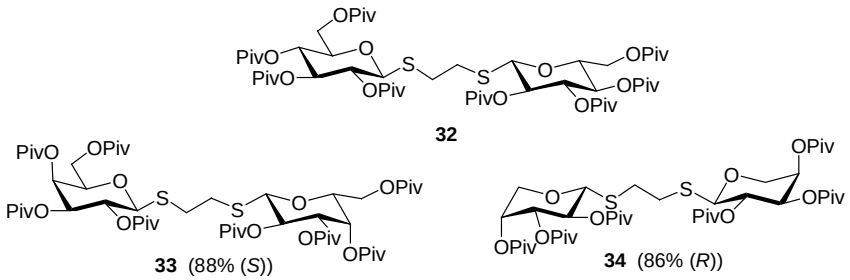

Figure 16. Dithioether ligands **32-34**. The enantioselectivities obtained in the allylic alkylation of substrate **S1** are also shown.

1.2.2.3. Heterodonor ligands

P-S ligands

Several combinations of P-S ligands have been studied in the allylic substitution reactions, such as phosphine-thioether, phospholane-thioether, phosphine-oxathiane, phosphite-thioether and phosphinite-thioether. In particular, the phosphine-thioether, phosphinite-thioether and phosphine-oxathiane have proven to be effective in enantioselective Pd-catalyzed allylic substitutions.

The ferrocenylphosphine-thiosugar ligand **35** (Figure 17) with multiple stereogenic units afforded an ee of 88% in the palladium allylic substitution of diethyl malonate to **S1**.[17a] However, when the thiosugar moiety was the sole stereogenic unit on ligands **36** (Figure 17), enantioselectivities were only moderate (ee's up to 64%).[17b]

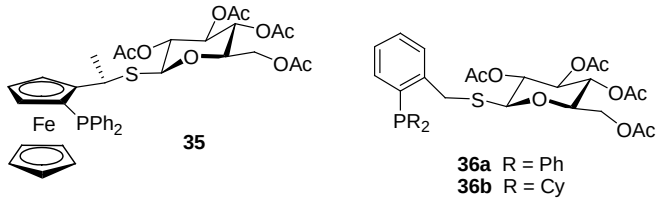

Figure 17. Phosphine-thioether ligands **35** and **36**.

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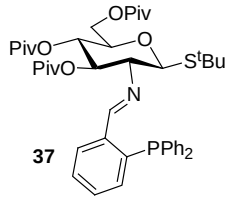
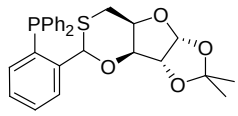
Khiar and co-workers reported the successful use of the phosphine-thioether ligand **37** (Figure 18) in the Pd-catalyzed asymmetric allylic alkylation of **S1** (ee's up to 90%).[18]



37

Figure 18. Phosphine-thioglucoside **37**.

In 2003, a phosphine-oxathiane ligand **38**, derived from D-(+)-xylose, has been developed for the Pd-catalyzed allylic substitution reactions (Figure 19). Good enantioselectivities have been obtained in the addition of dimethyl malonate and benzylamine to **S1** (ee's up to 91% and 94%, respectively).[19]



38

Figure 19. Phosphine-oxathiane ligand **38**.

More recently, a series of phosphinite-thioether ligands with furanoside backbone **39a-g** (Figure 20) were applied in the Pd-catalyzed allylic substitution of mono- and disubstituted linear and cyclic substrates (ee's up to 95%).[20] These ligands contained several thioether substituents with different electronic and steric properties. The authors found that this group had an important effect on catalytic performance. Thus, enantioselectivities were best when the bulkiest ligands **39a** and **39d** were

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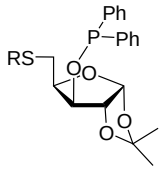
used. The replacement of the phosphinite group by a bulky biaryl phosphite lead to much lower enantioselectivity.[14b]

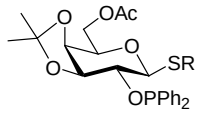


39

Ligand	R	%ee
a	^{i}Pr	93 (*S*)
b	Me	61 (*S*)
c	Ph	86 (*S*)
d	^{t}Bu	87 (*S*)
e	4-Me-C_6H_4	59 (*S*)
f	4-CF_3-C_6H_4	39 (*S*)
g	2,3-di-Me-C_6H_3	68 (*S*)

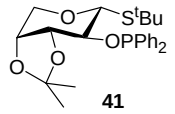
Figure 20. Phosphinite-thioether ligands **39**. The enantiomeric excesses obtained in the allylic alkylation of substrate **S1** are shown.

At the same time, simple phosphinite-thioether ligands **40** and **41** with pyranoside backbones (Figure 21) were successfully applied in Pd-catalyzed allylic substitution of **S1** (ee's up to 96%). Enantioselectivities were best when bulky *tert*-butyl substituents were present in the thioether moiety. Both enantiomers of the products were obtained by using pseudo-enantiomeric ligands **40a** and **41**.[21]



40

a R = ^{t}Bu; **b** R = 2-OMe-C_6H_4;
c R = 4-Me-C_6H_4



41

Figure 21. Phosphinite-thioether pseudo-enantiomers **40** and **41**.

P-N ligands

Several types of P,N-donor carbohydrate ligands have been developed for Pd-asymmetric allylic substitutions. In particular, many phosphorus-oxazoline ligands have produced excellent results.

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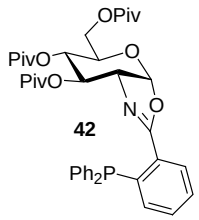
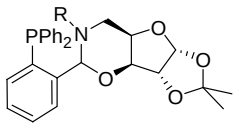
Kunz and co-workers developed a phosphine-oxazoline ligand **42** derived from D-glucosamine for the Pd-catalyzed allylic alkylation of symmetrically and non-symmetrically substituted allyl acetates with high enantioselectivities (ee's up to 98%) (Figure 22).[22] These results are in line with a nucleophilic attack *trans* to the phosphorus atom.



42

Figure 22. Phosphine-oxazoline ligand **42**.

In 2003, phosphine-oxazine ligands **43**, related to ligand **38**, has been developed for the Pd-catalyzed allylic substitution of **S1** (Figure 23). Enantioselectivities up to 75% were obtained.



43

	R	% ee
a	^{i}Pr	46
b	Bn	75
c	$CH_2C_{10}H_7$	49
d	(*R*)-CH(CH_3)Ph	73

Figure 23. Phosphine-oxazine ligand **43**.

Several phosphine-imine ligands with pyranoside backbone **44**-**49** have been developed for the Pd-catalyzed allylic substituion reactions (Figure 24).[23] The results indicated that having the imine-phosphine residue at C-2 (ligands **48**) provided better enantioselectivities than having it at C-1 position of the pyranoside backbone (ligands **44**-**47**). It is to note, that ligands with general structure **48** have provided enantioselectivities up to 99% in the amination of **S1** using morpholine as

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nucleophile.[23c] Recently, the imine group in ligands with general structure **48** has been replaced by an amine group (ligand **49**, Figure 24) providing also good results.[23d]

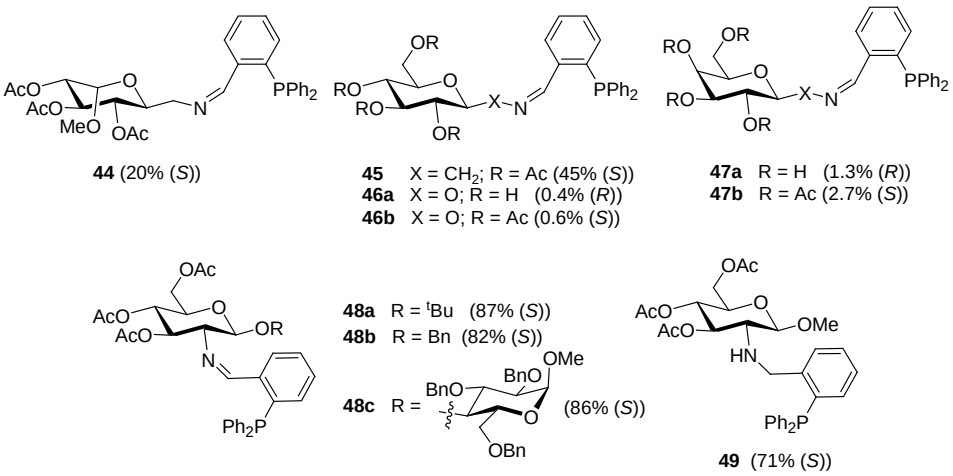

Figure 24. Phosphine-imine **44-48** and phosphine-amine **49** ligands. This figure also shows the enantioselectivities obtained in the Pd-allylic alkylation of **S1**.

Uemura and co-workers developed a series of phosphinite-oxazoline ligands **50** derived from D-glucosamine for the Pd-catalyzed allylic substitution reactions (Figure 25).[24] These ligands showed high enantioselectivity for **S1**, but enantioselectivites were low-to-moderate for unhindered linear and cyclic substrates. The results of the allylic alkylation of diethyl malonate to **S1** indicated that the best enantioselectivity was obtained with the smallest substituent on oxazoline (R = Me, ligand **50a**). Their results also indicate that the nucleophilic attack took place *trans* to the phosphorus atom thought and *endo* π-allyl Pd-intermediate.[24b]

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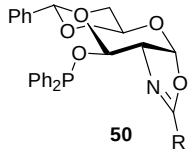
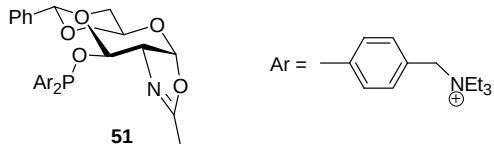


50

	R	%ee
a	Me	96 (*S*)
b	^{i}Pr	90 (*S*)
c	^{i}Bu	95 (*S*)
d	^{t}Bu	83 (*S*)
e	Ph	94 (*S*)
f	Bn	78 (*S*)

Figure 25. Phosphinite-oxazoline ligands **50**. This figure also shows the enantioselectivities obtained in the allylic alkylation of substrate **S1**.

Water-soluble ligand **51** (Figure 26), related to **50a**, were effective for the Pd-catalyzed allylic alkylation of different nucleophiles to **S1** in aqueous or biphasic media (ee's up to 85%).[25]



51

Figure 26. Phosphinite-oxazoline ligands **51**.

Recently, the replacement of the phosphinite group in ligands **50** by a phosphite moiety led to the formation of phosphite-oxazoline ligands **52-55a-d** (Figure 27).[26] The introduction of a biaryl phosphite moiety in the ligand design proved to be highly adventitious. Therefore, the new ligands **52-55** provided higher enantioselectivities and reaction rates than related phosphinite-oxazoline ligands in the allylic substitution (ee's up to 99%, TOF's up to 400 mol substrate x (mol Pd x h)$^{-1}$). Moreover, the presence of a flexible phosphite moiety opened up the possibility of using the Pd-phosphite-oxazoline catalytic systems to a wide range of different substrate types in this catalytic process (Figure 28).

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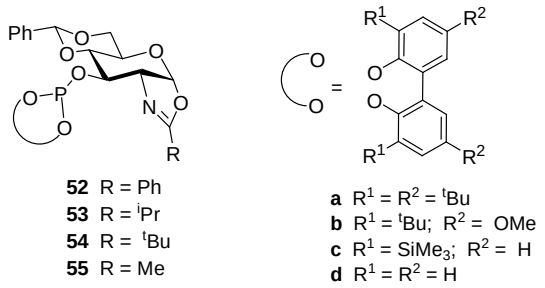

Figure 27. Phosphite-oxazoline ligands **52-55**.

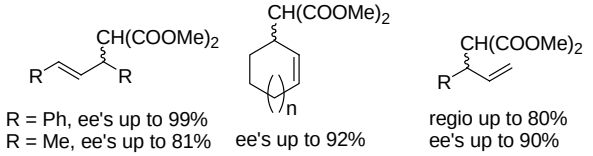

Figure 28. Acyclic and cyclic allylic esters tested with ligands **52-55**.

Pfaltz and co-workers have also applied a new phosphite-oxazoline ligand **56** (Figure 29) in the allylic alkylation of several substrates. Results show that enantioselectivities depend strongly on the kind of substrate used. This ligand showed good enantioselectivities in the reaction of 3-aryl-2-propenyl acetates (ee's up to 94%), whereas enantioselectivities were low in the reaction of substrate **S1** (ee's up to 20%).[27]

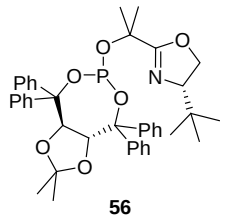

Figure 29. Phosphite-oxazoline ligand **56**.

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P-O ligands

Phosphine-amide ligands **57-62** (Figure 30) with pyranoside backbone have been extensively studied for the Pd-catalyzed allylic alkylation of **S1** with dimethyl malonate.[23c,28] The results clearly showed that enantioselectivity is highly affected by the configuration of the anomeric carbon, the chelate ring size formed upon coordination to Pd and the rigidity of the ligand. Therefore, ligands **57**, **61** and **62** that forms a six-membered chelate ring and with a β anomeric carbon afforded higher enantioselectivitives than ligands **58** (with an α anomeric carbon) and **60** (that form a seven membered chelate ring). Moreover the results between ligands **61** and **62** indicated a cooperative effect between stereocenters that resulted in a matched combination for ligand (*S*)-**61**.

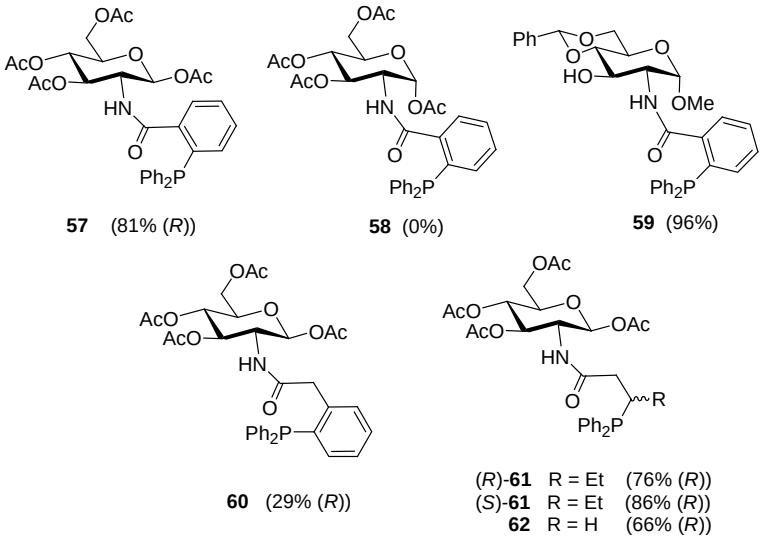

Figure 30. Phosphine-amide ligands **57-62**. This figure also shows the enantioselectivities obtained in the allylic alkylation of substrate **S1**.

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P-P' ligands

Recently, the phosphite-phosphoroamidite ligands **63** with pyranoside backbone (Figure 31) have been developed for the Pd-catalyzed allylic substitution reaction of several substrates. Enantioselectivities up to 89% have been obtained for disubstituted linear and cyclic substrates. [29]

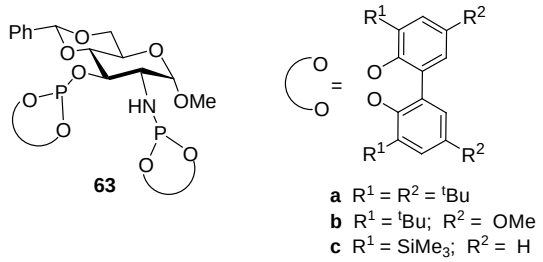

Figure 31. Phosphite-phosphoroamidite ligands **63**.

N-S ligands

Thioglucose-derived ligands **64**, containing a chiral oxazoline moiety (Figure 32), used as ligands in the palladium-catalyzed allylic alkylation of **S1** have provided some of the best results achieved in this reaction with mixed N,S-donor ligands.[30] The effects of the thiosugar substituents on enantioselectivity were mild. The success of this kind of system seems to lie in the combination of thiosugar function and the proximity of all stereogenic units to the palladium allylic fragment, because the Pd-N distance is shorter than the Pd-P distance in related phosphino-thiosugar palladium complexes.

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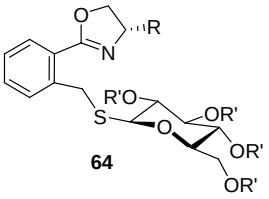
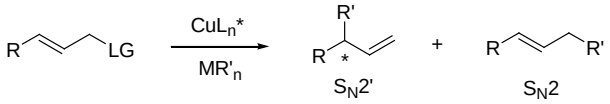


	R	R'	% ee
a	^{i}Pr	C(O)Me	93 (*S*)
b	^{i}Pr	C(O)^{t}Bu	97 (*S*)
c	Ph	C(O)Me	90 (*S*)
d	Ph	C(O)^{t}Bu	96 (*S*)

Figure 32. Thioether-oxazoline ligands **64**. This figure also shows the enantioselectivities obtained in the allylic alkylation of substrate **S1**.

1.3. Asymmetric Cu-catalyzed allylic alkylation

Complementary to the asymmetric Pd-catalyzed allylic substitution reactions, copper allows non-stabilized nucleophiles to be used. Increasing interest is being shown in catalytic systems employing Grignard, organozinc and organoaluminum reagents as the carbon nucleophiles and diboron as non–carbon nucleophile.[31] Most, Cu-catalyzed allylic substitution reactions employ a primary allylic compound as the substrate. A highly selective S_N2' substitution is required to obtain a chiral product (Scheme 2). Therefore, controlling the regioselectivity is also a major issue.



Scheme 2. Typical Cu-catalyzed asymmetric allylic alkylation.

1.3.1. Mechanism

The copper-catalyzed allylic substitution reactions proceed via initial formation of an organocopper(I) species **65**, which is formed by transmetallation between the organometallic compound (RMgX or Et_2Zn)

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and the copper catalyst (Figure 33). Mechanistic studies indicated that monoalkylcopper species (**65**) favor S_N2' attack while dialkylcuprates favor S_N2 attack.[31,32] Coordination of the substrate followed by oxidative addition of organocopper(I) complex **66**, leads to Cu(III) intermediate **67**. The regiochemistry is decided upon the relative kinetics of reductive elimination of the species **67** and/or isomerisation into the π-allyl Cu(III) intermediate **68**, later leading to the σ-allyl complex **69**. If the Cu(III) intermediate is formed from a monoalkylcopper(I) species there will be only one R' group on copper and a fast reductive elimination takes place, forming the desired S_N2' product. Rearrangement to allyl- **68** and finally primary σ-allyl-copper **69** should be slow compared to reductive elimination. With two R' groups on copper (dialkylcuprates), reductive elimination from Cu(III) intermediate **67** is slowed down and rearrangement to the primary σ-allyl-copper species **69** is favored, providing the non-desired achiral S_N2 product.

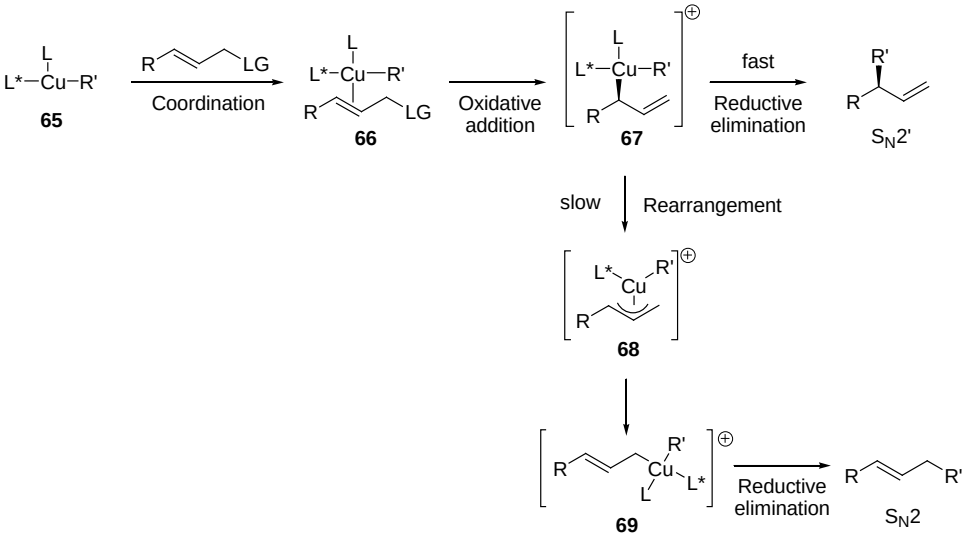

Figure 33. Proposed mechanism for the Cu-catalyzed allylic alkylation reactions.

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Although the Cu(III) intermediates predicted in the mechanism have not been isolated or detected spectroscopically, a study by Bäckvall and co-workers has given indirect evidence of their existence,[33] concomitant with the computational results of Nakamura.[34]

From this mechanism it is clear that experimental conditions are very important for the product outcome. In this context, the rate of addition of the organometallic compound employed, temperature and catalyst loading has been shown of importance for the regiochemical outcome. Therefore, an increased temperature, amount of catalyst and a slow addition of the organometallic reagent will favor the mono-alkylcopper species and hence the relative amount of S_N2' product.

1.3.2. Ligands

The first enantioselective Cu-catalyzed allylic alkylation reaction was reported by Bäckvall, van Koten and co-workers in 1995.[35a] The reaction of alkyl allylic acetates with Grignard reagents in the presence of the chiral copper thiolate **70a** as catalyst (Figure 34) gave moderate enantioselectivity (up to 42%). Later, Bäckvall and co-workers also developed a second **70b**[35b] and third generation **70c-d**[35c] of copper-thiolates, based on a ferrocene-backbone, that provided higher enantioselectivities (ee's up to 64%; Figure 34).

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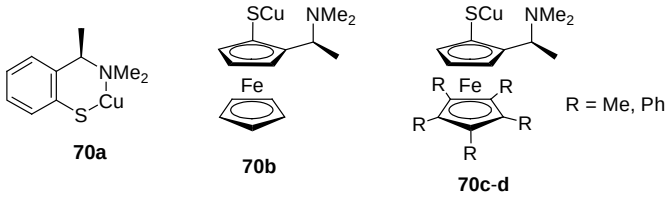
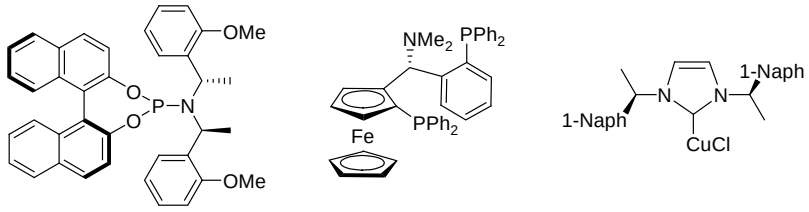


70a **70b** **70c-d**

Figure 34. Copper-thiolate compounds **70a-d**.

Based on these pioneering works, many authors have developed new ligands for the Cu-allylic alkylation using Grignard reagents. The selection of chiral ligands has mainly focused on P-donor[36] and carbene[37] ligands (Figure 35).



71a (ee's up to >91%) **71b** (ee's up to 98%) **71c** (ee's up to 70%)

Figure 35. Representative chiral ligands for Cu-catalyzed allylic alkylation using Grignard reagents.

In 1999 and 2000, Dubner and Knochel disclosed a different system, based on dialkylzinc reagents as primary organometallics, an amine as chiral ligand to copper bromide, and an allylic chloride.[38] The results were better when the allylic chloride is substituted by an aryl group, and when the zinc reagent is a hindered one, such as neopentyl group. In general, the Grignard and the diorganozinc catalytic systems are complementary. The dialkylzinc systems needs a polar solvent, whereas the Grignard system works better in the least polar solvent. With Grignard reagents, allylic acetates afford higher stereoselectivity than halides; the

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reverse is true with dialkylzinc reagents. An alkyl substituent works better than an aryl one on the allylic substrate with Grignard reagents.

A review of the most successful ligands used in the asymmetric allylic substitution with diorganozinc reagents as nucleophiles revealed five main trends: amines,[38,39] phosphorous,[40] sulfonamides,[41] peptide with imine core[42] and carbene[43] ligands (Figure 36).

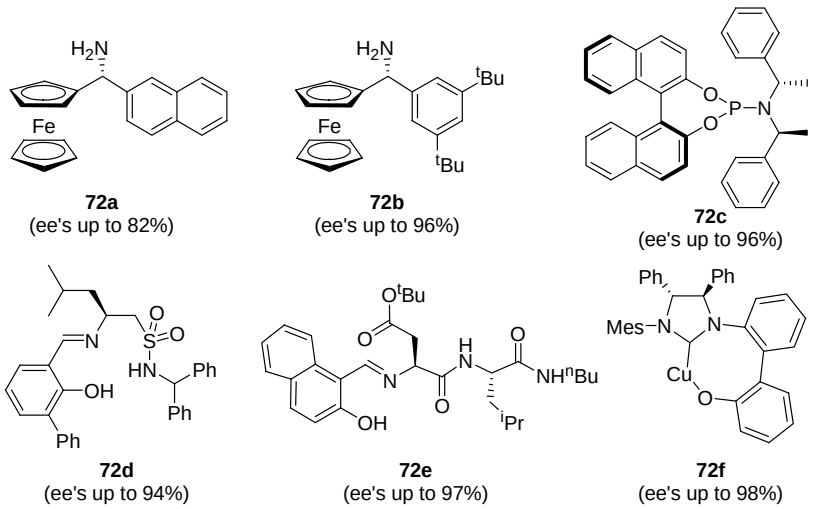

Figure 36. Representative chiral ligands for Cu-catalyzed allylic alkylation using diorganozinc reagents.

Recently, triorganoaluminum reagents have also been successfully applied using aminophosphine **73a**[44] (Figure 37), the previously mentioned phosphoroamidite **72c**[45] (Figure 36) and diaminocarbene **73b**[46] ligands (Figure 37). More recently, the use of boryl nucleophiles has also been described, allowing the preparation of chiral allylboronates in high enantioselectivitites using diphosphine **73c** (Figure 37).[47]

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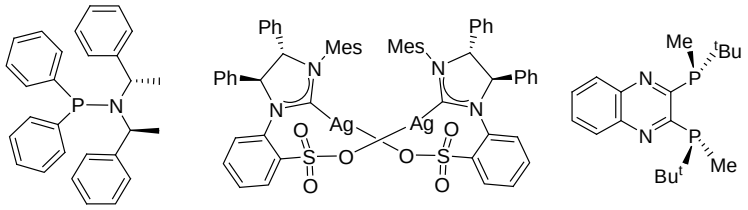
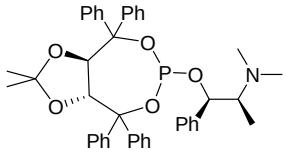


73a (ee's up to 94%) **73b** (ee's up to 98%) **73c** (ee's up to 96%)

Figure 37. Representative chiral ligands for Cu-catalyzed allylic alkylation using triorganoaluminum reagents and boryl nucleophiles.

To the best of our knowledgement only one report on the use of carbohydrate ligands has been applied to this process. This describes the application of a TADDOL-based phosphite ligand **74** (Figure 38) with ee's up to 83% on cinnamyl-type susbstrates. [48]



74

Figure 38. TADDOL-derived phosphite ligand **74**.

1.4. Asymmetric Cu-catalyzed 1,4-conjugate addition

The enantioselective conjugate addition (also called enantioselective Michael addition) of organometallic reagents to α,β-unsaturated compounds catalyzed by copper complexes is a useful synthetic process for asymmetric carbon-carbon bond formation (Scheme 3).[31d,49] This process is important in the synthesis of many biologically active compounds such as steroids and terpens.

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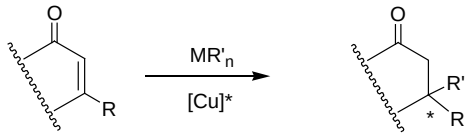

Scheme 3. Typical asymmetric Cu-catalyzed 1,4-addition of organometallic reagents to α,β-unsaturated compounds.

The past decade have seen dramatic breakthroughs in the area of catalytic asymmetric 1,4-addition of alkyl organometallic nucleophiles to enones.[31d,49] Most of the successful asymmetric versions of this chemistry have made use of oganozinc reagents, especially $ZnEt_2$, a trend started by Alexakis (Cu catalysis)[50] and Soai (Ni catalysis)[51]. The inherently low reactivity of organozinc reagents toward unsaturated carbonyl compounds has facilitated the development of a plethora of chiral phosphorus-based ligands (i.e. phosphoroamidites, phosphites, phosphonites, phosphines) capable of providing highly efficient ligand-accelerated catalysis with excellent enantioselectivities over a broad range of substrates. Therefore, viable ligand classes affording >95% enantiomeric excess for the addition of ZnR_2 to disubstituted cyclic and acyclic enones, lactones or lactams, nitro-olefins, amides and malonates are now available.[31d]

Trialkylaluminum reagents have recently appeared as an interesting alternative to organozinc reagents since they are also readily available and also offer additional hydro- and carboalumination possibilities for their preparation. Additionally, due to their higher reactivity, they allow Cu-catalyzed 1,4-addition to very challenging substrates (i.e. β-trisubstituted enones), which are inert to organozinc methodologies. Nowadays, very successful examples with cyclic and acyclic enones and nitro-olefins have been described.[31d]

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Although Grignard reagents were the first species to be used, their higher reactivity leads to uncatalyzed 1,2- and 1,4-additions, which limited their early application. Grignard reagents are cheaper, more readily available and easier to handle than diorganozinc. Considerable effort has therefore been undertaken in order to replace zinc reagents by Grignards in this process. It has turned out that ligand structures privileged for diethyl zinc additions are not effective for magnesium compounds. There have been recent breakthroughs that opened up the use of Grignard reagents for the highly active and enantioselective Cu-catalyzed conjugate addition of a wide range of substrates. Therefore, in addition to cyclic and acyclic enones, the less reactive α,β-unsaturated esters and thioesters can be performed with good enantioselectivities.[31d]

In the copper-catalyzed asymmetric 1,4-addition, the copper salt is also important for high catalytic activity and enantioselectivity. Copper (I) and copper (II) salts have been used. The true catalytic species is Cu(I), so the reduction of Cu(II) is the first step in the process. The copper (II) triflate is usually the salt of choice, though many other copper salts have demonstrated their power in this reaction. Recently, the use of copper (I) thiophene-2-carboxylate (CuTC) has emerged as a privileged copper precursor.[31d,49]

Cyclic and acyclic enones have been used as substrates in enantioselective copper-catalyzed conjugate addition (Figure 39). Traditionally, 2-cyclohexenone has been the substrate of choice for testing a new ligand. This cyclic enone avoids the *s-cis*/*s-trans* interconversion of acyclic substrates (Scheme 4).[31d,49] For acyclic enones, the most widely studied substrate is benzylideneacetone (Figure 39). To achieve a high catalytic performance with this acyclic substrate, the class

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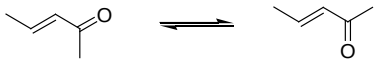
of ligands usually has to be different from those with cyclic substrates. Nitro-olefins, lactones, lactames, piperidines, alkylidenemalonates and α,β-unsaturated imides, esters and thioesthers are other classes of excellent Michael acceptors for this reaction.[31d,49] Again, the efficient ligands are different from the previous ones (Figure 39).

2-cyclohexenone 3-methyl-cyclohexenone benzylideneacetone nitrostyrene

Figure 39. The most common substrates in the copper-catalyzed asymmetric 1,4-addition.



s-trans *s-cis*

Scheme 4. *S-cis* and *s-trans* conformational interconversion.

1.4.1. Mechanism

The conjugate addition of organometallic reagents fits in the generally accepted mechanism of cuprate reactions.[31d,49] The difference lies in the nature of the reactive species, which involve a bimetallic cluster, where copper and the other metal (Li, Mg, Zn or Al) are intimately associated. To make things even more complex, it is well known that several species (with different stoichiometries) are in equilibrium and that the degree of enantioselectivity they provide may also be different. Nevertheless, a general scheme could be drawn, although no intermediate has been characterized (Figure 40).[31d,49]

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The usual Cu(II) salt is first reduced to Cu(I) by the organometallic reagent. This Cu(I) salt reacts with the primary organometallic reagent to form an organocopper reagent **75**. The latter reagent strongly coordinates to the oxygen atom of the enone (**76**) by the most oxophilic metal (Zn or Al). However, since stoichiometric reagents of this type have been shown to be unable to react further, complex **76** must be transformed to a higher order cuprate reagent **77**. The next step towards the conjugate addition is the formation of a π complex **78**. This is also the step which determines the absolute configuration of the adduct. At this stage, only one equivalent of the ligand remains, although the ratio of Cu to ligand is generally 1:2. Following this π complexation, the oxidative addition occurs to give Cu(III) intermediate **79**. Such a copper(III) intermediate was recently characterized by rapid injection NMR (RI-NMR) at -100 ºC in the analogous conjugate addition of Me_2CuLi to 2-cyclohexenone triggered by Me_3SiCN.[52,53] The reductive elimination step provides the zinc (or Al) enolate **80**, where the oxophilic metal is bound to the oxygen atom. The Cu species is then released to enter in a new catalytic cycle.

Detailed studies have been done by Schrader on many aspects of the conjugate addition of diethylzinc to cyclohexenone.[54] It is clear that the reductive elimination is the rate determining step. The nature of the substituents on the phosphorus ligand play a key role at this step, the higher the number of P-O bonds (versus P-N), the highest is the rate of addition.[55]

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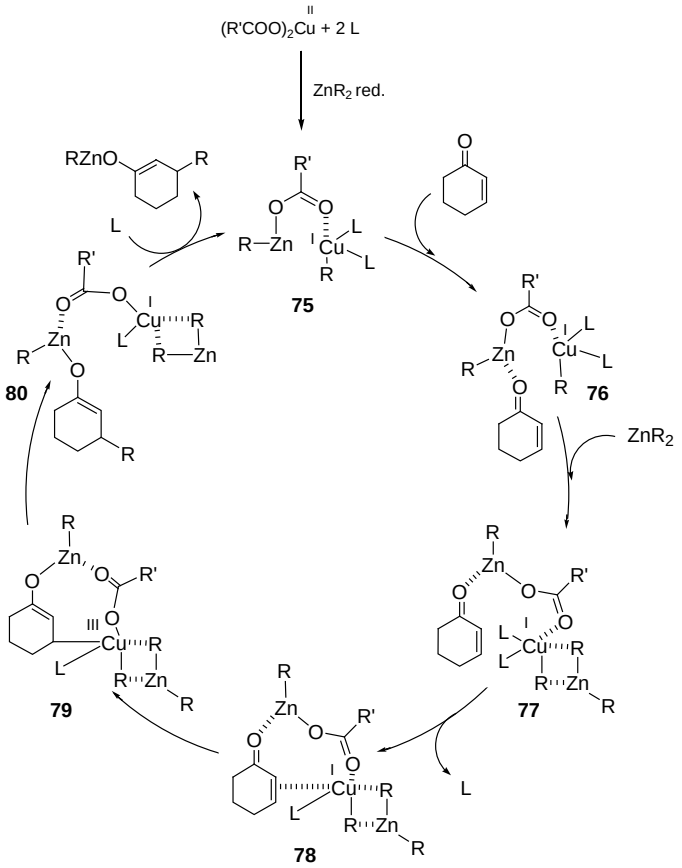

Figure 40. Proposed catalytic cycle for the Cu-catalyzed conjugate 1,4-addition using ZnR_2.

1.4.2. Ligands

The first enantioselective copper catalysts were reported by Lippard and co-workers in 1988.[56] The reaction of 2-cyclohexenone with Grignard reagents in the presence of the chiral aminotroponeimine copper complex **81a** as catalyst (Figure 41) gave the 1,4-adducts with low enantioselectivity (up to 14%). Selectivity increased to 74% ee with the addition of hexamethylphosphoric triamide (HMPA) and silyl halides.[57]

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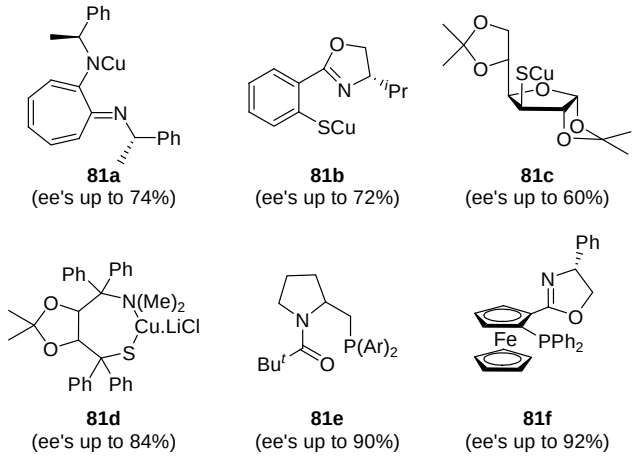
Subsequently, a variety of catalytic systems, mainly on the basis of Cu-thiolates[58] **70a** (Figure 34) and **81b-d** and phosphine-oxazoline ligand **81f**[59] were introduced for the conjugate addition of Grignard reagents (Figure 41). Although the scope remained limited and ee's infrequently reached the 90% level (Figure 41), high enantioselectivity (ee's up to 92%) was obtained in two examples.[58b,59]



81a (ee's up to 74%) **81b** (ee's up to 72%) **81c** (ee's up to 60%)

81d (ee's up to 84%) **81e** (ee's up to 90%) **81f** (ee's up to 92%)

Figure 41. Heterocuprate-based ligand and chiral ligands using Grignard reagents.

A breakthrough came in 2004 when Feringa and co-workers were able to identify the ligands Taniaphos **82a** and Josiphos **82b** (Figure 42) as chiral diphosphines suitable for a wide range of substrate types (ee's up to 98%).[60] Recently, Alexakis and co-workers described the successful application of a diaminocarbene **82c** (Figure 42) in the 1,4-addition to several β-trisubstituted enones (ee's up to 96%).[61]

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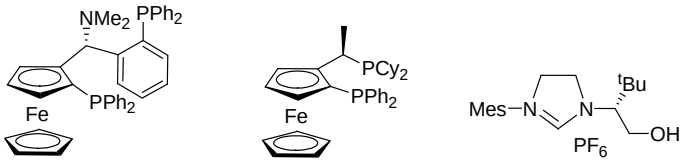
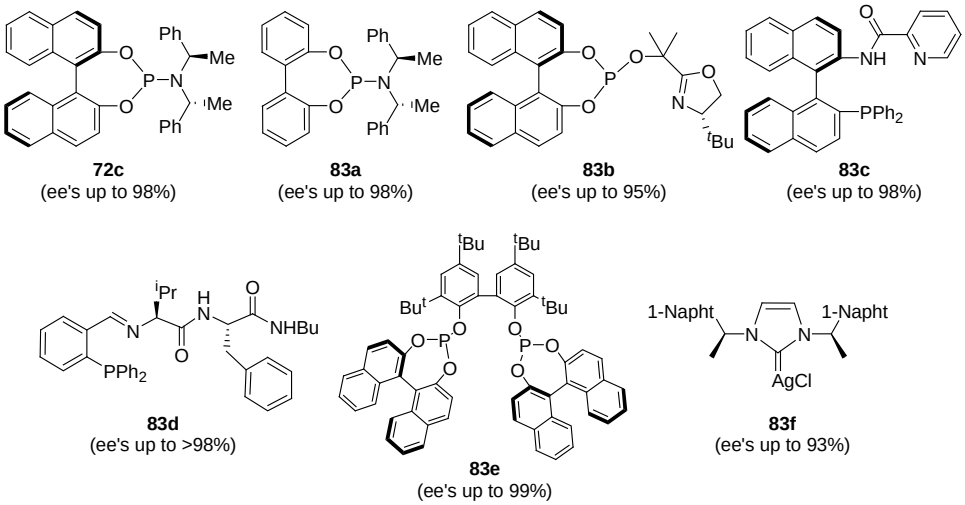


82a **82b** **82c**

Figure 42. Most successful ligands for the 1,4-addition using Grignard reagents.

Since the late 1990s many authors have focused on the dialkylzinc procedure and more recently in the use of trialkylaluminum reagents. The selection of chiral ligands for the highly enantioselective conjugate addition has mainly focused on P-donor and mixed P,N-donor ligands (Figure 43).[62] Most phosphorus ligands are of the phosphite (mainly monophosphite) and phosphoramidite type. Non-phosphorus ligands have scarcely been used, but recently the use of carbenes has emerged as suitable ligands for this process.[63] Some of the most representative ligands are shown in Figure 43.



72c (ee's up to 98%) **83a** (ee's up to 98%) **83b** (ee's up to 95%) **83c** (ee's up to 98%)

83d (ee's up to >98%) **83e** (ee's up to 99%) **83f** (ee's up to 93%)

Figure 43. Representative chiral ligands for 1,4-addition of diorganozinc and trialkylaluminum reagents to α,β-unsaturated compounds.

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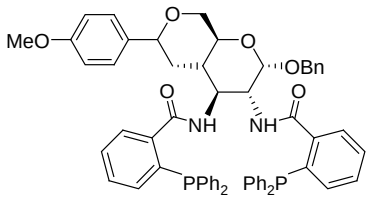
Although carbohydrate ligands have been successfully used in other enantioselective reactions,[2] there have been few reports on the highly enantioselective 1,4-addition using these systems. Notable examples, however, include diphosphine,[64] monophosphonite,[65] mono- and diphosphite,[66] and mixed amino-thiolate[58d,67] ligands. Other carbohydrate ligands, such as phosphoroamidite[65,66a,68] and mixed S-O,[69] N-P,[70] S-P[71] and P-P' heterodonor ligands, have also been tested with less success.

Here we present the most relevant catalytic data on the copper-catalyzed 1,4-addition of organometallic reagents to α,β-unsaturated compounds with carbohydrate ligands.

1.4.2.1. P-donor ligands

Phosphine ligands

Although several phosphine ligands have been applied,[31d] only the recently developed diphosphine **84** (Figure 44) has provide high enanioselectivities (ee's up to 95%) in Cu-catalyzed 1,4-additions of ZnR_2 to linear aliphatic enones.



84

Figure 44. Diphosphine ligand **84**.

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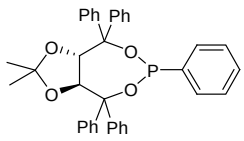
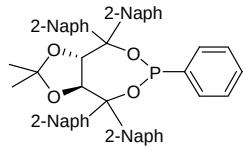
Phosphonite ligands

Alexakis used phosphonite ligands **85** (Figure 45), derived from (+)-TADDOL, in the asymmetric conjugate addition of diethylzinc to nitro-olefins[65a] and alkylidene malonates[65b] with good-to-moderate enantioselectivities. Ligand **85a** appears to be the optimal choice for the diethylzinc addition to aryl nitro-olefins (ee's up to 86%).



85a



85b

Figure 45. Phosphonite ligands **85** derived from (+)-TADDOL.

Phosphite ligands

Phosphite furanoside ligands **23-29** (Figure 12) were also applied in the Cu-catalyzed 1,4-addition of diethylzinc to cyclohexenone.[66b,c] Results show that enantioselectivity depends strongly on the absolute configuration of the C-3 stereogenic center and on the biaryl substituents, while the sense of enantiodiscrimination is predominantly controlled by the configuration of the biaryl groups of the phosphite moieties. The best enantioselectivites were obtained with ligands **23h** and **25g** with ee's up to 81% (*R*) and 84% (*S*), respectively. Interestingly, both enantiomers of the product can be obtained. Introducing a stereogenic center in C-5 had a positive effect on activity but did not affect enantioselectivity.

Alexakis and co-workers have developed a series of phosphite ligands **86**, derived from (-)-TADDOL and (+)-TADDOL (Figure 46). These ligands were applied in the Cu-catalyzed 1,4-addition of diethylzinc to 2-cyclohexenone (ee's up to 96%),[66e] benzalacetone (ee's up

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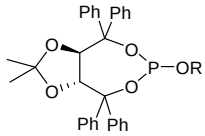
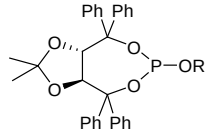
to 35%),[66a,e] chalcone (ee's up to 50%),[66a,e] nitro-olefins (ee's up to 96%)[65a] and alkylidene malonates (ee's up to 73%)[65b] (Figure 46).



86a

R = alkyl, cyclohexanyl, substituted cyclohexanyl, aryl

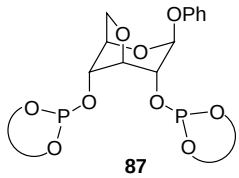


86b

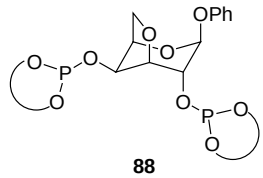
R = substituted cyclohexanyl

Figure 46. Basic structure of phosphite ligands **86**.

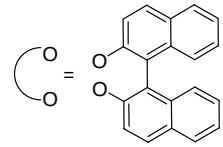
Recently, Chan and co-workers reported the synthesis of chiral pyranoside diphosphites **87** and **88**, derived from D-glucose and D-galactose, for the application in the Cu-catalyzed 1,4-addition of cyclic enones (Figure 47).[66d] The enantioselectivity depends on the absolute configuration of the C-4 stereogenic center of the ligand backbone, while the sense of enantioselectivity is mainly controlled by the configuration of the binaphthyl moieties. Therefore, the results were best with ligand **87b** (ee's up to 88%).



87



88



a $(S)^{ax}$
b $(R)^{ax}$

Figure 47. Pyranoside diphosphite ligands **87** and **88**.

Phosphoroamidite ligands

In the last few years several mono- and diphosphoroamidite ligands, derived from TADDOL, have been developed for the Cu-catalyzed 1,4-addition of diethylzinc to several substrates with poor-to-

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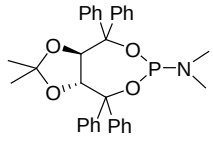
moderate enantioselectivity.[65,66a,68] However, Feringa and co-workers observed an unexpected improvement in enantioselectivity in the Cu-**89** (Figure 48) catalyzed addition of diethylzinc to cyclohexenone when they used powdered molecular sieves (ee's up to 71%).[68b]



89

Figure 48. Phosphoroamidite ligand **89** derived from TADDOL.

1.4.2.2. Heterodonor ligands

A series of heterodonor O-S, N-S and N-P ligands derived from TADDOL and D-glucosamine have been developed for the Cu-catalyzed 1,4-addition of organometallic reagents to cyclic and lineal enones.[58d,66a,e,67,72] The best enantioselectivities were obtained with the previously mentioned N-S ligand **81d**[58d,67] (Figure 41) and phosphite-oxazoline ligand **52c** (Figure 27) (ee's up to 84%).

1.5. Asymmetric Ni-catalyzed 1,2-addition

Nucleophilic 1,2-addition of organometallic reagents to carbonyl compounds constitutes one of the most fundamental operations in organic synthesis for the formation of chiral secondary alcohols.[73] In this context, catalytic addition of dialkylzincs to aldehydes has attracted much attention since many chiral alcohols are highly valuable intermediates for preparing chiral pharmaceutical and agricultural products. For alkylation reagents, trialkylaluminum compounds are more interesting than other

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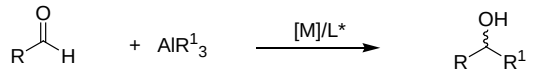
organometallic reagents because they are economically available in industrial scale from aluminum hydride and olefins.[74] Despite this advantage, trialkylaluminum are less documented.[75,76] In this respect, the few successful catalysts developed for the enantioselective addition of trialkylaluminum to aldehydes (Scheme 5) can be grouped in two types. The first group are the titanium complexes that usually afford high enantioselectivities, but the high catalyst loadings (10-20 mol%) and the slow turnover rate hamper their potential utility.[75a-d] The second ones are the recently studied nickel complexes that provide enantioselectivities similar to those using titanium complexes but with low catalyst loadings (1 mol%).[75e,f,76a]



Scheme 5. Metal-catalyzed 1,2-addition of trialkylaluminum to aldehydes.

Several aldehydes, such as aryl-, alkyl- and vinylaldehydes, have been tested as substrates. However, benzaldehyde has been the substrate of choice for testing a new ligand. The aluminum source is also an important parameter for high catalytic activity and enantioselectivity. Traditionally, commercially available trialkylaluminum reagents have been widely used. However, these reagents are often contamined with oxo-containing by-products formed through accidental exposure to traces of air and moisture, such impurities modify the reactivity of the reagent.[77] Recently, the group of Woodward reported the preparation of DABAL-Me_3 (Figure 49) as a new air-stable solid $AlMe_3$ adduct that is easily formed from the exposure of neat $AlMe_3$ to DABCO (1,4-diazobicyclo[2,2,2]octane).[75e]

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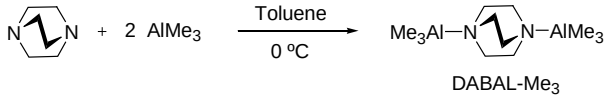

Figure 49. Formation of DABAL-Me_3**.**

1.5.1. Mechanism

The tentative mechanism proposed for the Ni-catalyzed 1,2-addition of trimethylaluminum reagents to aryl aldehydes is shown in Figure 50.[75f] The reductive generation of the active Ni(0)-catalyst **90** is followed by the formation of a π-aldehyde complex **91**, as showed possible by the seminal work of Walther who crystallized Ni(η^2-O=CHAr)(PCy_3)$_2$ (Ar = Ph, 2,4-$(MeO)_2C_6H_3$).[78] Then aluminum Lewis acid promoted the oxidative addition of the ketone complex **91** and produces Ni(II)-complex **92**. Finally, by reductive elimination, they generated the final product **93** and regenerate the catalytically active species **90**.

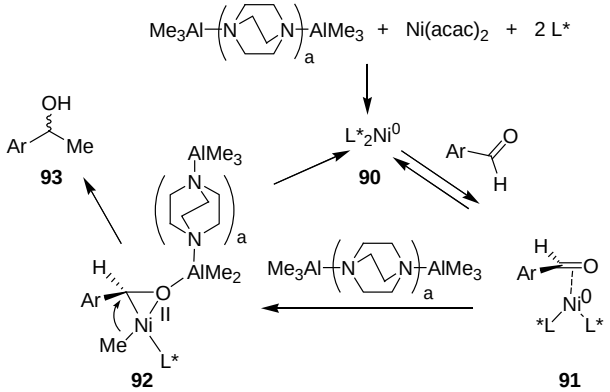

Figure 50. Proposed catalytic cycle for the Ni-catalyzed 1,2-addition of DABAL-Me_3 (a = 1) or $AlMe_3$ (a = 0) to aromatic aldehydes**.**

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1.5.2. Ligands

Woodward and co-workers reported the first asymmetric Ni-catalyzed 1,2-addition of trialkylaluminum reagents to aldehydes using phosphoroamidite and monophosphine ligands. High enantioselectivities (ee's up to 95%) were obtained using monophosphoroamidite ligand **72c** (Figure 36).[75e]

Next, we present the only two reports on the use of carbohydrate ligands in this reaction that have appeared after the pioneering work of Woodward and co-workers.

1.5.2.1. P-donor ligands

Phosphite ligands

A large family of carbohydrate-based monophosphite ligands **94-97** (Figure 51) derived from D-glucose, D-galactose and D-fructose has been successfully applied in the asymmetric Ni-catalyzed 1,2-addition of several aryl aldehydes (ee's up to 94%).[76a]

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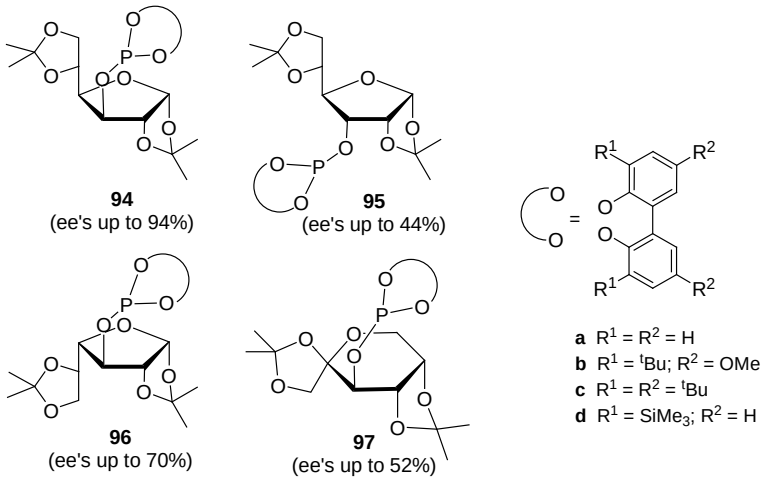

Figure 51. Phosphite ligands **94-97**. The maximum enantioselectivities achieved are also shown.

1.5.2.2. Heterodonor ligands

P-P' and P-N ligands

The previously mentioned carbohydrate-based phosphite-oxazoline **52-55** (Figure 27) and phosphite-phosphoroamidite ligands **63** (Figure 31) derived from D-glucosamine were also applied in the asymmetric Ni-catalyzed 1,2-addition of trialkylaluminum reagents to aldehydes giving poor-to-moderate enantioselectivities (ee's up to 59%).[76b]

1.6. References

[1] See for instance: a) Catalytic Asymmetric Synthesis; Ojima, I. (Ed); 2nd edition, Wiley-VCH, Weinheim, 2000. b) Applied Homogeneous Catalysis with Organometallic Compounds; Cornils, B.; Herrmann, W. A.

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Chapter 2

Objectives

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2. Objectives

The objective of this thesis is to develop new chiral ligands derived from carbohydrates for application as chiral auxiliaries in several important asymmetric catalytic reactions.

The more specific aims are:

1. To design and synthesize highly modular phosphite-phosphoroamidite (**L1**-**L4**), diphosphoroamidite (**L5**), monophosphoroamidite (**L6**-**L10**) and monophosphite (**L11**-**L14**) ligand libraries (Figure 1).

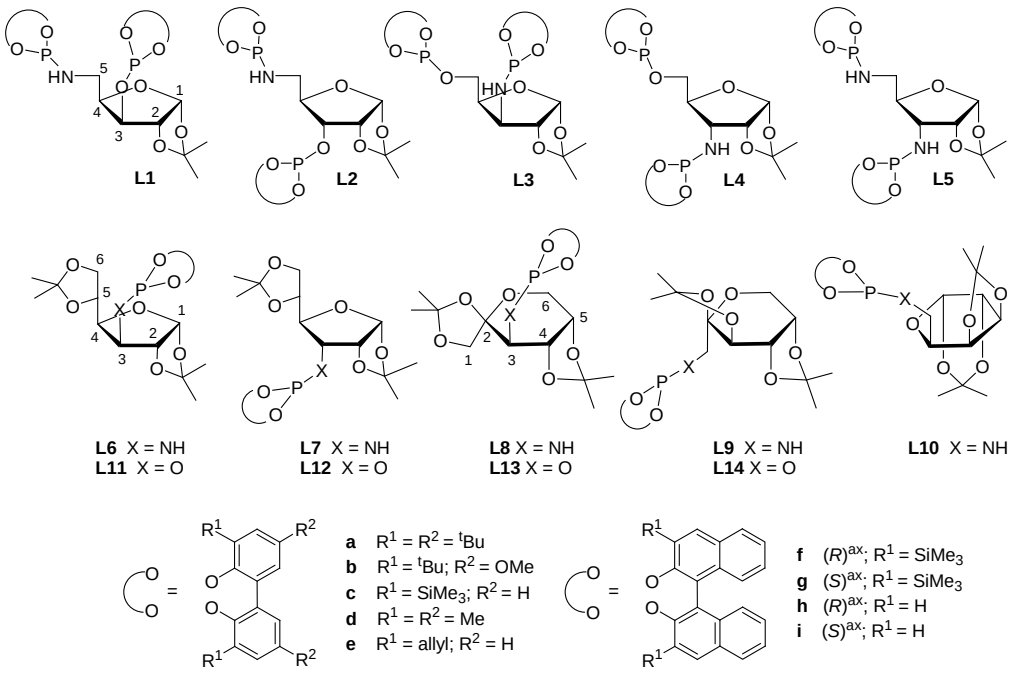

Figure 1. Phosphite-phosphoroamidite (**L1**-**L4**), diphosphoroamidite (**L5**), monophosphoroamidite (**L6**-**L10**) and monophosphite (**L11**-**L14**) ligand libraries synthesized in this thesis.

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These libraries are systematically designed to ensure a maximum diversity regarding electronic and steric properties of the ligand parameters that will ensure a wide scope in the asymmetric processes studied in this thesis. Therefore, the phosphite-phosphoroamidite ligand library is derived from inexpensive D-xylose and D-glucose. With this ligand library we investigated the effect of systematically varying the position of the phosphoroamidite group at either C-5 (ligands **L1** and **L2**) or C-3 (ligands **L3** and **L4**) of the furanoside backbone, the configuration at C-3 of the furanoside backbone and the substituents and configurations in the biaryl phosphite/phosphoroamidite moieties (**a**-**i**). The second ligand library (**L5**) is related to ligands **L2** and **L4** but we have replaced the phosphite moiety by a phosphoroamidite group. This apparently simple modification produces important changes in the structural and electronic properties of the ligands, which are know to play a crucial role on the catalytic performance. Finally, the monophosphoroamidite (**L6**-**L10**) and monophosphite (**L11**-**L14**) ligand libraries are derived from D-glucose, D-galactose and D-fructose, which lead to a wide range of carbohydrate backbones, and contain several substituents/configurations in the biaryl moiety (**a**-**i**).

2. To apply these ligand libraries in the asymmetric Pd-catalyzed allylic substitution (**L1**-**L4** and **L5**), asymmetric Cu-catalyzed allylic alkylation (**L1**-**L4**, **L5**, **L6**-**L10** and **L11**-**L14**), asymmetric Cu-catalyzed 1,4-conjugated addition of organometallic reagents to enones (**L1**-**L4**, **L5**, **L6**-**L10** and **L11**-**L14**) and asymmetric Ni-catalyzed addition of trialkylaluminum to aldehydes (**L1**-**L4**, **L5** and **L6**-**L10**).

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Chapter 3

Asymmetric Pd-catalyzed allylic substitution

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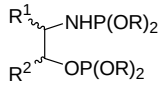
3. Asymmetric Pd-catalyzed allylic substitution

3.1. Background

As we discussed in the introduction, most of the chiral ligands developed for asymmetric allylic substitution are mixed bidentated donor ligands (such as P-N, P-S and S-N). The efficiency of this type of hard-soft heterodonor ligands has been mainly attributed to the different electronic effects of the donor atoms. Mixed phosphorus-nitrogen ligands have played a dominant role among the heterodonor ligands. Recently, a group of less electron-rich phosphorus compounds–phosphite-phosphoroamidite ligands–have also demonstrated their potential utility in this process. In this context, our group have successfully reported the use of a phosphite-phosphoroamidite ligands **1** possessing a 1,2-aminoalcohol backbone that overcomes the most common limitations of this process, such as low reaction rates and high substrate specificity (Figure 1).[1] Despite this success, reports on their use are rare.[1,2] This encourages further research into phosphite-phosphoroamidite ligands.



1

Figure 1. Phosphite-phosphoroamidite ligands **1**.

Less attention has been paid to catalysts containing homodonor ligands in asymmetric allylic substitution. However, homodonor ligands, such as P-P, N-N and S-S have also demonstrated their potential utility in this process, mainly based on the chiral discrimination induced by the C_2

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or C_1 backbone symmetry of the ligand. Most P-P ligands are diphosphines and diphosphites.[3] To our knowledge, diphosphoroamidite ligands have never been applied in this process, although they have shown to be excellent ligands for other type of metal-catalyzed asymmetric transformations.

In this chapter, we therefore report the synthesis of two carbohydrate-based ligand libraries: an heterodonor phosphite-phosphoroamidite (**L1**-**L4**) and an homodonor diphosphoroamidite (**L5**). We also report their use as catalysts precursors in asymmetric allylic substitution reactions. More specifically, in section 3.2 we report the synthesis and application of a furanoside phosphite-phosphoroamidite ligand library (**L1**-**L4**) in the Pd-catalyzed allylic substitution of several substrate types. This ligand library has four main advantages: (1) they can be prepared in a few steps from readily available D-xylose and D-glucose; (2) the π-acceptor character of the phosphite/phosphoroamidite moieties increases reaction rates; (3) the flexibility and larger bite angle created by the biaryl moieties increases versatility and (4) their modular nature enables the position of the phosphoroamidite group, configuration of C-3 of the furanoside backbone and the substituents/configurations in the biaryl phosphite/phosphoroamidite moieties to be easily and systematically varied. Thus, by carefully selecting the ligand components, high enantioselectivities (ee's up to 98%) and activities have been achieved in a wide range of substrates with different steric and electronic properties. The study of the Pd-1,3-diphenyl, 1,3-dimethyl and 1,3-cyclohexenyl allyl intermediates by NMR spectroscopy makes it possible to understand the catalytic behaviour observed. This study also indicates that the nucleophilic attack takes place predominantly at the allylic

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terminal carbon atom located *trans* to the phosphoroamidite moiety. On the basis of the previous ligand library, in next section 3.3, we designed a new furanoside ligand family (diphosphoroamite; **L5**) in which the phosphite moiety is replaced by a phosphoroamidite group, leading to an homodonor ligand library. These ligands were applied to the Pd-catalyzed allylic alkylation of several substrates types. Systematic variation of the ligand parameters indicates that catalytic performance is highly affected by the substituents and the axial chirality of the biaryl moieties of the ligand. Good-to-excellent activities and enantioselectivities (ee's up to 95%) have been obtained for several substrate types. The study of the 1,3-diphenyl and 1,3-cyclohexenyl Pd-π-allyl intermediates by NMR spectroscopy allows the understanding of the catalytic behaviour observed. This study indicates that the nucleophilic attack takes place predominantly at the allylic terminal carbon atom located *trans* to the phosphoroamidite moiety attached to C-5. Unfortunately, the preliminary studies using the monophosphoroamite (**L6**-**L10**) ligand library (Chapter 2, Figure 1) in several reaction conditions showed low activities and selectivities (ee's up to 10%) as has been previously observed using related monophosphites **L11**-**L14**.[4]

3.1.1. References

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3.2. Modular furanoside phosphite-phosphoroamidite, a readily available ligand library for asymmetric Pd-catalyzed allylic substitution reactions. Origin of enantioselectivity

Eva Raluy, Carmen Claver, Oscar Pàmies and Montserrat Diéguez in *Org. Lett.* **2007**, *9*, 49 and *Adv. Synth. Catal.* **2009**, *351*, 1648.

Abstract. A library of furanoside phosphite-phosphoroamidite ligands **L1-L4a-g** has been synthesized and screened in the Pd-catalyzed allylic substitution reactions of several substrate types. These series of ligands can be prepared from easily accessible D-xylose and D-glucose. Their modular nature enables the position of the phosphoroamidite group, configuration of C-3 of the furanoside backbone and the substituents/configurations in the biaryl phosphite/phosphoroamidite moieties to be easily and systematically varied. By carefully selecting the ligand components, therefore, high regio- and enantioselectivities (ee's up to 98%) and good activities have been achieved in a broad range of mono- and disubstituted hindered and unhindered linear and cyclic substrates. The NMR studies on the Pd-π-allyl intermediates provide a deeper understanding about the effect of the ligand parameters on the origin of enantioselectivity.

3.2.1. Introduction

The Pd-catalyzed asymmetric allylic substitution is an important tool in organic synthesis, allowing the formation of enantioselective carbon-carbon and carbon-heteroatom bonds.[1] Many chiral ligands

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(mainly P- and N- ligands), which possess either C_2- or C_1- symmetry, have provided high enantiomeric excesses for several types of disubstituted substrates.[1] Although, in general, there is still a problem of substrate specificity (for example, ee's are high in disubstituted linear hindered substrates and low in unhindered substrates, and vice versa) and reaction rates. On the other hand, monosubstituted substrates still require more active and more regio- and enantioselective Pd-catalysts.[1] Most chiral ligands developed for Pd-catalyzed asymmetric allylic substitution are mixed bidentate donor ligands (such as P-N, P-S, S-N and P-P').[1,2,3] The efficiency of this type of heterodonor ligands has mainly been attributed to the electronic effects of the donor atoms. Recently, a group of less electron-rich heterodonor compounds–phosphite-phosphoroamidite ligands–have also demonstrated their potential utility in this process, providing excellent enantioselectivities and activities.[3a,b] The presence of biaryl phosphite/phosphoroamidite moieties into the ligand design was beneficial because: (1) reaction rates increased thanks to the larger π-acceptor ability of these moieties,[3,4] and (2) substrate specificity decreased because the chiral pocket created (the chiral cavity in which the allyl is embedded) is flexible enough to enable perfect coordination of hindered and unhindered substrates.[5] Despite these advantages, only one series of phosphite-phosphoroamidite ligands possessing a 1,2-aminoalcohol backbone has been extensively studied.[3b] However, these ligands proved to be effective in the allylic substitution of disubstituted substrates but for monosubstituted substrates their regio- and enantioselectivities were moderate.[3b] On the other hand, the mechanistic aspects with these ligands are still not understood well enough for a priory prediction of the type of ligand needed for high selectivity. More

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research into the scope of the phosphite-phosphoroamidite ligands in this process is therefore needed. For this purpose, carbohydrates are particularly advantageous thanks to their low price and easy modular constructions.[6] In this chapter we report the synthesis and application of a new chiral phosphite-phosphoroamidite ligand library (Figure 1, **L1-L4a-g**) for the Pd-catalyzed allylic substitution reactions of several substrate types. We also discuss the synthesis and characterization of the Pd-π-allyl intermediates in order to provide greater insight into the origin of enantioselectivity with these catalytic systems. The library was synthesized and screened using a series of parallel reactors each equipped with 12 different positions. As well as biaryl phosphite/phosphoroamidite moieties being present in the ligand design, this ligand library also has the advantage of a flexible ligand scaffold that enables the ligands to be easily tuned in different ligand parameters and how the ligands affect catalytic performance to be explored. With this library (Figure 1), we therefore investigated the effect of systematically varying the position of the phosphoroamidite group at either C-5 (ligands **L1** and **L2**) or C-3 (ligands **L3** and **L4**) of the furanoside backbone, the configuration at C-3 of the furanoside backbone and the substituents and configurations in the biaryl phosphite/phosphoroamidite moieties (**a**-**g**). By carefully selecting the ligand parameters, we achieved high selectivities (regio- and enantioselectivities) and activities in different substrate types.

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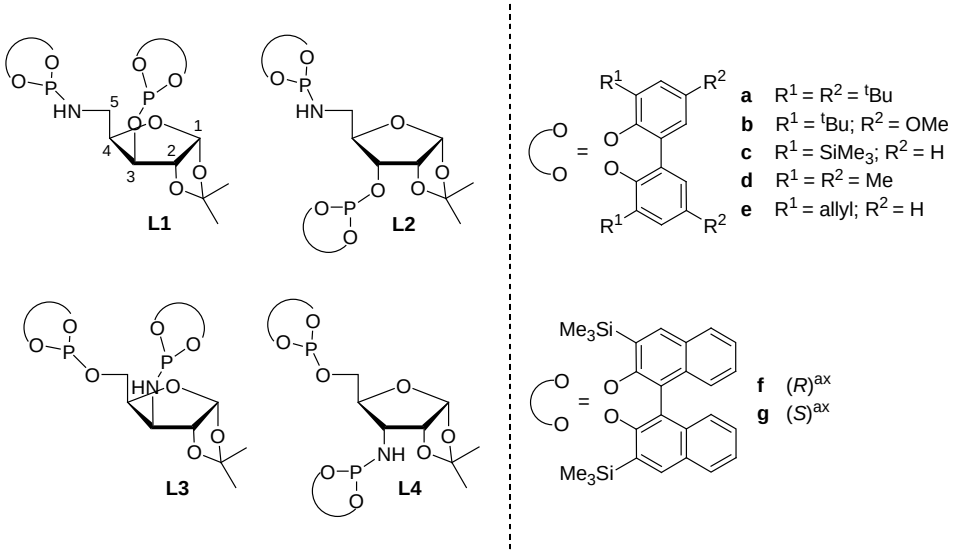

Figure 1. Library of phosphite-phosphoromidite ligands (**L1**-**L4a**-**g**) with furanoside backbone.

3.2.2. Results and Discussions

3.2.2.1. Synthesis of ligand library

The sequence of ligand synthesis is illustrated in Scheme 1. Ligands **L1**-**L4a**-**g** were synthesized very efficiently from the corresponding easily accessible monotosylated or monotriflated sugar derivatives (**3**, **8** and **12**, Scheme 1). Compounds **3**, **8** and **12** are easily made in few steps from the corresponding D-xylose or D-glucose.[7,8,9] These compounds (**3**, **8** and **12**) were chosen as intermediates for the preparation of ligands because they will easily allow to incorporate the various elements that will enable us to study the position of the phosphoroamidite (at either C-5 or C-3) as well as the configuration of C-3. Compounds **3**, **8** and **12** were treated with sodium azide to produce the desired azides **4**[10], **9**[11] and **13**[9] (Scheme 1, step (d)). Note that the

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azide formation follows an S_N2-like pathway, so for azides **9** and **13**, the absolute configuration of the stereogenic C-3 is inverted. At this point, the synthesis follow different pathways depending on the ligand to be prepared. Thus, aminoalcohol **5** is easily obtained by reduction of the azide **4** using triphenylphosphine.[10] For the preparation of aminoalcohol **7**, which differs from **5** in the configuration of C-3, the hydroxyl group at C-3 was inverted following a two step procedure that involves oxidation of the alcohol at C-3 using PCC and reduction of the ketone formed with $NaBH_4$ at low temperature.[12] Subsequent reduction of the azide **6** with triphenylphosphine, as for compound **5**, provides the corresponding aminoalcohol **7**.[12]

Aminoalcohols **11** and **15** have been synthesized following the same synthetic pathway. Therefore, compounds **9** and **13** were converted to the corresponding aldehydes **10** and **14**. This transformation takes place via acid-catalyzed selective ring opening of the 5,6-di-O-acetal ring to produce the corresponding 5,6-diols and subsequent treatment of the latter compounds with sodium metaperiodate to afford the desired compounds **10**[13] and **14**[14] (Scheme 1, step (g)). Compounds **10** and **14** were then converted to the corresponding aminoalcohols **11** and **15** by sequential reduction of the aldehyde group and the azide group by $NaBH_4$ and triphenylphosphine, respectively (Scheme 1, step (h)).[15]

The last step of the ligand synthesis is common for all of them (Scheme 1, step (i)). Therefore, treating the corresponding 1,3-aminoalcohols (**5**, **7**, **11** and **15**) with 2 equivalents of the appropriate *in situ* formed phosphorochloridite ($ClP(OR)_2$; $(OR)_2$ = **a-g**) in the presence of pyridine provided easy access to the desired phosphite-phosphoroamidite ligands **L1-L4a-g**. All the ligands were stable during

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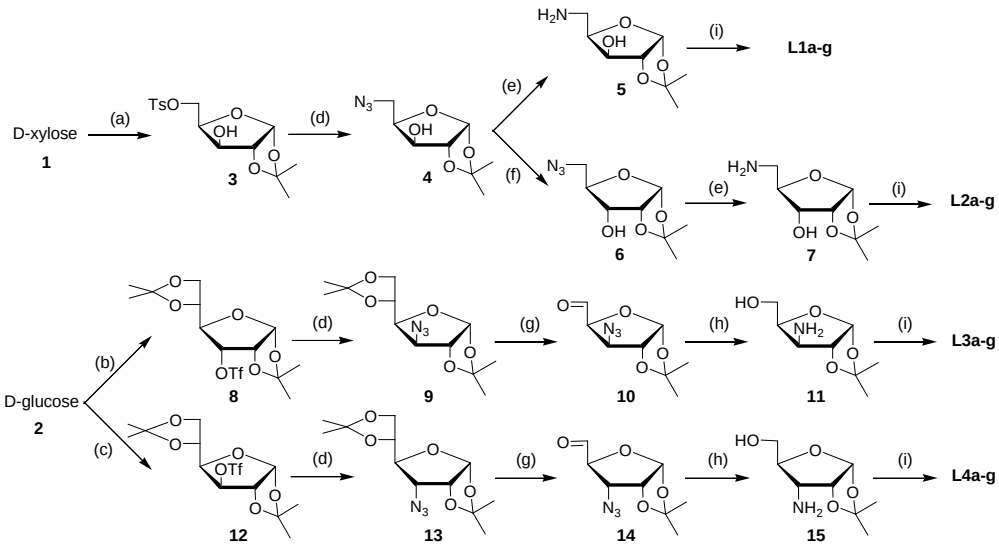
purification on neutral alumina under an atmosphere of argon and they were isolated as white solids. They were stable at room temperature and very stable to hydrolysis. Elemental analyses were in agreement with the structure assigned. The ^{1}H and ^{13}C NMR spectra were as expected for these C_1 ligands. Two signals for each compound was observed in the ^{31}P NMR spectrum (see Experimental Section). Rapid ring inversions (atropoisomerization) in the biphenyl-phosphorus moieties (**a-e**) occurred on the NMR time scale since the expected diastereoisomers were not detected by low-temperature phosphorus NMR.[16]



Scheme 1. Synthesis of phosphite-phosphoroamidite ligand library **L1-L4a-g**. (a) ref. 7. (b) ref. 8. (c) ref. 9. (d) DMF / NaN_3. (e) PPh_3 / THF / H_2O. (f) PCC /CH_2Cl_2 / Mol. Sieves 4Å; then $NaBH_4$ / EtOH / H_20. (g) AcOH / H_2O then $NaIO_4$ / $NaHCO_3$ / H_2O. (h) $NaBH_4$ / EtOH then PPh_3 / THF / H_2O. (i) $ClP(OR)_2$; $(OR)_2$ = **a-g** / Py / Toluene.

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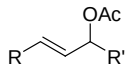
3.2.2.2. Allylic substitution of acyclic substrates

In this section we report the use of the chiral phosphite-phosphoroamidite (**L1-L4a-g**) ligands in the Pd-catalyzed allylic substitution (Figure 2) of linear disubstituted substrates with different steric properties: *rac*-1,3-diphenylprop-2-en-1-yl acetate **S1** (widely used as a model substrate) and *rac*-pent-3-en-2-yl acetate **S2**; and linear monosubstituted substrates: 1-(1-naphthyl)-2-propenyl acetate **S3** and 3-(1-naphthyl)-2-propenyl acetate **S4**. Two nucleophiles were tested. In all cases, the catalysts were generated *in situ* from π-allyl-palladium chloride dimer $[PdCl(\eta^3\text{-}C_3H_5)]_2$ and the corresponding ligand.[1]

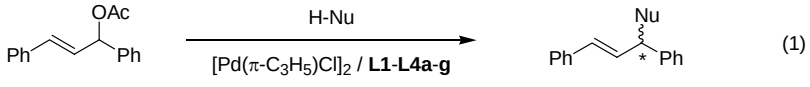


S1 R = R' = Ph
S2 R = R' = Me
S3 R = H; R' = 1-Naphtyl
S4 R = 1-Naphtyl; R' = H

Figure 2. Acyclic substrates.

3.2.2.2.1. Allylic substitution of rac-1,3-diphenylprop-2-en-1-yl acetate S1 using dimethyl malonate and benzylamine as nucleophiles

In the first set of experiments, we used the Pd-catalyzed asymmetric substitution reactions of **S1** (equation 1), with dimethyl malonate and benzylamine as nucleophiles, to scope the potential of the phosphite-phosphoroamidite ligand library **L1-L4a-g**. **S1** was chosen as a substrate because this reaction has been performed with a wide range of ligands enabling the direct comparison of the efficiency of the various ligands systems.[1]



S1 (1)

16 H-Nu = H-CH(COOMe)$_2$
17 H-Nu = H-NHCH$_2$Ph

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Initially, we determined the optimal reaction conditions by conducting a series of experiments in which the solvent and ligand-to-palladium ratio were varied. For this purpose we studied the effect of four solvents (tetrahydrofuran, toluene, dimethylformamide and dichloromethane) at three ligand-to-palladium ratios (L/Pd = 0.8, L/Pd = 1.1 and L/Pd = 2) with four ligands (**L1a**, **L2a**, **L3a** and **L4a**). Our results show that the efficiency of the process strongly depended on the nature of the solvent, whereas varying the ligand-to-palladium ratio has no effect (see Supporting Information). The best combination of activity and enantioselectivity was achieved with dichloromethane as solvent.

For the purpose of comparison, the rest of the ligands were tested under optimitzed conditions (i.e. a ligand-to-palladium ratio of 1.1 and dichloromethane as solvent). Table 1 shows the results when dimethyl malonate and benzylamine were used as nucleophiles. These results indicate that catalytic performance (activities and enantioselectivities) is highly affected by the position of the phosphoroamidite group at either C-5 or C-3 of the furanoside backbone, the configuration of C-3 and the substituents and configurations in the biaryl phosphite/phosphoroamidite moieties (**a**-**g**). Activities > 2000 mol **S1** x (mol Pd x h)$^{-1}$ and enantioselectivities up to 98% were obtained. Catalytic performance in the Pd-catalyzed allylic amination of **S1** followed the same trend as for the allylic alkylation of **S1** (Table 1). Although as expected, the activities were lower than in the alkylation reaction, they were higher than those obtained with other successful ligands.[1] The stereoselectivity of the amination was the same as for the alkylation reaction, though the CIP descriptor was inverted because of the change in the priority of the groups.

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We first studied the effect of the position of the phosphoroamidite group at either C-5 (ligands **L1** and **L2**) or C-3 (ligands **L3** and **L4**) of the furanoside backbone and the configuration of C-3. Ligands **L1** and **L2**, that contains the phosphoroamidite group at the C-5 position, produced better activities and enantioselectivities than ligands **L3** and **L4**, with the phosphoroamidite group at C-3 position. We also observed a cooperative effect between the position of the phosphoroamidite group and the configuration of carbon atom C-3 of the furanoside backbone. The results indicates that the matched combination is achieved with ligands **L1**, which has the phosphoroamidite moiety attached to C-5 and an *S* configuration of carbon atom C-3 of the tetrahydrofuran ring.

We next studied the effects of the biaryl phosphite/phosphoroamidite moieties using ligands **L1-L4a-c**,**f-g** (Table 1). It was observed that these moieties affected both activities and enantioselectivities of the reaction. The presence of methoxy groups in the *para* position of the biphenyl moieties has a positive effect on activity, but leads to lower enantioselectivities (Table 1, entries 2, 7, 12 and 15). We also observed a cooperative effect between the configuration of the biaryl moieties and the configuration of carbon atom C-3. The results indicated that the matched combination is achieved with ligand **L1g**, which has an *S* configuration at both carbon atom C-3 and in the biaryl phosphite/phosphoroamidite moieties (Table 1, entry 5).

In summary, the best result (on terms of activity and enantioselectivity) was obtained with ligand **L1g** (Table 1, entry 5, TOF's of 960 mol **S1** x (mol Pd x h)$^{-1}$ and ee's up to 98%), which contains the optimal combination of ligand parameters (position of the phosphoroamidite group, configuration at C-3 of the furanoside backbone

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and the substituents and configurations in the biaryl phosphite/phosphoroamidite moieties). These results clearly show the efficiency of using highly modular scaffolds in the ligand design.

Table 1. Selected results for the Pd-catalyzed allylic substitution of **S1** using the phosphite-phosphoroamidite ligand library **L1-L4a-g**.[a]

		H-Nu = H-CH(COOMe)$_2$		H-Nu = H-NHCH$_2$Ph	
Entry	Ligand	% Conv (t/min)[b]	% ee[c]	% Conv (t/h)[b]	% ee[c]
1	**L1a**	88 (15)	62 (*S*)	100 (6)	61 (*R*)
2[d]	**L1b**	100 (60)[e]	59 (*S*)[e]	100 (4)	56 (*R*)
3	**L1c**	72 (15)	69 (*S*)	86 (6)	67 (*R*)
4	**L1f**	71 (30)	6 (*S*)	69 (6)	12 (*R*)
5[d]	**L1g**	99 (120)[f]	98 (*S*)[f]	98 (6)	97 (*R*)
6	**L2a**	64 (15)	55 (*S*)	64 (6)	54 (*R*)
7[d]	**L2b**	83 (15)	52 (*S*)	100 (5)	51 (*R*)
8	**L2c**	13 (15)	33 (*S*)	41 (6)	25 (*R*)
9	**L2f**	12 (120)	80 (*S*)	21 (6)	75 (*R*)
10	**L2g**	15 (120)	12 (*S*)	27 (6)	11 (*R*)
11	**L3a**	41 (15)	42 (*R*)	52 (6)	43 (*S*)
12[d]	**L3b**	84 (15)	40 (*R*)	89 (6)	33 (*S*)
13	**L3c**	58 (15)	48 (*R*)	43 (6)	44 (*S*)
14	**L4a**	72 (15)	49 (*S*)	64 (6)	43 (*R*)
15[d]	**L4b**	93 (15)	42 (*S*)	100 (6)	41 (*R*)
16[d]	**L4c**	52 (15)	56 (*S*)	32 (6)	49 (*R*)

[a] All reactions were run at 25 ºC. 0.5 mol% [PdCl(η^3-C_3H_5)]$_2$. 1.1 mol% ligand. CH_2Cl_2 as solvent. BSA (1.5 mmol). Dimethyl malonate (1.5 mmol). KOAc as base. [b] Conversion percentage determined by ^{1}H-NMR. [c] Enantiomeric excesses determined by HPLC. Absolute configuration drawn in parentheses. [d] Isolated yields of **16** and **17** were > 93% based on recovered starting material. [e] Reaction carried out using 0.05 mol% of catalyst. TOF = 2280 mol **S1** x (mol Pd x h)$^{-1}$ measured after 5 minutes. [f] Reaction carried out using 0.05 mol% of catalyst. TOF = 960 mol **S1** x (mol Pd x h)$^{-1}$ measured after 5 minutes.

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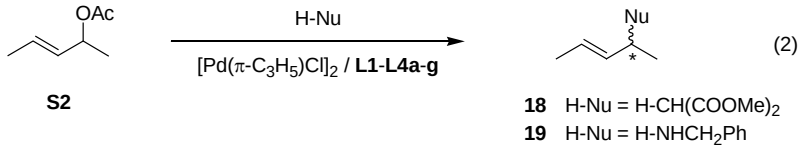
3.2.2.2.2. Allylic substitution of rac-pent-3-en-2-yl acetate S2 using dimethyl malonate and benzylamine as nucleophiles

We also screened the phosphite-phosphoramidite ligand library **L1-L4a-g** in the allylic substitution of the linear substrate **S2** (equation 2).



Substrate **S2** is less sterically demanding than substrate **S1**, which we used before. Enantioselectivity for **S2** is therefore more difficult to control than with hindered substrates such as **S1**. If ee's are to be high, the ligand must create a small chiral pocket (the chiral cavity in which the allyl is embedded) around the metal centre, mainly because of the presence of less sterically demanding methyl *syn* substituents.[1] There are therefore fewer successful catalyst systems for the Pd-catalyzed allylic substitution of this substrate than for the allylic substitution of hindered substrates such as **S1**.[3b,5,17] Due to the flexibility conferred by the biaryl phosphite/phosphoroamidite moieties, we expect to obtain also good enantioselectivities for this substrate.

Preliminary investigations into the solvent and ligand-to-palladium ratio revealed a different trend in solvent effect than with the previously tested substrate **S1**. Enantioselectivities and activities were best when THF was used and the ligand-to-palladium ratio was 1.1 (see Supporting Information).

The results of using the phosphite-phosphoroamidite ligand library **L1-L4a-g** in the optimized conditions are shown in Table 2 (see also

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Supporting Information for more results on the allylic amination reaction). Again, activities and enantioselectivities were affected by the position of the phosphoroamidite group at either C-5 or C-3 of the furanoside backbone, the configuration of C-3 and the substituents and configurations in the biaryl phosphite/phosphoroamidite moieties. However, the effect of these parameters was different from their effect on the substitution of hindered substrate **S1**. Thus, enantioselectivities were best with ligands **L2g** and **L4g** (ee's up to 84%; Table 2, entries 18–21). These results, which clearly show again the efficiency of using highly modular scaffolds in the ligand design, are among the best reported for this type of unhindered substrates.[3b,5,17]

Regarding the effects of the position of the phosphoroamidite group at either C-5 (ligands **L1** and **L2**) or C-3 (ligands **L3** and **L4**) of the furanoside backbone and the configuration of C-3, in contrast to **S1**, the enantioselectivity is mainly affected by the configuration of C-3, while the effect of position of the phosphoroamidite is less pronounced. Therefore, ligands **L2** and **L4** that contains an *R*-configuration at C-3 provides higher enantioselectivities than ligands **L1** and **L3** with an opposite configuration at C-3. However, the sense of enantioselectivity is controlled by both the position of the phosphoroamidite group and the configuration of C-3. Therefore, ligands **L1** and **L4** gave *R*-substitution products, whereas ligands **L2** and **L3** gave *S*-substitution products.

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Table 2. Selected results for the Pd-catalyzed allylic substitution of **S2** using ligand library **L1-L4a-g**.[a]

Entry	Ligand	% Conv (t/h)[b]	% ee[c]
1	**L1a**	100 (0.5)	10 (*R*)
2[d]	**L1b**	100 (0.3)	8 (*R*)
3	**L1c**	100 (0.5)	34 (*R*)
4	**L1f**	100 (0.5)	58 (*S*)
5	**L1g**	100 (0.5)	39 (*R*)
6[d]	**L2a**	100 (0.5)	16 (*S*)
7[d]	**L2b**	100 (0.3)	9 (*S*)
8	**L2c**	48 (0.5)	36 (*S*)
9	**L2f**	43 (0.5)	21 (*S*)
10	**L2g**	42 (0.5)	74 (*S*)
11	**L3a**	100 (0.5)	10 (*S*)
12[d]	**L3b**	100 (0.3)	6 (*S*)
13	**L3c**	100 (0.5)	31 (*S*)
14	**L4a**	100 (0.5)	16 (*R*)
15[d]	**L4b**	100 (0.3)	12 (*R*)
16	**L4c**	100 (0.5)	43 (*R*)
17	**L4g**	51 (0.5)	72 (*R*)
18[d,e]	**L2g**	82 (4)	84 (*S*)
19[d,e]	**L4g**	68 (4)	83 (*R*)
20[f]	**L2g**	74 (20)	72 (*S*)
21[f]	**L4g**	65 (20)	71 (*R*)

[a] T = 25 ºC. 0.5 mol% $[PdCl(\eta^3\text{-}C_3H_5)]_2$. THF as solvent. 1.1 mol% ligand. **S2** (0.5 mmol). BSA (1.5 mmol). Dimethyl malonate (1.5 mmol). KOAc as base. [b] Conversion measured by GC. Reaction time shown in parentheses. [c] Enantiomeric excesses measured by GC. The absolute configuration appears in parentheses. [d] Isolated yields of **18** were > 92% based on recovered **S2**. [e] T = 0 ºC. [f] Using benzylamine as nucleophile.

The effect of the substituents of the biphenyl phosphite/phosphoroamidite moieties on catalytic performance is similar to the effect in the previous substitution of **S1**. However, the cooperative

effect between the configuration of the biaryl phosphite/phosphoroamidite moieties and the configurations of the ligand backbone is different. This resulted in a matched combination for ligands **L2g** and **L4g**, which have an *R*-configuration at carbon atom C-3 and an *S*-configuration in the biaryl phosphite/phosphoroamidite moieties.

In summary, the results indicates that the size of the chiral pocket is mainly controlled by the configuration of carbon atom C-3 and the substituents/configuration of the biaryl moieties. Thus, ligands **L2** and **L4** lead to a smaller chiral pocket and therefore to higher enantioselectivities than ligands **L1** and **L3**. Moreover, both enantiomers of the substitution products **18** and **19** can be obtained in high enantioselectivity by simple changing the position of the phosphoroamidite in ligands **L2** and **L4**. Interestingly, comparing these excellent results with the poor enantioselectivity obtained with the related diphosphite ligands (ee's up to 59%),[4b] we can conclude that the introduction of a phosphoroamidite moiety has been highly advantageous.

3.2.2.2.3. Allylic substitution of monosubstituted linear substrates S3 and S4

To further study the potential of these readily available ligands, we also tested **L1**-**L4a-g** in the the regio- and stereoselective allylic alkylation of 1-(1-naphthyl)-2-propenyl acetate **S3** and 3-(1-naphthyl)-2-propenyl acetate **S4** with dimethyl malonate as nucleophile (equation 3).

For these substrates, not only does the enantioselectivity of the process need to be controlled but regioselectivity is also a problem because a mixture of regioisomers can be obtained. Most Pd-catalysts developed to date favour the formation of achiral linear product **21** rather

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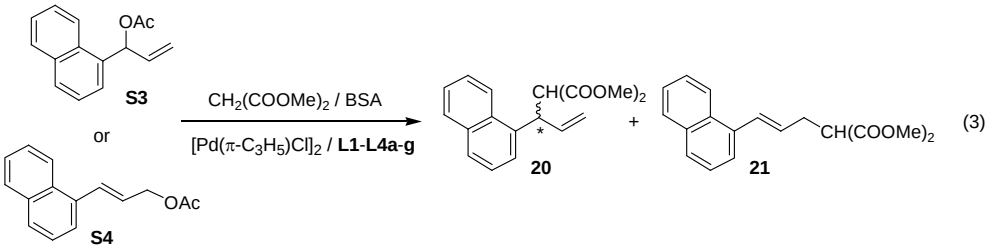
than the desired branched isomer **20**.[18] The development of highly regio- and enantioselective Pd-catalysts is therefore still a challenge.[5a,c,19]



(3)

The results obtained with the phosphite-phosphoroamidite ligand library **L1-L4a-g** are summarized in Table 3. High activities and enantioselectivities up to 90% combined with regioselectivities up to 75% in favour of the branched product **20** were obtained, under standard reaction conditions, with the Pd/**L2f** and Pd/**L4f** catalyst systems. The results indicated that the selectivity (regio- and enantioselectivity) is mainly affected by the configuration of C-3 and the substituents/configuration in the biaryl moieties, while the effect of position of the phosphoroamidite is less pronounced. The trade-off between regio- and enantioselectivities was therefore best for ligands that contain an *R*-configuration at C-3 (ligands **L2** and **L4**) and either bulky *tert*-butyl groups at both *ortho* and *para* positions of the biphenyl moieties or bulky *R*-binaphthyl phosphite-phosphoroamidite moieties.

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Table 3. Selected results for the Pd-catalyzed allylic alkylation of monosubstituted substrate **S3** and **S4** using the ligand library **L1**-**L4a**-**g** under standard conditions.[a]

Entry	Ligand	Substrate	% Conv[b] (min)	**20**/**21**[c]	% ee[d]
1	**L1a**	**S3**	100 (120)	20/80	21 (*S*)
2	**L1b**	**S3**	100 (120)	30/70	17 (*S*)
3	**L1c**	**S3**	100 (120)	35/65	51 (*S*)
4	**L1f**	**S3**	100 (120)	70/30	7 (*R*)
5	**L1g**	**S3**	100 (120)	65/35	66 (*S*)
6	**L2a**	**S3**	100 (120)	70/30	71 (*S*)
7	**L2b**	**S3**	100 (120)	70/30	9 (*S*)
8	**L2c**	**S3**	100 (120)	35/65	65 (*S*)
9[e]	**L2f**	**S3**	100 (180)	70/30	90 (*S*)
10	**L2g**	**S3**	100 (120)	60/40	61 (*S*)
11	**L3a**	**S3**	100 (120)	55/45	36 (*R*)
12	**L3b**	**S3**	100 (120)	40/60	5 (*R*)
13	**L3c**	**S3**	100(120)	45/65	30 (*R*)
14	**L4a**	**S3**	100 (120)	60/40	73 (*S*)
15	**L4b**	**S3**	100 (120)	60/40	6 (*S*)
16	**L4c**	**S3**	100 (120)	25/75	63 (*S*)
17	**L4f**	**S3**	68 (120)	75/25	89 (*S*)
18[e]	**L2f**	**S4**	100 (180)	70/30	90 (*S*)

[a] All reactions were run at 25 ºC. 1 mol% $[PdCl(\eta^3\text{-}C_3H_5)]_2$. Dichloromethane as solvent. 2.2 mol% ligand. Substrate (0.5 mmol). BSA (1.5 mmol). Dimethyl malonate (1.5 mmol). KOAc as base. [b] Reaction time in minutes shown in parentheses. [c] Percentage of branched (**20**) and linear (**21**) isomers [d] Enantiomeric excesses of **20** determined by HPLC. The absolute configuration appears in parentheses. [e] Isolated yields of **20** were 67%.

These results are among the best reported for this type of substrates.[5a,c,19] Therefore, the replacement of a phosphite moiety by a phosphoroamidite group in related diphosphite ligands have lead again to

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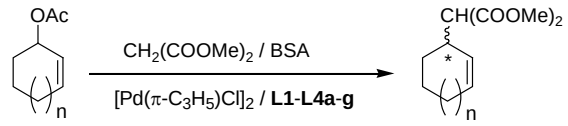
higher regio- (up to 75% vs up to 29%[4b]) and enantioselectivities (up to 90% vs up to 33%[4b]). In addition, the efficiency of the ligand design is also corroborated by the fact that these Pd-phosphite-phosphoroamidite catalysts provided higher combination of regio- and enantioselectioselectivities than with previously published 1,2-aminoalcohol-based phosphite-phosphoroamidite ligands.[3b]

3.2.2.3. Allylic alkylation of cyclic substrates

Encouraged by the excellent results obtained for several di- and monosubstituted linear substrates, we examined the allylic alkylation of cyclic substrates **S5** and **S6**. The enantioselectivity with these substrates is difficult to control, mainly because of the presence of less sterically *anti* substituents. These *anti* substituents are thought to play a crucial role in the enantioselection observed with cyclic substrates in the corresponding Pd-allyl intermediates.[1]

In this section we show that the chiral phosphite-phosphoroamidite ligand library **L1**-**L4a-g** applied above to the Pd-catalyzed allylic substitution of linear substrates (**S1**-**S4**) can also be used for cyclic substrates (ee's up to 91%). We tested two cyclic substrates (equation 4): *rac*-cyclohex-2-en-1-yl acetate **S5** (which is widely used as a model substrate) and *rac*- cyclohep-2-en-1-yl acetate **S6**.



(4)

S5 n = 1
S6 n = 2

22 n = 1
23 n = 2

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Preliminary investigations into the solvent effect and ligand-to-palladium ratio showed the same trends as with the previously tested unhindered linear substrate **S2**. The trade-off between enantioselectivities and reaction rates was therefore optimum with THF and a ligand-to-palladium ratio of 1.1 (see Supporting Information).

The results of using the phosphite-phosphoroamidite ligand library **L1**-**L4a**-**g** under the optimized conditions are shown in Table 4. We also obtained high activities and enantioselectivities (up to 91%) in the allylic substitution of cyclic substrates **S5** and **S6** with Pd/**L2a** and Pd/**L3a**.

Activities followed the same trend as those observed in the alkylation of **S1** and **S2**. However, the effect of the ligand parameters on the enantioselectivity was different from the effect observed in the substitution of the linear substrates **S1** and **S2**. Although, we observed a cooperative effect between the position of the phosphoroamidite group and the configuration of carbon atom C-3, in contrast to substitution of **S1** and **S2**, this resulted in a matched combination for ligands **L2** and **L3**. Ligands **L2** have the phosphoroamidite group at C-5 position and an *R*-configuration at C-3, while ligands **L3** have the phosphoroamidite group at C-3 position and an *S*-configuration at C-3 stereocenter. Moreover, unlike the substitution of **S1** and **S2**, the presence of bulky *tert*-butyl groups at both *ortho* and *para* positions of the biaryl moieties have a extremely positive effect on enantioselectivity.

Interestingly, the sense of enantioselectivity is mainly governed by the configuration of C-3. Thus, both enantiomers of the substitution products **22** and **23** can be accessed in high enantioselectivities by simple changing the configuration of C-3 (Table 4, entries 6 and 11).

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Table 4. Selected results for the Pd-catalyzed allylic alkylation of **S5** and **S6** using the phosphite-phosphoroamidite ligand library **L1**-**L4a-g**.[a]

		S5		**S6**	
Entry	Ligand	% Conv (t/min)[b]	% ee[c]	% Conv (t/h)[b]	% ee[c]
1[d]	**L1a**	100 (120)	12 (*R*)	63 (6)	17 (*R*)
2	**L1b**	100 (120)	4 (*R*)	75 (6)	8 (*R*)
3	**L1c**	72 (120)	40 (*R*)	45 (6)	49 (*R*)
4	**L1f**	20 (120)	19 (*R*)	13 (6)	17 (*R*)
5	**L1g**	26 (120)	67 (*S*)	11 (6)	64 (*S*)
6[d]	**L2a**	100 (120)	85 (*S*)	52 (6)	91 (*S*)
7	**L2b**	100 (120)	65 (*S*)	69 (6)	66 (*R*)
8	**L2c**	33 (120)	32 (*S*)	39 (6)	35 (*R*)
9	**L2f**	11 (120)	52 (*R*)	9 (6)	43 (*R*)
10	**L2g**	10 (120)	78 (*S*)	10 (6)	78 (*S*)
11[d]	**L3a**	100 (120)	80 (*R*)	46 (6)	81 (*R*)
12	**L3b**	100 (120)	53 (*R*)	65 (6)	49 (*R*)
13	**L3c**	62 (120)	27 (*R*)	45 (6)	32 (*R*)
14[d]	**L4a**	100 (120)	57 (*S*)	65 (6)	55 (*S*)
15	**L4b**	100 (120)	50 (*S*)	77 (6)	54 (*S*)
16	**L4c**	42 (120)	24 (*S*)	32 (6)	26 (*S*)

[a] All reactions were run at 25 ºC. 0.5 mol% $[PdCl(\eta^3\text{-}C_3H_5)]_2$. THF as solvent. 1.1 mol% ligand. Substrate (0.5 mmol). BSA (1.5 mmol). Dimethyl malonate (1.5 mmol). KOAc as base. [b] Conversion measured by GC. Reaction time shown in parentheses. [c] Enantiomeric excesses measured by GC. The absolute configuration appears in parentheses. [d] Isolated yields of **22** and **23** > 93% based on recovered starting material.

To sum up, the best enantioselectivities were therefore obtained with ligands **L2a** and **L3a**, which have bulky substituents at the *ortho* and *para* positions of the biaryl moieties and the appropriate combination of the position of the phosphoroamidite group and the configuration at C-3. These results are among the best reported for this type of unhindered

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substrates.[1f,5a,c,17a,20] Again the replacement of a phosphite moiety by a phosphoroamidite group in the ligand design lead to higher enantioselectivities than when the corresponding diphosphite ligands are used (ee's up to 34%).[4b]

3.2.2.4. Origin of enantioselectivity. Study of the Pd-π-allyl intermediates

To provide further insight into how ligand parameters affect catalytic performance, we studied the Pd-π-allyl compounds **24-34**, $[Pd(\eta^3\text{-allyl})(L)]BF_4$ (L = phosphite-phosphoroamidite ligands), since they are key intermediates in the allylic substitution reactions studied.[1] These ionic palladium complexes, which contain 1,3-diphenyl, 1,3-dimethyl or cyclohexenyl allyl groups, were prepared using the previously described method from the corresponding Pd-allyl dimer and the appropriate ligand in the presence of silver tetrafluoroborate (Scheme 2).[21] The complexes were characterized by elemental analysis and by ^1H, ^{13}C and ^{31}P NMR spectroscopy. The spectral assignments (see Experimental Section) were based on information from ^1H-^1H, ^{31}P-^1H and ^{13}C-^1H correlation measurements in combination with ^1H-^1H NOESY experiments. Unfortunately, we were unable to obtain any crystal of sufficient quality to perform X-ray diffraction measurements.

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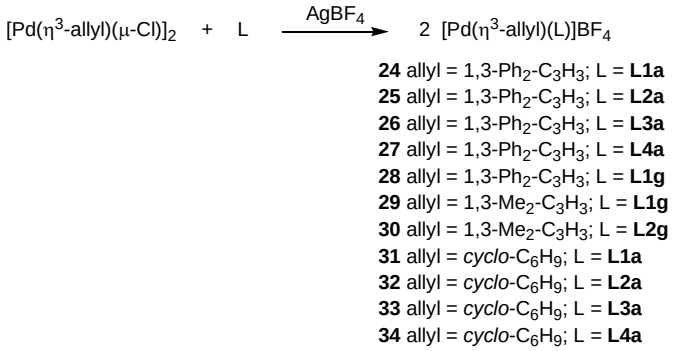

Scheme 2. Preparation of $[Pd(\eta^3\text{-allyl})(L)]BF_4$ complexes **24**-**34**.

3.2.2.4.1. Palladium 1,3-diphenyl-allyl complexes

When the phosphite-phosphoroamidite ligand library **L1**-**L4a-g** was used in the allylic substitution of substrate **S1**, the catalytic results indicated that enantioselectivity is highly affected by the ligand parameters. A phosphoroamite group attached at C-5 of the furanoside backbone, an *S*-configuration at C-3 of the tetrahydrofuran ring and an *S*-binaphthyl phosphite/phosphoroamidite moieties are therefore required if enantioselectivity is to be high. To understand this catalytic behaviour, we studied Pd-π-allyl complexes **24-28**, which contain ligands **L1a**, **L2a**, **L3a**, **L4a** and **L1g**, respectively. With complexes **24-27**, we contemplated the four possible combinations of varying the position of the phosphoroamidite group and the configuration of carbon atom C-3 and their study will allow to understand the effect of these parameters. Finally with complex **28**, we studied the matched combination of the observed cooperative effect between the configuration at C-3 and the configuration of the biaryl phosphite/phosphoroamidite moieties.

The VT-NMR (30 ºC to -80 ºC) study of Pd-allyl intermediate **24**, which contains ligand **L1a**, had a mixture of two isomers in equilibrium in a ratio of 2:1 (see Experimental Section).[22] Both isomers were

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unambiguously assigned by NMR (^{1}H, ^{31}P, ^{13}C, ^{1}H-^{1}H, ^{1}H-^{13}C and ^{1}H-^{31}P correlation and NOESY experiments) to the two *syn*/*syn endo* **A** and *exo* **B** isomers (Scheme 3). In both isomers, the NOE indicates interactions between both terminal protons of the allyl group and also between the central allyl proton with *ortho* hydrogens of both phenyl groups of the allyl ligand, which clearly indicates a *syn*/*syn* disposition (Figure 3). Moreover, hydrogen H-3 of the sugar backbone shows a NOE interaction with one of the terminal allyl protons of the major isomer **A**, while in **B** isomer this interaction appears with the central allyl proton. Such interactions can be explained by assuming a *syn*/*syn endo* disposition for isomer **A** and a *syn*/*syn exo* disposition for isomer **B** (Figure 3). For both isomers, the carbon NMR chemical shifts indicate that the more electrophilic allyl carbon terminus is *trans* to the phosphoroamidite moiety. Assuming that the nucleophilic attack takes place at the more electrophilic allyl carbon terminus[1] and on the basis of the observed stereochemical outcome of the reaction (62% (*S*) in product **16**), and as the enantiomeric excess of alkylation product **16** differs from the diastereoisomeric excess (de = 33% (*R*)) of the Pd-intermediates, the **B** isomer must react faster than the **A** isomer. To prove this we also studied the reactivity of the Pd-intermediates with sodium malonate at low temperature by *in situ* NMR (Figure 4). Our results show that the minor isomer **B** reacts around 10 times faster than isomer **A**. If we take into account the relative reaction rates and the abundance of both isomers, the calculated ee should be 66% (*S*), which matches the ee obtained experimentally.[23] We can therefore conclude that the nucleophilic attack takes place predominantly at the allyl terminus *trans* to the phosphoroamidite moiety of the minor **B** Pd-intermediate. This is also

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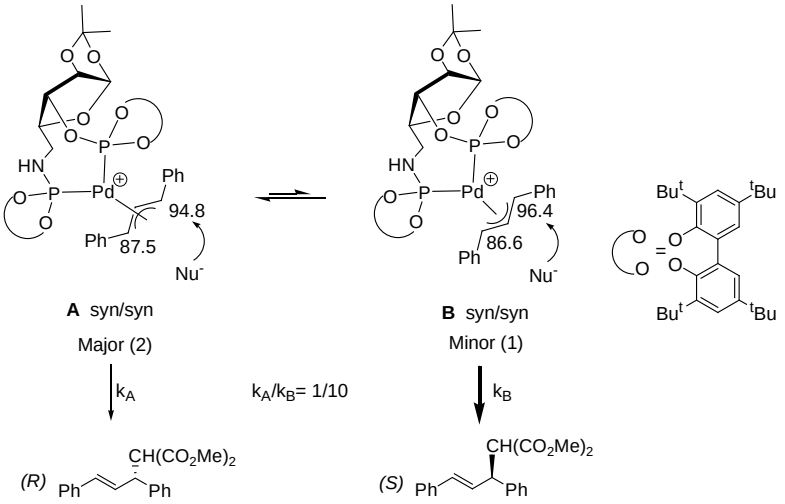
consistent with the fact that, for both isomers, the most electrophilic allylic terminal carbon atom is the one *trans* to the phosphoroamidite in the minor **B** isomer.



Scheme 3. Diastereoisomer Pd-allyl intermediates for **S1** with ligand **L1a**. The relative amounts of each isomer are drawn in parenthesis. The chemical shifts (in ppm) of the allylic terminal carbons are shown.

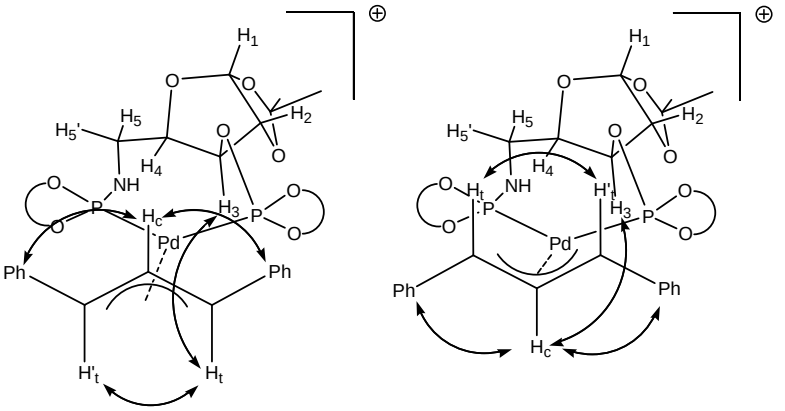


Figure 3. Relevant NOE contacts from NOESY experiment of [Pd(η^3-1,3-diphenylallyl)(**L1a**)]BF_4 (**24**) isomers.

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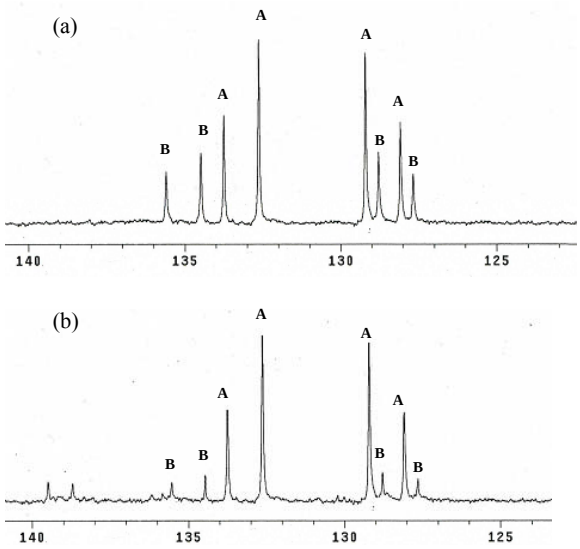

Figure 4. $^{31}P\{^{1}H\}$NMR spectra of [Pd(η^3-1,3-diphenylallyl)(**L1a**)]BF_4 (**24**) in CD_2Cl_2 at –60 ^{o}C (a) before the addition of sodium malonate and (b) after the addition of sodium malonate.

The VT-NMR study of Pd-allyl intermediate **25**, which contains ligand **L2a**, also had a mixture of two *syn*/*syn endo* **A** and *exo* **B** isomers but in a ratio of 1:1 (see Experimental Section). In both isomers, the NOE indicates interactions between both terminal protons of the allyl group and also between the central allyl proton with *ortho* hydrogens of both phenyl groups of the allyl ligand, which clearly indicates a *syn*/*syn* disposition (Figure 5). Moreover, hydrogen H-3 of the sugar backbone shows a NOE interaction with the central allyl proton of the major isomer **A**, while in **B** isomer this interaction appears with one of the terminal allyl protons. Such interactions can be explained by assuming a *syn*/*syn endo* disposition for isomer **A** and a *syn*/*syn exo* disposition for isomer **B** (Figure 5). Also, the more electrophilic allyl carbon terminus was *trans* to

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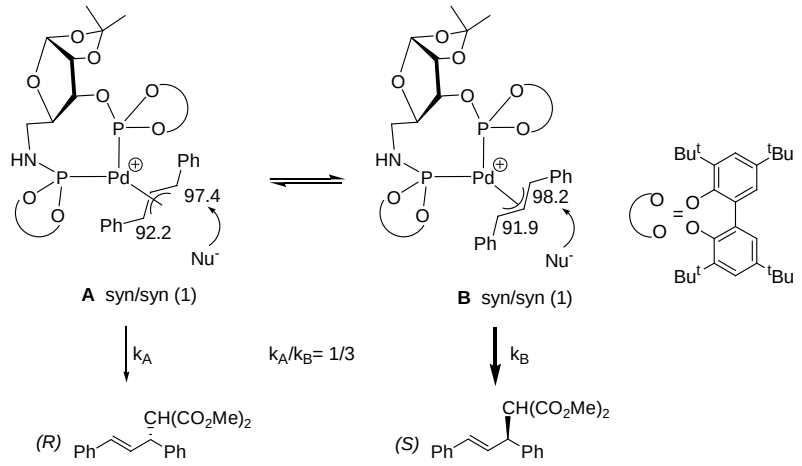
the phosphoroamidite moiety (Scheme 4). However, an important difference between complexes **24** and **25** is the lower electronic differentiation between the more electrophilic allylic terminus carbon atoms of both isomers (**A** and **B**) in complex **25** ($\Delta(\delta^{13}C) \approx 0.8$ ppm) than in complex **24** ($\Delta(\delta^{13}C) \approx 1.6$ ppm). This low electronic differentiation can explain the lower enantioselectivity obtained with Pd/**L2a** respect to Pd/**L1a**. In accordance, the reactivity of the Pd-intermediates with sodium malonate at low temperature by *in situ* NMR indicates that isomer **B** in complex **25** reacts only 3 times faster than isomer **A**.



Scheme 4. Diastereoisomer Pd-allyl intermediates for **S1** with ligand **L2a**. The relative amounts of each isomer are drawn in parenthesis. The chemical shifts (in ppm) of the allylic terminal carbons are shown.

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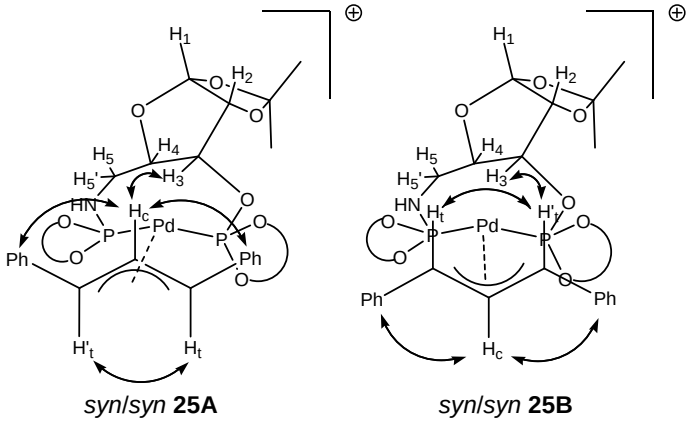

Figure 5. Relevant NOE contacts from NOESY experiment of [Pd(η^3-1,3-diphenylallyl)(**L2a**)]BF_4 (**25**) isomers.

The VT-NMR study of Pd-allyl intermediate **26**, which contains ligand **L3a**, had also a mixture of two *syn*/*syn endo* **A** and *exo* **B** isomers in a ratio of 1:2 (Scheme 5). Again, the more electrophilic allylic carbon terminus was *trans* to the phosphoroamidite moiety. Unlike complex **24**, the effect of changing the position of the phosphoroamidite moiety produces a lower electronic differentiation between the more electrophilic allylic terminus carbon atoms of both isomers (**A** and **B**) of complex **26** ($\Delta(\delta^{13}C) \approx 0.2$ ppm) than in complex **24** ($\Delta(\delta^{13}C) \approx 1.6$ ppm). This low electronic differentiation suggests that the nucleophile can attack both isomers at a similar rate and fully accounts for the enantioselectivity observed.[24]

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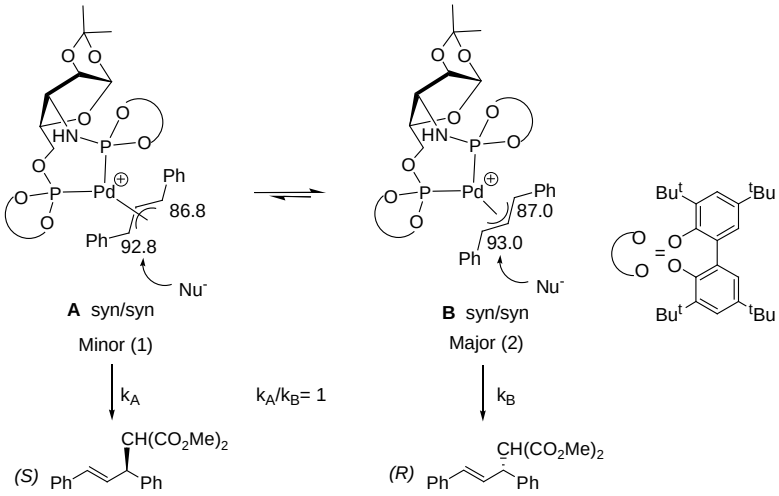

Scheme 5. Diastereoisomer Pd-allyl intermediates for **S1** with ligand **L3a**. The relative amounts of each isomer are drawn in parenthesis. The chemical shifts (in ppm) of the allylic terminal carbons are shown.

The VT-NMR study of Pd-1,3-diphenyl allyl intermediate **27**, which contains ligand **L4a**, indicated the presence of a mixture of two *syn*/*syn endo* **A** and *exo* **B** isomers in a ratio of 1:1.2 (Scheme 6). In comparison with complex **26**, which contains ligand **L3a**, we found that the relative amount of isomer **A** with respect to **B** increased as well as the electronic differentiation between the more electrophilic allylic terminus carbon atoms of both isomers (**A** and **B**). These indicate that the nucleophilic attack takes place preferentially at the allylic terminus *trans* to the phosphoroamidite moiety of the **A** Pd-intermediate.[25] These facts explain the higher enantioselectivity obtained with Pd/**L4a** than with Pd/**L3a**.

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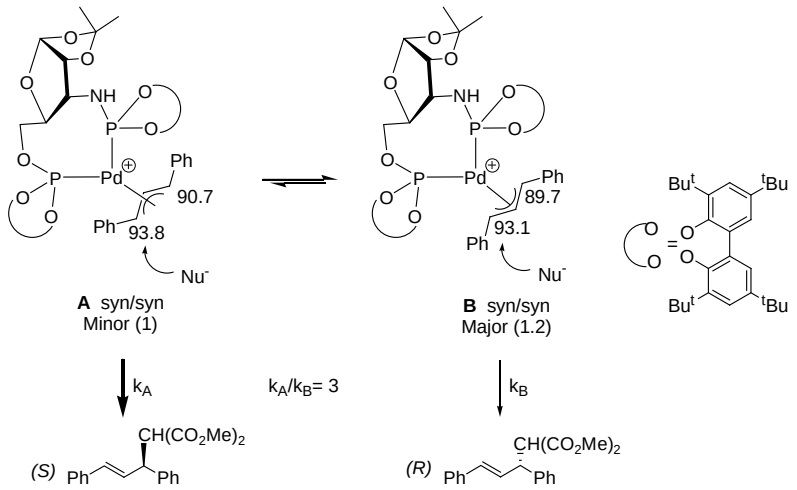

Scheme 6. Diastereoisomer Pd-allyl intermediates for **S1** with ligand **L4a**. The relative amounts of each isomer are drawn in parenthesis. The chemical shifts (in ppm) of the allylic terminal carbons are shown.

Finally, we studied the palladium intermediate [Pd(η^3-1,3-diphenylallyl)(**L1g**)]BF_4 (**28**), which contains enantiopure *S*-binaphthyl ligand **L1g**. This ligand provides the highest enantioselectivity and therefore contemplates the correct combination of ligand parameters (position of the phosphoroamidite moiety, configuration of C-3 at the ligand backbone and the substituents/configuration at the biaryl moieties). The VT-NMR study performed showed a mixture of the two *syn*/*syn endo* **A** and *exo* **B** isomers in a ratio of 1:4 (Scheme 7). Again, for both isomers, the carbon NMR chemical shifts indicate that the most electrophilic allylic carbon terminus is *trans* to the phosphoroamidite moiety. Comparing with the other Pd-1,3-diphenyl allyl intermediates studied **24-27**, this presents the highest electronic differentiation between the more electrophilic allylic terminus carbon atoms of both isomers (**A** and **B**) ($\Delta(\delta^{13}C) \approx 3.1$ ppm) and also the highest population of the fast

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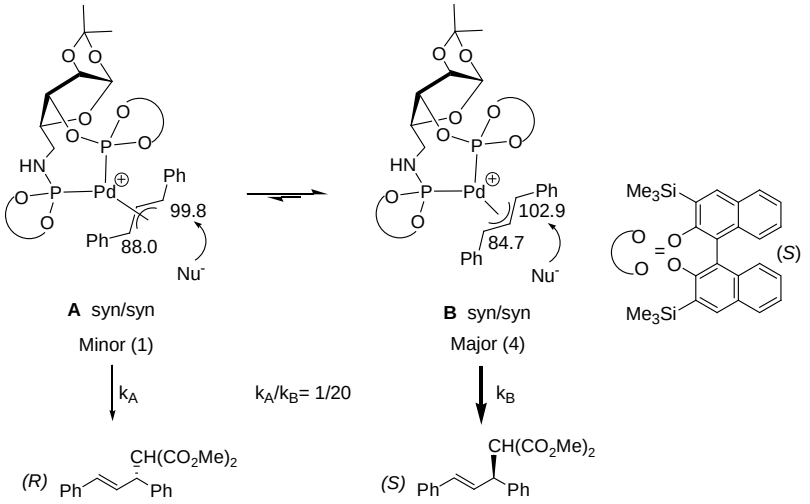
reacting isomer **B**.[26] These facts are in agreement with the high enantioselectivity observed using this ligand.



Scheme 7. Diastereoisomer Pd-allyl intermediates for **S1** with ligand **L1g**. The relative amounts of each isomer are drawn in parenthesis. The chemical shifts (in ppm) of the allylic terminal carbons are shown.

3.2.2.4.2. Palladium 1,3-dimethyl-allyl complexes

When the phosphite-phosphoroamidite ligand library **L1-L4a-g** was used in the allylic substitution of substrate **S2**, the catalytic results revealed a different trend regarding the effect of the ligand parameters than with the previously hindered substrates **S1**. The enantioselectivity is mainly therefore affected by the configuration of C-3, while the effect of position of the phosphoroamidite is less pronounced. Therefore, ligands **L2** and **L4** that contains an *R*-configuration at C-3 provides higher enantioselectivities than ligands **L1** and **L3** with an opposite configuration at C-3. To understand this catalytic behavior, we studied Pd-π-allyl complexes **29** and **30**, which contain ligands **L1g** and **L2g**, respectively. While ligand **L2g**, which has an *R*-configuration at C-3,

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provided high enantioselectivities (Table 2, entries 18 and 19, ee's up to 84%), ligand **L1g**, with an opposite configuration at C-3, was less enantioselective (Table 2, entry 5, ee's up to 39%).

For both Pd-1,3-dimethyl allyl intermediates **29** (**L1g**) and **30** (**L2g**), the study of the VT-NMR (35 °C to –80 °C) indicated the presence of a mixture of two isomers (**A** and **B**) at a ratio of 1:1 for complex **29** and at a ratio of 1:1.2 for complex **30** (Scheme 8). All species were assigned by NOE to the *syn*/*syn endo* **A** and *exo* **B** isomers (Scheme 8). For both complexes, the NOE indicates interactions between both terminal protons of the allyl group and also between the central allyl proton with methyl protons of the allyl ligand, which clearly indicates a *syn*/*syn* disposition for all the isomers (Figure 6). For isomers **29A** and **30B**, hydrogen H-3 of the sugar backbone shows a NOE interaction with one of the terminal allyl protons, while in **29B** and **30A** isomers this interaction appears with the central allyl proton. Such interactions can be explained by assuming a *syn*/*syn endo* disposition for isomers **A** and a *syn*/*syn exo* disposition for isomers **B** (Figure 6). As for the previous 1,3-diphenylallyl intermediates, the NMR data indicate that the more electrophilic allyl terminal carbon is *trans* to the phosphoroamidite moiety. However, for complex **29** the most electophilic allylic terminal carbon is located in isomer **A**, while for complex **30** it is located at isomer **B**. This together with the facts that for complex **30** both the population of the faster reacting isomer and the relative reaction rates are higher[27] than for complex **29** explains the difference in enantioselectivities observed for both catalytic systems.

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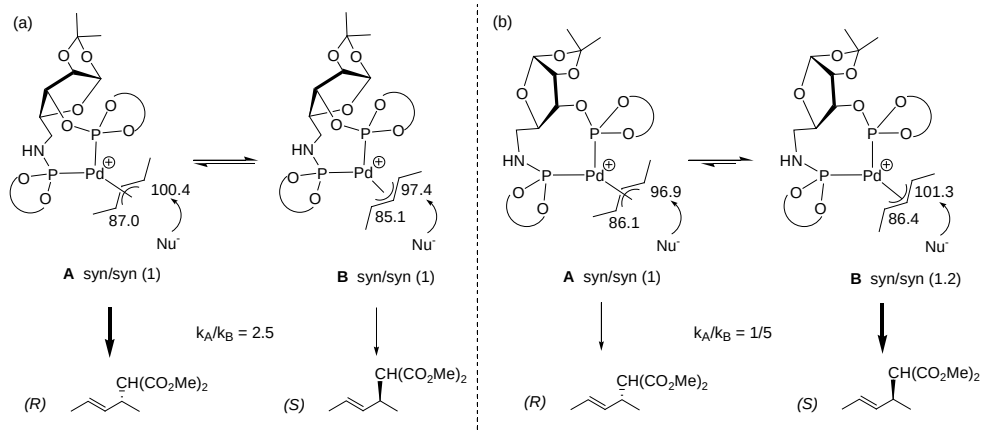

Scheme 8. Diastereoisomer Pd-allyl intermediates (a) **29** for **S2** with ligand **L1g** and (b) **30** for **S2** with ligand **L2g**. The relative amounts of each isomer are drawn in parenthesis. The chemical shifts (in ppm) of the allylic terminal carbons are shown.

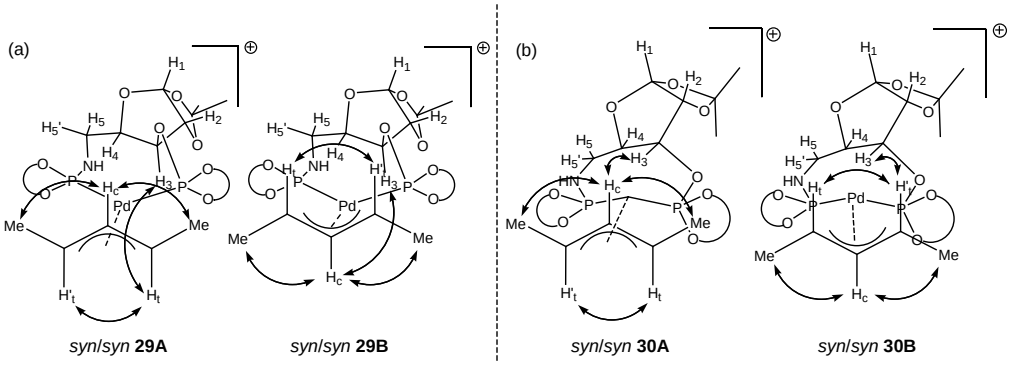

Figure 6. Relevant NOE contacts from NOESY experiments of: (a) [Pd(η^3-1,3-dimethylallyl)(**L1g**)]BF_4 (**29**) isomers and (b) [Pd(η^3-1,3-dimethylallyl)(**L2g**)]BF_4 (**30**) isomers.

3.2.2.4.3. Palladium 1,3-cyclohexenyl-allyl complexes

When the phosphite-phosphoroamidite ligand library **L1-L4a-g** was used in the allylic substitution of cyclic substrates **S5** and **S6**, the catalytic results showed that the effect of the ligand parameters on the

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enantioselectivity was different from the effect observed in the substitution of the linear substrates **S1** and **S2**. The best results were obtained with ligands **L2** and **L3**, which have either the phosphoroamidite group at C-5 position and an *R*-configuration at C-3 or the phosphoroamidite group at C-3 position and an *S*-configuration at C-3 stereocenter, while the other combinations provided lower enantioselectivity. To understand this catalytic behavior, we studied Pd-π-allyl complexes **31**-**34**, which contain ligands **L1a**, **L2a**, **L3a** and **L4a**.

The VT NMR (35 °C to –80 °C) of Pd intermediates **31**-**34**, which contains ligands **L1a**, **L2a**, **L3a** and **L4a**, showed a mixture of the two possible isomers in a ratio of 1:1.2, 1:1.2, 1:1.3 and 1.2:1, respectively (Schemes 9 and 10). All the isomers were unambiguously assigned by NOE to the *endo* **A** and *exo* **B** isomers (Figure 7). Therefore, for isomers **32A** and **34A**, the NOE indicates interactions between the H-3 of the furanoside backbone and the central allyl proton, while for isomers **32B** and **34B** this interaction appears with one of the methylene hydrogens of the allyl ligand (Figure 7a). However, for isomers **31B** and **33B**, the NOE indicates interactions between H-3 and the central allyl proton and also between H-5 and one of the methylene hydrogens of the allyl ligand (Figure 7b). For all isomers, the carbon NMR chemical shifts indicated that the most electrophilic allylic terminus carbon is *trans* to the phosphoroamidite moiety. The *in situ* NMR study of the reactivity of the Pd-intermediates with sodium malonate at low temperature showed that: (a) for complexes **32** and **33**, the most reacting isomer correspond to the major isomers **A** ($k_A/k_B > 8$); (b) for complex **34**, the most reacting isomer is **B** ($k_A/k_B \approx 1/3$) and (c) for complex **31**, both isomers reacts at a similar rate ($k_A/k_B \approx 1$). In addition, for complexes **32** and **33**, the electronic

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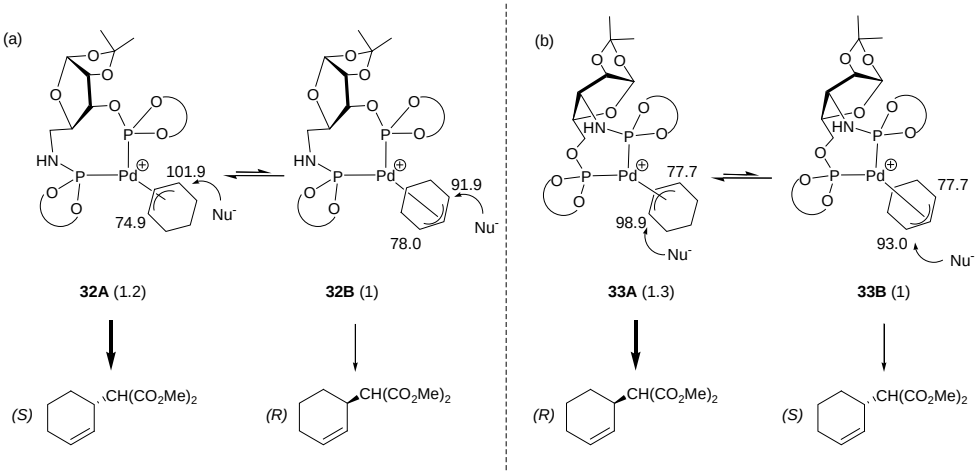
differentiation between the more electrophilic allylic terminus carbon atoms of both isomers (**A** and **B**) ($\Delta(\delta^{13}C) \approx 10$ and 5.9 ppm, respectively) are higher than in complexes **34** and **31** ($\Delta(\delta^{13}C) \approx 3.2$ and 0.5 ppm, respectively). All these facts explain the highest enantioselectivity observed with complexes **32** and **33**.



Scheme 9. Diastereoisomer Pd-allyl intermediates: (a) **32** for **S5** with ligand **L2a** and (b) **33** for **S5** with ligand **L3a**. The relative amounts of each isomer are drawn in parenthesis. The chemical shifts (in ppm) of the allylic terminal carbons are shown.

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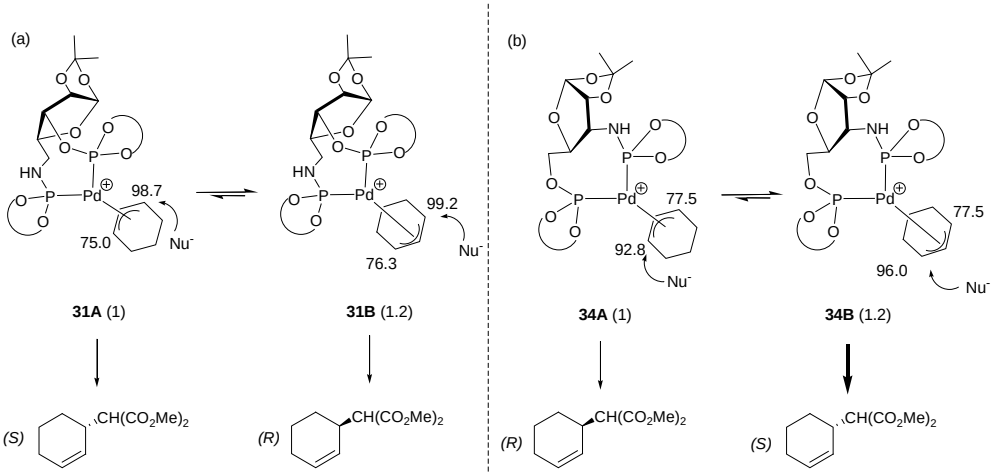

Scheme 10. Diastereoisomer Pd-allyl intermediates: (a) **31** for **S5** with ligand **L1a** and (b) **34** for **S5** with ligand **L4a**. The relative amounts of each isomer are drawn in parenthesis. The chemical shifts (in ppm) of the allylic terminal carbons are shown.

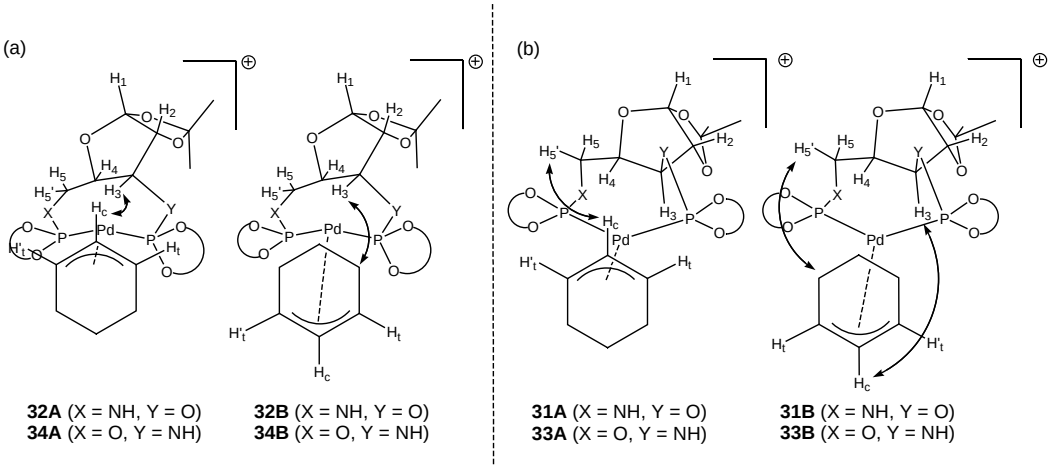

Figure 7. Relevant NOE contacts from NOESY experiment for: (a) complexes **32** and **34** and (b) complexes **31** and **33**.

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3.2.3. Conclusions

A library of furanoside phosphite-phosphoroamidite ligands **L1-L4a-g** has been synthesized for the Pd-catalyzed allylic substitution reactions of several substrates with different electronic and steric properties. These ligands have the advantage that they are prepared efficiently from commercial D-xylose and D-glucose, inexpensive natural chiral feedstocks. In addition, the π-acceptor character and flexibility of the phosphite/phosphoroamidites moieties increases reaction rates and versatility. Moreover, the modular nature of the ligand library enables the position of the phosphoroamidite group, configuration at C-3 of the furanoside backbone and the substituents/configurations in the biaryl phosphite/phosphoroamidite moieties to be easily and systematically varied, so activities and enantioselectivities can be maximized for each substrate as required. By carefully selecting the ligand components, therefore, high regio- and enantioselectivities (ee's up to 98%) and good activities (TOF's > 2000 mol substrate x (mol Pd x h)$^{-1}$), have been achieved in a broad range of mono- and disubstituted linear hindered and unhindered substrates and cyclic substrates. It should be noted that for substrates **S2**, **S5** and **S6**, both enantiomers of substitution products can be obtained with high enantioselectivities by simply changing either the absolute configuration of C-3 or the position of the phosphoroamidite group. In addition, the efficiency of this ligand design is also corroborated by the fact that these Pd-phosphite-phosphoroamidite catalysts provided higher enantioselectivity than their diphosphite analogues in several substrate types.[4b] Moreover, this ligand design allow us to overcome the drawback of moderate regioselectivities in Pd-catalyzed allylic

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substitution of monosubsituted substrates **S3** and **S4** using 1,2-aminoalcohol-based phosphite-phosphoroamidite ligands, which has recently emerged as a one of the most successful catalyst type developed for this process.[3b] These results open up the allylic substitution of a wide range of substrates to the potential effective use of readily available and highly modular sugar-based phosphite-phosphoroamidite ligands.

Study of the Pd-1,3-diphenyl, 1,3-dimethyl and 1,3-cyclohexenyl allyl intermediates by NMR spectroscopy makes it possible to understand the catalytic behavior observed. Therefore, for enantioselectivities to be high, the position of the phosphoroamidite group, absolute configuration of C-3 and the substituents/configurations of the biaryl moieties need to be correctly combined in order to increase the electronic differentiation between the most electrophilic allylic terminus carbon atoms of the isomers formed and/or also form predominantly the isomer that reacts faster with the nucleophile. It also indicates that the nucleophilic attack takes place predominantly at the allylic terminal carbon atom located *trans* to the phosphoroamidite moiety.

3.2.4. Experimental Section

3.2.4.1. General Considerations.

All reactions were carried out using standard Schlenk techniques under an atmosphere of argon. Solvents were purified and dried by standard procedures. Phosphorochloridites are easily prepared in one step from the corresponding biaryls.[28] Phosphite-phosphoroamidite ligands **L1-L2a-c** were prepared as previously described.[29] Compounds **3**,[7] **4-5**,[10] **6-7**,[12] **8**,[8] **9**,[11] **10**,[13] **12-13**[9] and **14**[14] have been previously prepared.

ISBN:978-84-692-9762-9/DL:T-202-2010

Racemic substrates **S1-S6** were prepared as previously reported.[30,31,32,33] $[Pd(\eta^3\text{-}1,3\text{-}Ph_2\text{-}C_3H_3)(\mu\text{–}Cl)]_2$,[34] $[Pd(\eta^3\text{-}1,3\text{-}Me_2\text{-}C_3H_3)(\mu\text{–}Cl)]_2$[35] and $[Pd(\eta^3\text{-cyclohexenyl})(\mu\text{–}Cl)]_2$[36] were prepared as previously described. ^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 done based on ^1H-^1H gCOSY, ^1H-^{13}C gHSQC and ^1H-^{31}P gHMBC experiments.

3.2.4.2. General synthesis of aminoalcohols 11 and 15.

The corresponding crude aldehyde **10** or **14** (3 g, 14 mmol) was taken up in 200 mL of water. Sodium borohydride (3.6 g, 95 mmol) was added in several portions and the mixture was stirred at 25 ºC for 16 h. The mixture was extracted with dicloromethane (3 x 25 mL). The dried extract was evaporated and purified by flash chromatography (dicloromethane: acetone, 9:2) to give the corresponding azido-alcohols as white solids. 3-azido-3-deoxy-5-*O*-acetyl-1,2-*O*-isopropylidene-α-D-xylofuranose (2.8 g, 93% yield). ^1H NMR, δ: 1.36 (s, 3H, CH_3), 1.57 (s, 3H, CH_3), 1.98 (s, 1H), 3.61 (m, 1H), 3.70 (m, 1H), 3.98 (m, 1H), 4.14 (m, 1H), 4.75 (m, 1H), 5.81 (d, 1H, J = 4.2 Hz). 3-azido-3-deoxy-5-*O*-acetyl-1,2-*O*-isopropylidene-α-D-ribofuranose (1.7 g, 58% yield). ^1H NMR, δ: 1.52 (s, 3H, CH_3), 1.75 (s, 3H, CH_3), 2.1 (s, 1H), 3.84 (m, 1H), 3.93 (m, 1H), 4.03 (d, 1H), 4.36 (m, 1H), 4.68 (d, 1H), 5.93 (d, 1H, J = 4.2 Hz).

The corresponding azido-alcohol (2 g, 9 mmol) was dissolved in a mixture of tetrahydrofuran:water (50 mL, 4:1). Triphenylphosphine (5.4 g, 19 mmol) was then added and the mixture was stirred at room

ISBN:978-84-692-9762-9/DL:T-202-2010

temperature overnight. Then, tetrahydrofuran was removed by evaporation in vacuo and the residue extracted twice with diethyl ether. The aqueous phase was concentrated in vacuo to give the corresponding aminoalcohols as white solids: **11** (1.5 g, 88% yield). ^{1}H NMR, δ: 1.29 (s, 3H, CH_3), 1.48 (s, 3H, CH_3), 1.98 (s, 3H), 3.14 (m, 1H), 3.77 (m, 1H), 3.83 (m, 2H), 4.41 (m, 1H), 5.73 (d, 1H, J = 3.6 Hz). **15** (1.5 g, 88%). ^{1}H NMR, δ: 1.29 (s, 3H, CH_3), 1.50 (s, 3H, CH_3), 2.02 (s, 3H), 3.50 (m, 1H), 3.92 (m, 2H), 4.24 (m, 1H), 4.41 (m, 1H), 5.95 (d, 1H, J = 4.0 Hz).

3.2.4.3. General procedure for the preparation of phosphite-phosphoroamidite ligands L1-L4a-g.

Phosphorochloridite (2.2 mmol) produced *in situ* was dissolved in toluene (5 mL) and pyridine (0.36 mL, 4.6 mmol) was added. Amino-alcohol (1 mmol) was azeotropically dried with toluene (3 x 1 mL) and then dissolved in toluene (10 mL), to which pyridine (0.36 mL, 4.6 mmol) was added. The amino-alcohol solution was transferred slowly at 0 ºC to the solution of phosphorochloridite. The reaction mixture was warmed up to 80 ºC and stirred overnight, and the pyridine salts were removed by filtration. Evaporation of the solvent gave a white foam, which was purified by flash chromatography (toluene/NEt_3 = 100/1) to produce the corresponding ligand as white powder.

L1d: Yield: 0.30 g, 42 %. ^{31}P NMR (C_6D_6), δ: 135.3 (s), 145.1 (s). ^{1}H NMR (C_6D_6), δ: 1.07 (s, 3H, CH_3), 1.21 (s, 3H, CH_3), 2.08 (s, 3H, CH_3), 2.10 (s, 6H, CH_3), 2.11 (s, 3H, CH_3), 2.20 (s, 3H, CH_3), 2.26 (s, 3H, CH_3), 2.29 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 3.08 (m, 1H, NH), 3.29 (m, 2H, H-5 and H-5'), 4.03 (m, 1H, H-4), 4.45 (d, 1H, H-2, $^{3}J_{2\text{-}1}$ = 4.0 Hz), 4.53 (m, 1H, H-3), 5.74 (d, 1H, H-1, $^{3}J_{1\text{-}2}$ = 4.0 Hz), 6.8-7.2 (m, 8H,

ISBN:978-84-692-9762-9/DL:T-202-2010

CH=). ^{13}C NMR (C_6D_6), δ: 17.4 (CH_3), 17.7 (CH_3), 17.9 (CH_3), 21.1 (CH_3), 26.3 (CH_3), 27.9 (CH_3), 28.1 (CH_3), 58.5 (m, C-3), 64.1 (C-5), 79.5 (C-4), 86.8 (C-2), 105.1 (C-1), 112.1 (CMe_2), 126.0 (CH=), 128.9 (CH=), 129.7 (CH=), 130.3 (C), 130.4 (C), 130.5 (C), 131.6 (CH=), 131.8 (CH=), 132.3 (CH=), 133.8 (C), 134.1 (C), 134.3 (C), 147.1 (C), 147.2 (C), 147.3 (C), 147.5 (C). Anal. calcd (%) for $C_{40}H_{45}NO_8P_2$: C 65.84, H 6.22, N 1.92; found: C 65.81, H 6.26, N 1.90.

L1e: Yield: 0.32 g, 41 %. ^{31}P NMR (C_6D_6), δ: 141.3 (s), 146.1 (s). ^{1}H NMR (C_6D_6), δ: 0.98 (s, 3H, CH_3), 1.29 (s, 3H, CH_3), 3.11 (m, 1H, NH), 3.25 (m, 2H, H-5 and H-5'), 3.33-3.62 (m, 8H, CH_2), 4.11 (m, 1H, H-4), 4.37 (d, 1H, H-2, $^3J_{2\text{-}1}$ = 4.0 Hz), 4.50 (m, 1H, H-3), 4.99 (m, 8H, CH_2=), 5.72 (d, 1H, H-1, $^3J_{1\text{-}2}$ = 4.0 Hz), 5.91 (m, 4H, CH=), 6.8-7.2 (m, 12H, CH=). ^{13}C NMR (C_6D_6), δ: 26.0 (CH_3), 26.7 (CH_3), 34.6 (CH_2), 34.7 (CH_2), 34.9 (CH_2), 39.5 (d, C-5, $J_{C\text{-}P}$ = 15.2 Hz), 77.4 (C-3), 80.9 (C-4), 84.9 (C-2), 105.0 (C-1), 111.6 (CMe_2), 115.8 (CH_2=), 116.0 (CH_2=), 116.3 (CH_2=), 116.8 (CH_2=), 124.4 (CH=), 125.2 (CH=), 128.4 (CH=), 128.6 (CH=), 129.4 (CH=), 129.5 (CH=), 130.3 (CH=), 130.5 (CH=), 131.4 (C), 131.9 (C), 132.1 (C), 132.4 (C), 132.5 (C), 136.2 (CH= allyl), 136.8 (CH= allyl), 136.9 (CH= allyl), 147.8 (C), 149.0 (C), 149.3 (C). Anal. calcd (%) for $C_{44}H_{45}NO_8P_2$: C 67.95, H 5.83, N 1.80; found: C 68.02, H 5.87, N 1.82.

L1f: Yield: 0.39 g, 35 %. ^{31}P NMR (C_6D_6), δ: 146.5 (s), 148.4 (s). ^{1}H NMR (C_6D_6), δ: 0.06 (s, 9H, $SiCH_3$), 0.39 (s, 9H, $SiCH_3$), 0.52 (s, 9H, $SiCH_3$), 0.54 (s, 9H, $SiCH_3$), 0.91 (s, 3H, CH_3), 1.21 (s, 3H, CH_3), 2.84 (m, 1H, H-5'), 3.01 (m, 1H, H-5), 3.33 (m, 1H, N-H), 4.53 (m, 1H, H-4), 4.70 (d, 1H, H-2, $^3J_{1\text{-}2}$ = 3.6 Hz), 4.87 (dd, 1H, H-3, $^3J_{3\text{-}4}$ = 2.8 Hz, $^2J_{P\text{-}H}$ = 11.2 Hz), 5.84 (d, 1H, H-1, $^3J_{1\text{-}2}$ = 3.6 Hz), 6.7-8.2 (m, 20H, CH=). ^{13}C

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NMR (C_6D_6), δ: 0.1 ($SiCH_3$), 0.6 ($SiCH_3$), 0.9 ($SiCH_3$), 1.0 ($SiCH_3$), 26.5 (CH_3), 27.1 (CH_3), 39.8 (d, C-5, $^2J_{C\text{-}P}$ = 5.3 Hz), 78.5 (d, C-3, $^2J_{C\text{-}P}$ = 9.1 Hz), 81.0 (C-4), 85.1 (d, C-2, $^3J_{C\text{-}P}$ = 3.0 Hz), 105.8 (C-1), 112.3 (CMe_2), 125.0 (CH=), 125.1 (CH=), 125.7 (CH=), 127.2 (CH=), 127.5 (CH=), 127.6 (CH=), 127.7 (CH=), 128.8 (CH=), 128.9 (CH=), 129.2 (CH=), 131.1 (C), 131.7 (C), 131.8 (C), 132.1 (C), 132.5 (C), 134.6 (C), 134.9 (C), 135.0 (C),.137.6 (CH=), 137.7 (CH=), 138.2 (CH=), 138.3 (CH=), 138.6 (CH=), 151.0 (C), 152.4 (C), 153.7 (C), 154.2 (C). Anal. calcd (%) for $C_{60}H_{69}NO_8P_2Si_4$: C 65.13, H 6.29, N 1.27; found: C 65.07, H 6.28, N 1.29.

L1g: Yield: 0.42 g, 38 %. ^{31}P NMR (C_6D_6), δ: 145.3 (s), 149.5 (s). ^{1}H NMR (C_6D_6), δ: 0.20 (s, 9H, $SiCH_3$), 0.52 (s, 9H, $SiCH_3$), 0.54 (s, 9H, $SiCH_3$), 0.55 (s, 3H, CH_3), 0.57 (s, 9H, $SiCH_3$), 1.28 (s, 3H, CH_3), 3.24 (m, 3H, H-5, H-5', N-H), 3.51 (d, 1H, H-2, $^3J_{2\text{-}1}$ = 3.6 Hz), 4.20 (m, 1H, H-4), 4.65 (dd, 1H, H-3, $^3J_{3\text{-}4}$ = 3.2 Hz, $^2J_{3\text{-}P}$ = 7.6 Hz), 5.65 (d, 1H, H-1, $^3J_{1\text{-}2}$ = 3.6 Hz), 6.9-8.2 (m, 20H, CH=). ^{13}C NMR (C_6D_6), δ: 0.4 ($SiCH_3$), 0.6 (CH_3, $SiMe_3$), 0.7 ($SiCH_3$), 0.8 ($SiCH_3$), 25.7 (CH_3), 27.0 (CH_3), 40.5 (d, C-5, $^2J_{C\text{-}P}$ = 12.9 Hz), 77.7 (d, C-3, $^2J_{C\text{-}P}$ = 4.5 Hz), 81.9 (C-4), 84.9 (C-2), 105.5 (C-1), 111.6 (CMe_2), 125.1 (CH=), 125.2 (CH=), 125.6 (CH=), 126.0 (CH=), 127.1 (CH=), 127.3 (CH=), 127.5 (CH=), 128.8 (CH=), 129.1 (CH=), 129.6 (CH=), 131.4 (C), 131.6 (C), 131.8 (C), 131.9 (C), 132.9 (C), 133.0 (C), 134.9 (C), 135.0 (C), 137.3 (CH=), 137.7 (CH=), 137.9 (CH=), 152.0 (C), 152.6 (C), 153.2 (C), 154.5 (C). Anal. calcd (%) for $C_{60}H_{69}NO_8P_2Si_4$: C 65.13, H 6.29, N 1.27; found: C 65.11, H 6.29, N 1.24.

L2d: Yield: 0.42 g, 57 %. ^{31}P NMR (C_6D_6), δ: 136.9 (s), 144.9 (s). ^{1}H NMR (C_6D_6), δ: 1.04 (s, 3H, CH_3), 1.27 (s, 3H, CH_3), 2.07 (s, 3H,

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CH_3), 2.11 (s, 6H, CH_3), 2.19 (s, 6H, CH_3), 2.28 (s, 3H, CH_3), 2.29 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 2.95 (m, 1H, NH), 3.69 (m, 1H, H-3), 4.13 (m, 1H, H-5'), 4.22 (m, 2H, H-4, H-5), 4.35 (m, 1H, H-2), 5.52 (d, 1H, H-1, $^3J_{1-2}$ = 4.0 Hz), 6.8-7.2 (m, 8H, CH=). ^{13}C NMR (C_6D_6), δ: 17.1 (CH_3), 17.2 (CH_3), 17.3 (CH_3), 21.2 (CH_3), 26.8 (CH_3), 27.2 (CH_3), 40.4 (m, C-5), 68.9 (C-3), 76.3 (C-4), 78.4 (C-2), 104.2 (C-1), 111.1 (CMe_2), 126.0 (CH=), 128.9 (CH=), 129.7 (CH=), 130.3 (C), 130.2 (C), 130.5 (C), 131.6 (CH=), 131.9 (CH=), 132.5 (CH=), 133.8 (C), 134.1 (C), 134.3 (C), 147.1 (C), 147.2 (C), 147.3 (C), 147.5 (C). Anal. calcd (%) for $C_{40}H_{45}NO_8P_2$: C 65.84, H 6.22, N 1.92; found: C 65.88, H 6.24, N 1.89.

L2e: Yield: 0.33 g, 43 %. ^{31}P NMR (C_6D_6), δ: 139.8 (s), 143.3 (s). ^{1}H NMR (C_6D_6), δ: 1.12 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 2.94 (m, 1H, NH), 3.13 (m, 1H, H-5), 3.25 (m, 1H, H-5'), 3.32-3.64 (b, 8H, CH_2), 4.02 (m, 3H, H-2, H-3, H-4), 5.03 (m, 8H, CH_2=), 5.27 (d, 1H, H-1, $^3J_{1-2}$ = 4.2 Hz), 5.92 (m, 4H, CH=), 6.8-7.2 (m, 12H, CH=). ^{13}C NMR (C_6D_6), δ: 26.6 (CH_3), 26.9 (CH_3), 34.2 (CH_2), 34.4 (CH_2), 34.6 (CH_2), 34.9 (CH_2), 40.3 (m, C-5, J_{C-P} = 15.2 Hz), 69.3 (C-3), 75.3 (C-4), 79.4 (C-2), 103.2 (C-1), 112.3 (CMe_2), 115.8 (CH_2=), 116.0 (CH_2=), 116.2 (CH_2=), 116.4 (CH_2=), 124.0 (CH=), 124.5 (CH=), 128.2 (CH=) 128.4 (CH=), 129.1 (CH=), 129.3 (CH=), 129.9 (CH=), 130.0 (CH=), 131.2 (C), 131.4 (C), 131.8 (C), 131.9 (C), 132.3 (C), 135.4 (CH= allyl), 135.6 (CH= allyl), 135.7 (CH= allyl), 135.9 (CH= allyl), 147.7 (C), 149.1 (C), 149.2 (C). Anal. calcd (%) for $C_{44}H_{45}NO_8P_2$: C 67.95, H 5.83, N 1.80; found: C 68.01, H 5.81, N 1.82.

L2f: Yield: 0.34 g, 31 %. ^{31}P NMR (C_6D_6), δ: 142.2 (s), 150.2 (s). ^{1}H NMR (C_6D_6), δ: 0.34 (s, 9H, $SiCH_3$), 0.51 (s, 9H, $SiCH_3$), 0.52 (s, 9H, $SiCH_3$), 0.54 (s, 9H, $SiCH_3$), 0.99 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 3.03

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(m, 1H, H-5'), 3.21 (m, 1H, H-5), 3.26 (m, 2H, H-2, N-H), 4.07 (m, 1H, H-4), 4.21 (m, 1H, H-3), 4.95 (d, 1H, H-1, $^{3}J_{1-2}$ = 3.6 Hz), 6.9-8.2 (m, 20H, CH=). ^{13}C NMR (C_6D_6), δ: 0.7 ($SiCH_3$), 0.8 ($SiCH_3$), 26.6 (CH_3), 27.2 (CH_3), 42.3 (d, C-5, $^{2}J_{C-P}$ = 5.3 Hz), 73.8 (C-3), 78.7 (C-4), 79.2 (C-2), 103.9 (C-1), 113.1 (CMe_2), 125.1 (CH=), 125.2 (CH=), 125.5 (CH=), 127.1 (CH=), 127.3 (CH=), 127.4 (CH=), 127.5 (CH=), 127,6 (CH=), 128.7 (CH=), 129.1 (CH=), 129.2 (CH=), 129.6 (CH=), 131.4 (C), 131.8 (C), 132.6 (C), 132.9 (C), 133.0 (C), 133.8 (C), 134.5 (C), 134.9 (C), 136.9 (CH=), 137.6 (CH=), 137.7 (CH=), 137.9 (CH=), 152.3 (C), 153.2 (C), 154.5 (C), 154.8 (C). Anal. calcd (%) for $C_{60}H_{69}NO_8P_2Si_4$: C 65.13, H 6.29, N 1.27; found: C 65.24, H 6.21, N 1.28.

L2g: Yield: 0.12 g, 11 %.^{31}P NMR (C_6D_6), δ: 141.7 (br). ^{1}H NMR (C_6D_6), δ: 0.33 (s, 9H, $SiCH_3$), 0.46 (s, 9H, $SiCH_3$), 0.57 (s, 9H, $SiCH_3$), 0.59 (s, 9H, $SiCH_3$), 1.14 (s, 3H, CH_3), 1.50 (s, 3H, CH_3), 2.43 (m, 2H, H-5', NH), 3.22 (m, 1H, H-5), 3.65 (m, 1H, H-3), 4.43 (m, 1H, H-2), 4.81 (m, 1H, H-4), 5.29 (d, 1H, H-1, $^{3}J_{1-2}$ = 4.0 Hz), 6.6-8.4 (m, 20H, CH=). ^{13}C NMR (C_6D_6), δ: 0.0 ($SiCH_3$), 0.3 ($SiCH_3$), 0.5 ($SiCH_3$), 1.0 ($SiCH_3$), 27.4 (CH_3), 27.7 (CH_3), 42.1 (m, C-5), 77.2 (C-3), 77.9 (C-4), 79.3 (C-2), 105.1 (C-1), 114.0 (CMe_2), 124.0 (CH=), 124.2 (CH=), 124.3 (CH=), 126.2 (CH=), 126.3 (CH=), 126.5 (CH=), 127.4 (CH=), 127,6 (CH=), 127.8 (CH=), 127.9 (CH=), 128.8 (CH=), 129.0 (CH=), 129.2 (CH=), 129.6 (CH=), 130.0 (C), 130.2 (C), 130.3 (C), 134.2 (C), 134.3 (C), 134.5 (C), 135.1 (C), 138.4 (CH=), 138.5 (CH=), 138.7 (CH=), 152.5 (C), 152.7 (C), 152.9 (C). Anal. calcd (%) for $C_{60}H_{69}NO_8P_2Si_4$: C 65.13, H 6.29, N 1.27; found: C 64.99, H 6.32, N 1.22.

L3a: Yield: 0.54 g, 51 %. ^{31}P NMR (C_6D_6), δ: 142.9 (s), 147.5 (s). ^{1}H NMR (C_6D_6), δ: 1.09 (s, 3H, CH_3), 1.27 (s, 9H, CH_3, ^{t}Bu), 1.28 (s, 9H,

ISBN:978-84-692-9762-9/DL:T-202-2010

CH_3, ^{t}Bu), 1.29 (s, 9H, CH_3, ^{t}Bu), 1.30 (s, 9H, CH_3, ^{t}Bu), 1.32 (s, 3H, CH_3), 1.53 (s, 9H, CH_3, ^{t}Bu), 1.57 (s, 9H, CH_3, ^{t}Bu), 1.60 (s, 9H, CH_3, ^{t}Bu), 1.64 (s, 9H, CH_3, ^{t}Bu), 2.96 (m, 1H, NH), 3.90 (m, 1H, H-3), 4.19 (m, 1H, H-5), 4.24 (m, 1H, H-5'), 4.32 (m, 1H, H-4), 4.35 (d, 1H, H-2, $^3J_{2\text{-}1}$ = 3.2 Hz), 5.67 (d, 1H, H-1, $^3J_{1\text{-}2}$ = 3.2 Hz), 7.0-7.7 (m, 8H, CH=). ^{13}C NMR (C_6D_6), δ: 26.9 (CH_3), 27.3 (CH_3), 31.7 (CH_3, ^{t}Bu), 31.8 (CH_3, ^{t}Bu), 31.9 (CH_3, ^{t}Bu), 32.0 (CH_3, ^{t}Bu), 32.1 (CH_3, ^{t}Bu), 32.2 (CH_3, ^{t}Bu), 35.0 (C, ^{t}Bu), 35.1 (C, ^{t}Bu), 36.0 (C, ^{t}Bu), 36.1 (C, ^{t}Bu), 58.0 (d, C-3, $J_{C\text{-}P}$ = 7.5 Hz), 64.3 (d, C-5, $J_{C\text{-}P}$ = 9.9 Hz), 79.5 (C-4), 86.6 (d, C-2, $J_{C\text{-}P}$ = 5.3 Hz), 104.9 (C-1), 111.9 (CMe_2), 124.5 (CH=), 124.7 (CH=), 124.8 (CH=), 127.5 (CH=), 128.9 (CH=), 129.6 (CH=), 134.0 (C), 134.1 (C), 134.3 (C), 140.5 (C), 140.9 (C), 141.0 (C), 141.1 (C), 146.9 (C), 147.1 (C), 147.4 (C). Anal. calcd (%) for $C_{64}H_{93}NO_8P_2$: C 72.08, H 8.79, N 1.31; found: C 72.45, H 8.83, N 1.29.

L3b: Yield: 0.44 g, 45 %. ^{31}P NMR (C_6D_6), δ: 140.3 (s), 148.0 (s). ^{1}H NMR (C_6D_6), δ: 1.12 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 1.46 (s, 9H, CH_3, ^{t}Bu), 1.49 (s, 9H, CH_3, ^{t}Bu), 1.51 (s, 9H, CH_3, ^{t}Bu), 1.54 (s, 9H, CH_3, ^{t}Bu), 3.18 (m, 1H, NH), 3.32 (s, 3H, CH_3-O), 3.34 (s, 6H, CH_3-O), 3.37 (s, 3H, CH_3-O), 4.00 (m, 1H, H-3), 4.27 (m, 2H, H-5 and H-5'), 4.34 (d, 1H, H-2, $^3J_{2\text{-}1}$ = 3.6 Hz), 4.42 (m, 1H, H-4), 5.80 (d, 1H, H-1, $^3J_{1\text{-}2}$ = 3.6 Hz), 6.6-7.2 (m, 8H, CH=). ^{13}C NMR (C_6D_6), δ: 26.7 (CH_3), 27.3 (CH_3), 31.4 (CH_3, ^{t}Bu), 31.5 (CH_3, ^{t}Bu), 31.6 (CH_3, ^{t}Bu), 31.7 (CH_3, ^{t}Bu), 35.7 (C, ^{t}Bu), 35.8 (C, ^{t}Bu), 35.9 (C, ^{t}Bu), 36.0 (C, ^{t}Bu), 55.4 (CH_3-O), 55.5 (CH_3-O), 58.4 (d, C-3, $J_{C\text{-}P}$ = 6.0 Hz), 63.9 (d, C-5, $J_{C\text{-}P}$ = 6.1 Hz), 79.6 (C-4), 86.6 (d, C-2, $J_{C\text{-}P}$ = 6.1 Hz), 105.1 (C-1), 112.0 (CMe_2), 113.3 (CH=), 113.6 (CH=), 113.8 (CH=), 114.9 (CH=), 115.2 (CH=), 126.0 (CH=), 128.0 (CH=), 128.8 (CH=), 134.6 (C), 134.7 (C), 134.8 (C), 142.7

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(C), 142.9 (C), 143.0 (C), 156.6 (C), 156.7 (C), 156.8 (C). Anal. calcd (%) for $C_{52}H_{69}NO_{12}P_2$: C 64.92, H 7.23, N 1.46; found: C 65.02, H 7.33, N 1.52.

L3c: Yield: 0.49 g, 54 %. ^{31}P NMR (C_6D_6), δ: 138.5 (s), 149.7 (s). ^{1}H NMR (C_6D_6), δ: 0.33 (s, 9H, CH_3-Si), 0.35 (s, 9H, CH_3-Si), 0.38 (s, 9H, CH_3-Si), 0.40 (s, 9H, CH_3-Si), 1.06 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 3.21 (m, 1H, NH), 3.95 (m, 1H, H-3), 4.18 (m, 2H, H-5 and H-5'), 4.35 (m, 1H, H-4), 4.41 (d, 1H, H-2, $^{3}J_{2\text{-}1}$ = 3.6 Hz), 5.87 (d, 1H, H-1, $^{3}J_{1\text{-}2}$ = 3.6 Hz), 6.9-7.4 (m, 12H, CH=). ^{13}C NMR (C_6D_6), δ: 0.45 (CH_3-Si), 0.63 (CH_3-Si), 0.67 (CH_3-Si), 0.73 (CH_3-Si), 26.8 (CH_3), 27.2 (CH_3), 58.5 (d, C-3, $J_{C\text{-}P}$ = 3.1 Hz), 63.7 (C-5), 79.2 (C-4), 86.4 (d, C-2, $J_{C\text{-}P}$ = 8.7 Hz), 105.1 (C-1), 112.1 (CMe_2), 125.1 (CH=), 125.5 (CH=), 128.8 (CH=), 131.7 (C), 131.8 (C), 132.0 (C), 132.5 (CH=), 132.9 (CH=), 133.0 (CH=), 135.7 (CH=), 135.9 (CH=), 155.1 (C), 155.2 (C), 156.0 (C), 156.1 (C). Anal. calcd (%) for $C_{44}H_{61}NO_8P_2Si_4$: C 58.31, H 6.78, N 1.55; found: C 58.55, H 6.81, N 1.59.

L3d: Yield: 0.42 g, 57 %. ^{31}P NMR (C_6D_6), δ: 136.7 (s), 144.2 (s). ^{1}H NMR (C_6D_6), δ: 1.04 (s, 3H, CH_3), 1.26 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 2.07 (s, 6H, CH_3), 2.08 (s, 3H, CH_3), 2.18 (s, 3H, CH_3), 2.28 (s, 3H, CH_3), 2.29 (s, 6H, CH_3), 2.32 (s, 3H, CH_3), 3.03 (m, 1H, NH), 3.79 (m, 1H, H-3), 4.16 (m, 1H, H-5), 4.23 (m, 2H, H-4, H-5'), 4.32 (d, 1H, H-2, $^{3}J_{1\text{-}2}$ = 4.0 Hz), 5.59 (d, 1H, H-1, $^{3}J_{1\text{-}2}$ = 4.0 Hz), 6.7-7.2 (m, 8H, CH=). ^{13}C NMR (C_6D_6), δ: 17.1 (CH_3), 17.2 (CH_3), 17.3 (CH_3), 21.2 (CH_3), 26.8 (CH_3), 27.2 (CH_3), 58.2 (d, C-3, $J_{C\text{-}P}$ = 6.8 Hz), 63.8 (C-5), 79.3 (C-4), 87.0 (C-2), 105.0 (C-1), 112.1 (CMe_2), 126.0 (CH=), 128.9 (CH=), 129.7 (CH=),130.3 (C), 130.4 (C), 130.5 (C), 131.6 (CH=), 131.8 (CH=), 132.3 (CH=), 133.8 (C), 134.1 (C), 134.3 (C), 147.1 (C), 147.2 (C), 147.3 (C),

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147.5 (C). Anal. calcd (%) for $C_{40}H_{45}NO_8P_2$: C 65.84, H 6.22, N 1.92; found: C 65.76, H 6.19, N 1.90.

L3e: Yield: 0.39 g, 50 %. ^{31}P NMR (C_6D_6), δ: 142.3 (s), 145.2 (s). ^{1}H NMR (C_6D_6), δ: 1.04 (s, 3H, CH_3), 1.25 (s, 3H, CH_3), 3.11 (m, 1H, NH), 3.43 (m, 1H, H-3), 3.58 (m, 5H, H-4, CH_2), 4.08 (m, 1H, H-5), 4.19 (m, 2H, H-4, H-5'), 4.42 (d, 1H, H-2, $^{3}J_{1\text{-}2}$ = 3.6 Hz), 5.09 (m, 4H, CH_2=), 5.48 (d, 1H, H-1, $^{3}J_{1\text{-}2}$ = 3.6 Hz), 5.94 (m, 2H, CH=), 6.8-7.2 (m, 12H, CH=). ^{13}C NMR (C_6D_6), δ: 26.8 (CH_3), 27.3 (CH_3), 35.0 (CH_2), 35.1 (CH_2), 35.3 (CH_2), 35.6 (CH_2), 53.6 (d, C-3, $J_{C\text{-}P}$ = 7.2 Hz), 63.9 (d, C-5, $J_{C\text{-}P}$ = 3.6 Hz), 80.6 (C-4), 85.6 (C-2), 104.9 (C-1), 112.5 (CMe_2), 116.7 (CH_2=), 116.8 (CH_2=), 125.6 (CH=), 125.9 (CH=), 129.0 (CH=), 129.4 (CH=), 129.6 (CH=), 130.3 (CH=), 132.6 (C), 132.8 (C), 133.2 (C), 136.9 (CH= allyl), 137.7 (CH= allyl), 137.9 (CH= allyl), 138.1 (CH= allyl), 148.7 (C), 149.1 (C), 149.3 (C). Anal. calcd (%) for $C_{44}H_{45}NO_8P_2$: C 67.95, H 5.83, N 1.80; found: C 67.99, H 5.86, N 1.81.

L4a: Yield: 0.37 g, 34 %. ^{31}P NMR (C_6D_6), δ: 145.3 (s), 149.9 (s). ^{1}H NMR (C_6D_6), δ: 1.10 (s, 3H, CH_3), 1.25 (s, 9H, CH_3, ^{t}Bu), 1.27 (s, 18H, CH_3, ^{t}Bu), 1.28 (s, 12H, CH_3 and CH_3, ^{t}Bu), 1.56 (s, 9H, CH_3, ^{t}Bu), 1.57 (s, 9H, CH_3, ^{t}Bu), 1.61 (s, 9H, CH_3, ^{t}Bu), 1.68 (s, 9H, CH_3, ^{t}Bu), 3.09 (m, 1H, NH), 3.49 (m, 1H, H-2), 3.56 (m, 1H, H-3), 3.77 (m, 1H, H-4), 4.00 (m, 1H, H-5), 4.41 (m, 1H, H-5'), 5.53 (d, 1H, H-1, $^{3}J_{1\text{-}2}$ = 3.6 Hz), 7.0-7.6 (m, 8H, CH=). ^{13}C NMR (C_6D_6), δ: 26.3 (CH_3), 26.7 (CH_3), 31.3 (CH_3, ^{t}Bu), 31.5 (CH_3, ^{t}Bu), 31.6 (CH_3, ^{t}Bu), 31.7 (CH_3, ^{t}Bu), 34.5 (C, ^{t}Bu), 35.4 (C, ^{t}Bu), 35.5 (C, ^{t}Bu), 35.6 (C, ^{t}Bu), 53.8 (d, C-3, $J_{C\text{-}P}$ = 9.8 Hz), 64.5 (d, C-5, $J_{C\text{-}P}$ = 10.6 Hz), 79.8 (C-4), 80.5 (m, C-2), 104.0 (C-1), 111.8 (CMe_2), 123.9 (CH=), 124.1 CH=), 124.4 (CH=), 126.3 (CH=), 126.8 (CH=), 126.9 (CH=), 127.3 (CH=), 128.4 (CH=), 133.6 (C), 133.8

(C), 133.9 (C), 140.4 (C), 140.7 (C), 140.8 (C), 146.3 (C), 146.4 (C), 146.5 (C). nal. calcd (%) for $C_{64}H_{93}NO_8P_2$: C 72.08, H 8.79, N 1.31; found: C 72.66, H 8.92, N 1.33.

L4b: Yield: 0.37 g, 38 %. ^{31}P NMR (C_6D_6), δ: 144.7 (s), 149.2 (s). ^{1}H NMR (C_6D_6), δ: 1.07 (s, 3H, CH_3), 1.25 (s, 3H, CH_3), 1.51 (s, 9H, CH_3, ^{t}Bu), 1.52 (s, 9H, CH_3, ^{t}Bu), 1.55 (s, 9H, CH_3, ^{t}Bu), 1.58 (s, 9H, CH_3, ^{t}Bu), 3.28 (m, 1H, NH), 3.31 (s, 9H, CH_3-O), 3.34 (s, 9H, CH_3-O), 3.68 (m, 1H, H-3), 3.82 (m, 2H, H-2 and H-3), 4.12 (m, 1H, H-5), 4.49 (m, 1H, H-5'), 5.57 (d, 1H, H-1, $^3J_{1\text{-}2}$ = 3.6 Hz), 6.6-7.2 (m, 8H, CH=). ^{13}C NMR (C_6D_6), δ: 26.7 (CH_3), 27.1 (CH_3), 31.5 (CH_3, ^{t}Bu), 31.6 (CH_3, ^{t}Bu), 31.7 (CH_3, ^{t}Bu), 31.8 (CH_3, ^{t}Bu), 35.7 (C, ^{t}Bu), 35.8 (C, ^{t}Bu), 35.9 (C, ^{t}Bu), 36.0 (C, ^{t}Bu), 54.3 (d, C-3, $J_{C\text{-}P}$ = 15.1 Hz), 55.4 (CH_3-O), 55.5 (CH_3-O), 64.2 (d, C-5, $J_{C\text{-}P}$ = 10.6 Hz), 80.4 (C-4), 81.2 (m, C-2), 104.6 (C-1), 112.3 (CMe_2), 113.2 (CH=), 113.6 (CH=), 113.7 (CH=), 113.9 (CH=), 114.9 CH=), 115.0 (CH=), 115.1 (CH=), 126.0 (CH=), 128.0 (CH=), 128.9 (CH=), 134.6 (C), 134.7 (C), 134.8 (C), 135.0 (C), 143.1 (C), 143.2 (C), 143.3 (C), 156.6 (C), 156.7 (C). Anal. calcd (%) for $C_{52}H_{69}NO_{12}P_2$: C 64.92, H 7.23, N 1.46; found: C 65.11, H 7.29, N 1.42.

L4c: Yield: 0.39 g, 43 %. ^{31}P NMR (C_6D_6), δ: 143.7 (s), 149.8 (s). ^{1}H NMR (C_6D_6), δ: 0.31 (s, 9H, CH_3-Si), 0.32 (s, 9H, CH_3-Si), 0.37 (s, 9H, CH_3-Si), 0.40 (s, 9H, CH_3-Si), 1.03 (s, 3H, CH_3), 1.25 (s, 3H, CH_3), 3.15 (m, 1H, NH), 3.24 (m, 1H, H-3), 3.50 (m, 1H, H-2), 3.79 (m, 2H, H-4 and H-5), 4.32 (m, 1H, H-5'), 5.41 (d, 1H, H-1, $^3J_{1\text{-}2}$ = 3.6 Hz), 6.9-7.4 (m, 12H, CH=). ^{13}C NMR (C_6D_6), δ: 0.5 (CH_3-Si), 0.6 (CH_3-Si), 0. 7 (CH_3-Si), 26.8 (CH_3), 27.1 (CH_3), 54.0 (d, C-3, $J_{C\text{-}P}$ = 2.7 Hz), 65.3 (d, C-5, $J_{C\text{-}P}$ = 4.9 Hz), 80.4 (C-4), 80.9 (m, C-2), 104.5 (C-1), 112.3 (CMe_2), 125.0 (CH=), 125.1 (CH=), 125.3 (CH=), 125.7 (CH=), 132.0 (C), 132.1

(C), 132.4 (C), 132.5 (CH=), 132.8 (CH=), 132.9 (CH=), 133.1 (CH=), 135.3 (CH=), 135.7 (CH=), 135.9 (CH=), 155.6 (C), 155.7 (C). Anal. calcd (%) for $C_{44}H_{61}NO_8P_2Si_4$: C 58.31, H 6.78, N 1.55; found: C 58.44, H 6.79, N 1.52.

L4d: Yield: 0.35 g, 49 %. ^{31}P NMR (C_6D_6), δ: 139.3 (s), 143.9 (s). ^{1}H NMR (C_6D_6), δ: 1.04 (s, 3H, CH_3), 1.21 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 2.07 (s, 3H, CH_3), 2.10 (s, 3H, CH_3), 2.11 (s, 3H, CH_3), 2.29 (s, 3H, CH_3), 2.30 (s, 6H, CH_3), 2.33 (s, 3H, CH_3), 3.35 (m, 1H, NH), 3.54 (m, 1H, H-4), 3.61 (m, 1H, H-3), 3.88 (m, 1H, H-2), 4.05 (m, 1H, H-5), 4.31 (m, 1H, H-5'), 5.43 (d, 1H, H-1, $^3J_{1\text{-}2}$ = 3.6 Hz), 6.7-7.2 (m, 8H, CH=).^{13}C NMR (C_6D_6), δ: 17.1 (CH_3), 17.2 (CH_3), 17.3 (CH_3), 17.5 (CH_3), 21.1 (CH_3), 21.2 (CH_3), 21.3 (CH_3), 26.8 (CH_3), 27.1 (CH_3), 53.4 (d, C-3, $J_{C\text{-}P}$ = 14.4 Hz), 62.6 (d, C-5, $J_{C\text{-}P}$ = 5.3 Hz), 80.8 (C-2), 81.0 (C-4), 104.8 (C-1), 112.3 (CMe_2), 126.0 (CH=), 128.7 (CH=), 128.8 (CH=), 129.6 (CH=), 130.2 (C), 130.6 (C), 130.7 (C), 131.4 (CH=), 131.6 (CH=), 131.8 (CH=), 131.9 (CH=), 132.2 (C), 132.4 (C), 133.9 (C), 134.0 (C), 146.9 (C), 147.2 (C), 147.5 (C). Anal. calcd (%) for $C_{40}H_{45}NO_8P_2$: C 65.84, H 6.22, N 1.92; found: C 65.86, H 6.24, N 1.94.

L4e: Yield: 0.29 g, 39 %. ^{31}P NMR (C_6D_6), δ: 142.3 (s), 145.8 (s). ^{1}H NMR (C_6D_6), δ: 1.04 (s, 3H, CH_3), 1.20 (s, 3H, CH_3), 3.24 (m, 1H, H-3), 3.36 (m, 1H, H-4), 3.58 (m, 5H, NH, CH_2), 3.78 (m, 1H, H-2), 3.92 (m, 1H, H-5), 4.21 (m, 1H, H-5'), 5.01 (m, 4H, CH_2=), 5.42 (d, 1H, H-1, $^3J_{1\text{-}2}$ = 3.6 Hz), 5.94 (m, 2H, CH=), 6.8-7.2 (m, 12H, CH=). ^{13}C NMR (C_6D_6), δ: 26.7 (CH_3), 27.0 (CH_3), 35.1 (CH_2), 35.2 (CH_2), 35.3 (CH_2), 35.5 (CH_2), 53.6 (d, C-3, $J_{C\text{-}P}$ = 12 Hz), 63.3 (d, C-5, $J_{C\text{-}P}$ = 6.2 Hz), 80.6 (C-2 and C-4), 104.7 (C-1), 112.3 (CMe_2), 116.7 (CH_2=), 116.8 (CH_2=), 125.2 (CH=), 125.4 (CH=), 128.9 (CH=) 129.6 (CH=), 129.7 (CH=),

ISBN:978-84-692-9762-9/DL:T-202-2010

130.1 (CH=), 132.6 (C), 132.8 (C), 133.3 (C), 136.8 (CH= allyl), 137.1 (CH= allyl), 137.2 (CH= allyl), 137.3 (CH= allyl), 148.8 (C), 149.2 (C), 149.3 (C). Anal. calcd (%) for $C_{44}H_{45}NO_8P_2$: C 67.95, H 5.83, N 1.80; found: C 67.94, H 5.82, N 1.84.

L4f: Yield: 0.53 g, 49 %. ^{31}P NMR (C_6D_6), δ: 141.6 (s), 149.3 (s). ^{1}H NMR (C_6D_6), δ: 0.40 (s, 9H, CH_3-Si), 0.41 (s, 9H, CH_3-Si), 0.47 (s, 9H, CH_3-Si), 0.57 (s, 9H, CH_3-Si), 1.03 (s, 3H, CH_3), 1.25 (s, 3H, CH_3), 3.15 (m, 1H, NH), 3.38 (m, 1H, H-3), 3.58 (m, 1H, H-2), 3.89 (m, 1H, H-4), 4.13 (m, 2H, H-5, H-5'), 5.27 (d, 1H, H-1, $^3J_{1\text{-}2}$ = 3.6 Hz), 6.8-8.2 (m, 20H, CH=). ^{13}C NMR (C_6D_6), δ: 0.6 (CH_3-Si), 0.7 (CH_3-Si), 0.8 (CH_3-Si), 26.6 (CH_3), 27.0 (CH_3), 53.8 (d, C-3, $J_{C\text{-}P}$ = 8.4 Hz), 64.5 (C-5), 80.3 (C-2), 80.5 (m, C-4), 104.4 (C-1), 112.2 (CMe_2), 125.1 (CH=), 125.2 (CH=), 125.5 (CH=), 127.1 (CH=), 127.3 (CH=), 127.4 (CH=), 127.5 (CH=), 127,6 (CH=), 128.7 (CH=), 129.1 (CH=), 129.2 (CH=), 129.6 (CH=), 131.4 (C), 131.8 (C), 132.8 (C), 133.1 (C), 133.4 (C), 134.5 (C), 134.9 (C), 136.9 (CH=), 137.6 (CH=), 137.9 (CH=), 152.7 (C), 152.8 (C), 153.4 (C), 153.9 (C). Anal. calcd (%) for $C_{60}H_{69}NO_8P_2Si_4$: C 65.13, H 6.29, N 1.27; found: C 65.32, H 6.31, N 1.33.

L4g: Yield: 0.51 g, 47%. ^{31}P NMR (C_6D_6), δ: 144.3 (s), 153.1 (s). ^{1}H NMR (C_6D_6), δ: 0.34 (s, 9H, CH_3-Si), 0.46 (s, 9H, CH_3-Si), 0.55 (s, 9H, CH_3-Si), 0.57 (s, 9H, CH_3-Si), 0.95 (s, 3H, CH_3), 0.98 (s, 3H, CH_3), 3.42 (m, 2H, NH, H-3), 3.69 (m, 1H, H-4), 3.82 (m, 1H, H-5'), 4.22 (m, 1H, H-2), 4.49 (m, 1H, H-5), 5.41 (d, 1H, H-1, $^3J_{1\text{-}2}$ = 3.6 Hz), 6.8-8.2 (m, 20H, CH=). ^{13}C NMR (C_6D_6), δ: 0.0 (CH_3-Si), 0.3 (CH_3-Si), 0.6 (CH_3-Si), 26.4 (CH_3), 26.5 (CH_3), 54.6 (m, C-3), 63.9 (C-5), 79.9 (C-2), 81.0 (C-4), 104.2 (C-1), 112.0 (CMe_2), 124.8 (CH=), 125.2 (CH=), 125.5 (CH=), 126.7 (CH=), 127.0 (CH=), 127.6 (CH=), 128.4 (CH=), 128.6

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(CH=), 129.1 (CH=), 130.8 (C), 131.2 (C), 131.4 (C), 132.5 (C), 132.6 (C), 132.7 (C), 134.0 (C), 134.5 (C), 136.6 (CH=), 137.0 (CH=), 137.4 (CH=), 137.5 (CH=), 152.3 (C), 152.6 (C), 154.4 (C), 154.2 (C). Anal. calcd (%) for $C_{60}H_{69}NO_8P_2Si_4$: C 65.13, H 6.29, N 1.27; found: C 65.45, H 6.38, N 1.29.

3.2.4.4. General procedure for the preparation of [Pd(η^3-allyl)(L)]BF_4 complexes 24-34.

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, 0.5 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 adding hexane as pale yellow solids.

[Pd(η^3-1,3-diphenylallyl)(L1a)]BF_4 (24). Isomer **A** (66%): ^{31}P NMR (CD_2Cl_2, 233 K), δ: 128.6 (d, 1P, P-O, $^2J_{P\text{-}P}$ = 181.9 Hz), 133.2 (d, 1P, P-N, $^2J_{P\text{-}P}$ = 181.9 Hz). ^{1}H NMR (CD_2Cl_2, 233 K), δ: 1.15 (s, 3H, CH_3), 1.23 (s, 3H, CH_3), 1.28 (s, 9H, CH_3, ^{t}Bu), 1.31 (s, 18H, CH_3, ^{t}Bu), 1.43 (s, 18H, CH_3, ^{t}Bu), 1.53 (s, 9H, CH_3, ^{t}Bu), 1.59 (s, 9H, CH_3, ^{t}Bu), 1.63 (s, 9H, CH_3, ^{t}Bu), 3.42 (m, 2H, H-5 and H-5'), 3.52 (m, 1H, NH), 3.82 (m, 1H, H-2), 4.05 (m, 1H, H-4), 4.66 (m, 1H, H-3), 5.14 (m, 2H, CH allyl terminal), 5.79 (d, 1H, H-1, $^3J_{1\text{-}2}$ = 3.6 Hz), 6.62 (m, 1H, CH allyl central), 6.8-7.8 (m, 18H, CH=). ^{13}C NMR (CD_2Cl_2, 233 K), δ: 26.1 (CH_3), 26.8 (CH_3), 31.1 (CH_3, ^{t}Bu), 31.3 (CH_3, ^{t}Bu), 31.5 (CH_3, ^{t}Bu), 31.7 (CH_3, ^{t}Bu), 32.1 (CH_3, ^{t}Bu), 32.3 (CH_3, ^{t}Bu), 34.6-36.0 (C, ^{t}Bu), 39.3 (d, C-5, $J_{C\text{-}P}$ = 14.1 Hz), 76.4 (b, C-4), 82.9 (C-2), 83.4 (d, C-3, $J_{C\text{-}P}$ = 13.2

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Hz), 87.5 (dd, CH allyl *trans* to P-O, $J_{C\text{-}P}$ = 40.3 Hz, $J_{C\text{-}P}$ = 8.5 Hz), 94.8 (dd, CH allyl *trans* to P-N, $J_{C\text{-}P}$ = 30.7 Hz, $J_{C\text{-}P}$ = 6.6 Hz), 104.9 (C-1), 112.6 (m, CH allyl central), 112.7 (CMe_2), 124.0-150.0 (aromatic carbons). Isomer **B** (34%): ^{31}P NMR (CD_2Cl_2, 233 K), δ: 128.2 (d, 1P, P-O, $^2J_{P\text{-}P}$ = 179.1 Hz), 135.1 (d, 1P, P-N, $^2J_{P\text{-}P}$ = 179.1 Hz). ^{1}H NMR (CD_2Cl_2, 233 K), δ: 1.09 (s, 3H, CH_3), 1.23 (s, 3H, CH_3), 1.31 (s, 9H, CH_3, ^{t}Bu), 1.34 (s, 9H, CH_3, ^{t}Bu), 1.46 (s, 18H, CH_3, ^{t}Bu), 1.53 (s, 18H, CH_3, ^{t}Bu), 1.64 (s, 18H, CH_3, ^{t}Bu), 3.42 (m, 3H, NH, H-5 and H-5'), 3.88 (m, 1H, H-2), 4.18 (m, 1H, H-4), 4.90 (m, 1H, H-3), 5.05 (m, 1H, CH allyl terminal), 5.17 (m, 1H, CH allyl terminal), 5.74 (d, 1H, H-1, $^3J_{1\text{-}2}$ = 4.0 Hz), 6.66 (m, 1H, CH allyl central), 6.8-7.8 (m, 18H, CH=). ^{13}C NMR (CD_2Cl_2, 233 K), δ: 26.0 (CH_3), 26.6 (CH_3), 31.0 (CH_3, ^{t}Bu), 31.1 (CH_3, ^{t}Bu), 31.3 (CH_3, ^{t}Bu), 31.4 (CH_3, ^{t}Bu), 31.9 (CH_3, ^{t}Bu), 32.3 (CH_3, ^{t}Bu), 34.6-36.0 (C, ^{t}Bu), 39.7 (d, C-5, $J_{C\text{-}P}$ = 14.8 Hz), 76.6 (b, C-4), 82.9 (C-2), 83.3 (m, C-3), 86.6 (dd, CH allyl *trans* to P-O, $J_{C\text{-}P}$ = 34.6 Hz, $J_{C\text{-}P}$ = 8.7 Hz), 96.4 (dd, CH allyl *trans* to P-N, $J_{C\text{-}P}$ = 34.8 Hz, $J_{C\text{-}P}$ = 7.2 Hz), 104.9 (C-1), 112.3 (CMe_2), 113.4 (m, CH allyl central), 124.0-150.0 (aromatic carbons). Anal. calcd (%) for $C_{79}H_{105}BF_4NO_8P_2Pd$: C 65.35, H 7.29, N 0.96; found: C 65.43, H 7.32, N 0.99.

[Pd(η^3-1,3-diphenylallyl)(L2a)]BF$_4$ (25). Isomer **A** (50%): ^{31}P NMR (CD_2Cl_2, 233 K), δ: 146.2 (d, 1P, P-O, $^2J_{P\text{-}P}$ = 149.4 Hz), 148.2 (d, 1P, P-N, $^2J_{P\text{-}P}$ = 149.4 Hz). ^{1}H NMR (CD_2Cl_2, 233 K), δ: 1.18 (s, 3H, CH_3), 1.24 (s, 3H, CH_3), 1.32 (s, 9H, CH_3, ^{t}Bu), 1.33 (s, 9H, CH_3, ^{t}Bu), 1.45 (s, 18H, CH_3, ^{t}Bu), 1.49 (s, 9H, CH_3, ^{t}Bu), 1.53 (s, 9H, CH_3, ^{t}Bu), 1.65 (s, 18H, CH_3, ^{t}Bu), 3.57 (m, 2H, H-5 and H-5'), 3.92 (m, 2H, NH, H-4), 4.10 (m, 1H, H-3), 4.64 (m, 1H, H-2), 5.07 (m, 1H, CH allyl terminal), 5.23 (m, 1H, CH allyl terminal), 5.62 (d, 1H, H-1, $^3J_{1\text{-}2}$ = 4.0 Hz), 6.52

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(m, 1H, CH allyl central), 6.7-7.8 (m, 18H, CH=). ^{13}C NMR (CD_2Cl_2, 233 K), δ: 25.8 (CH_3), 26.2 (CH_3), 30.8-32.5 (CH_3, ^{t}Bu), 34.6-36.0 (C, ^{t}Bu), 38.5 (m, C-5), 73.8 (C-4), 76.3 (C-2), 77.8 (d, C-3, J_{C-P} = 8.9 Hz), 92.2 (m, CH allyl *trans* to P-O), 97.4 (dd, CH allyl *trans* to P-N, J_{C-P} = 33.7 Hz, J_{C-P} = 7.2 Hz), 104.0 (C-1), 114.5 (m, CH allyl central), 115.1 (CMe_2), 124.0-150.0 (aromatic carbons). Minor isomer **B** (50%): ^{31}P NMR (CD_2Cl_2, 233 K), δ: 145.4 (d, 1P, P-O, $^2J_{P-P}$ = 120.6 Hz), 148.3 (d, 1P, P-N, $^2J_{P-P}$ = 120.6 Hz). ^{1}H NMR (CD_2Cl_2, 233 K), δ: 1.24 (s, 3H, CH_3), 1.27 (s, 3H, CH_3), 1.29 (s, 9H, CH_3, ^{t}Bu), 1.33 (s, 18H, CH_3, ^{t}Bu), 1.45 (s, 9H, CH_3, ^{t}Bu), 1.51 (s, 9H, CH_3, ^{t}Bu), 1.56 (s, 9H, CH_3, ^{t}Bu), 1.64 (s, 18H, CH_3, ^{t}Bu), 3.57 (m, 2H, H-5 and H-5'), 3.92 (m, 2H, NH, H-4), 4.25 (m, 1H, H-3), 4.72 (m, 1H, H-2), 5.23 (m, 1H, CH allyl terminal), 5.34 (m, 1H, CH allyl terminal), 5.69 (d, 1H, H-1, $^3J_{1-2}$ = 4.0 Hz), 6.62 (m, 1H, CH allyl central), 6.7-7.8 (m, 18H, CH=). ^{13}C NMR (CD_2Cl_2, 233 K), δ: 25.9 (CH_3), 26.1 (CH_3), 30.8-32.5 (CH_3, ^{t}Bu), 34.6-36.0 (C, ^{t}Bu), 38.5 (m, C-5), 73.8 (C-4), 76.6 (C-2), 77.4 (d, C-3, J_{C-P} = 10.0 Hz), 91.9 (m, CH allyl *trans* to P-O), 98.2 (dd, CH allyl *trans* to P-N, J_{C-P} = 30.4 Hz, J_{C-P} = 6.6 Hz), 103.8 (C-1), 113.8 (m, CH allyl central), 115.1 (CMe_2), 124.0-150.0 (aromatic carbons) Anal. calcd (%) for $C_{79}H_{105}BF_4NO_8P_2Pd$: C 65.35, H 7.29, N 0.96; found: C 65.22, H 7.21, N 1.02.

[Pd(η^3-1,3-diphenylallyl)(L3a)]BF$_4$ (26). Isomer **A** (34%): ^{31}P NMR (CD_2Cl_2, 213 K), δ: 124.2 (d, 1P, P-O, $^2J_{P-P}$ = 159.9 Hz), 133.2 (d, 1P, P-N, $^2J_{P-P}$ = 159.9 Hz). ^{1}H NMR (CD_2Cl_2, 213 K), δ: 1.18 (s, 3H, CH_3), 1.29 (s, 9H, CH_3, ^{t}Bu), 1.32 (s, 18H, CH_3, ^{t}Bu), 1.45 (s, 9H, CH_3, ^{t}Bu), 1.49 (s, 3H, CH_3), 1.59 (s, 18H, CH_3, ^{t}Bu), 1.64 (s, 9H, CH_3, ^{t}Bu), 1.65 (s, 9H, CH_3, ^{t}Bu), 4.05 (m, 2H, H-3, NH), 4.34 (m, 2H, H-5 and H-

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5'), 4.45 (m, 1H, H-4), 4.52 (m, 1H, H-2), 5.11 (m, 1H, CH allyl terminal), 5.35 (m, 1H, CH allyl terminal), 5.72 (d, 1H, H-1, $^{3}J_{1-2}$ = 3.6 Hz), 6.62 (m, 1H, CH allyl central), 6.8-7.8 (m, 18H, CH=). ^{13}C NMR (CD_2Cl_2, 213 K), δ: 26.3 (CH_3), 27.1 (CH_3), 30.5-33.5 (CH_3, ^{t}Bu), 35.0-36.3 (C, ^{t}Bu), 56.3 (m, C-3), 65.4 (m, C-5), 75.6 (C-4), 79.7 (C-2), 86.8 (m, CH allyl *trans* to P-O), 92.8 (m, CH allyl *trans* to P-N), 104.8 (C-1), 111.9 (CMe_2), 113.4 (m, CH allyl central), 124.0-150.0 (aromatic carbons). Isomer **B** (66%): ^{31}P NMR (CD_2Cl_2, 213 K), δ: 123.8 (d, 1P, $^{2}J_{P-P}$ = 156.2 Hz), 135.2 (d, 1P, $^{2}J_{P-P}$ = 156.2 Hz). ^{1}H NMR (CD_2Cl_2, 213 K), δ: 1.15 (s, 3H, CH_3), 1.30 (s, 9H, CH_3, ^{t}Bu), 1.35 (s, 18H, CH_3, ^{t}Bu), 1.41 (s, 3H, CH_3), 1.47 (s, 9H, CH_3, ^{t}Bu), 1.55 (s, 18H, CH_3, ^{t}Bu), 1.62 (s, 18H, CH_3, ^{t}Bu), 4.09 (m, 2H, H-3, NH), 4.35 (m, 2H, H-5 and H-5'), 4.42 (m, 1H, H-4), 4.71 (m, 1H, H-2), 5.02 (m, 1H, CH allyl terminal), 5.55 (m, 1H, CH allyl terminal), 5.81 (d, 1H, H-1, $^{3}J_{1-2}$ = 4.0 Hz), 6.69 (m, 1H, CH allyl central), 6.8-7.8 (m, 18H, CH=). ^{13}C NMR (CD_2Cl_2, 213 K), δ: 26.0 (CH_3), 27.4 (CH_3), 30.5-33.5 (CH_3, ^{t}Bu), 35.0-36.3 (C, ^{t}Bu), 56.5 (C-3), 65.8 (m, C-5), 75.9 (C-4), 80.2 (m, C-2), 87.0 (m, CH allyl *trans* to P-O), 93.0 (m, CH allyl *trans* to P-N), 104.9 (C-1), 111.9 (CMe_2), 113.9 (m, CH allyl central), 124.0-150.0 (aromatic carbons). Anal. calcd (%) for $C_{79}H_{105}BF_4NO_8P_2Pd$: C 65.35, H 7.29, N 0.96; found: C 65.63, H 7.42, N 1.09.

[Pd(η^{3}-1,3-diphenylallyl)(L4a)]BF$_4$ (27). Isomer **A** (45%): ^{31}P NMR (CD_2Cl_2, 253 K), δ: 124.1 (d, 1P, P-O, $^{2}J_{P-P}$ = 181.8 Hz), 135.1 (d, 1P, P-N, $^{2}J_{P-P}$ = 181.8 Hz). ^{1}H NMR (CD_2Cl_2, 253 K), δ: 1.21 (s, 3H, CH_3), 1.29 (s, 9H, CH_3, ^{t}Bu), 1.31 (s, 3H, CH_3), 1.35 (s, 18H, CH_3, ^{t}Bu), 1.42 (s, 9H, CH_3, ^{t}Bu), 1.45 (s, 9H, CH_3), 1.48 (s, 9H, CH_3, ^{t}Bu), 1.64 (s, 9H, CH_3, ^{t}Bu), 1.65 (s, 9H, CH_3, ^{t}Bu), 3.45 (m, 1H, NH), 3.56 (m, 1H, C-

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3), 3.98 (m, 1H, H-4), 4.05 (m, 2H, H-5 and H-5'), 5.11 (m, 1H, CH allyl terminal), 5.25 (m, 1H, CH allyl terminal), 5.42 (m, 1H, H-2), 5.74 (d, 1H, H-1, $^3J_{1\text{-}2}$ = 3.6 Hz), 6.71 (m, 1H, CH allyl central), 6.8-7.8 (m, 18H, CH=). ^{13}C NMR (CD_2Cl_2, 253 K), δ: 26.0 (CH_3), 26.8 (CH_3), 31.0-33.0 (CH_3, ^{t}Bu), 34.8-36.1 (C, ^{t}Bu), 56.8 (m, C-3), 68.7 (m, C-5), 73.8 (C-4), 79.3 (C-2), 90.7 (m, CH allyl *trans* to P-O), 93.8 (m, CH allyl *trans* to P-N), 103.4 (C-1), 112.5 (CMe_2), 111.5 (m, CH allyl central), 124.0-150.0 (aromatic carbons). Isomer **B** (55%): ^{31}P NMR (CD_2Cl_2, 253 K), δ: 123.5 (d, 1P, P-O, $^2J_{P\text{-}P}$ = 170.3 Hz), 136.4 (d, 1P, P-N, $^2J_{P\text{-}P}$ = 170.3 Hz). ^{1}H NMR (CD_2Cl_2, 253 K), δ: 1.18 (s, 3H, CH_3), 1.25 (s, 9H, CH_3, ^{t}Bu), 1.33 (s, 3H, CH_3), 1.39 (s, 18H, CH_3, ^{t}Bu), 1.51 (s, 18H, CH_3, ^{t}Bu), 1.60 (s, 18H, CH_3, ^{t}Bu), 1.65 (s, 9H, CH_3, ^{t}Bu), 3.51 (m, 1H, NH), 3.62 (m, 1H, C-3), 4.03 (m, 1H, H-4), 4.11 (m, 2H, H-5 and H-5'), 5.02 (m, 1H, CH allyl terminal), 5.21 (m, 1H, CH allyl terminal), 5.22 (m, 1H, H-2), 5.94 (d, 1H, H-1, $^3J_{1\text{-}2}$ = 4.0 Hz), 6.68 (m, 1H, CH allyl central), 6.8-7.8 (m, 18H, CH=). ^{13}C NMR (CD_2Cl_2, 253 K), δ: 25.8 (CH_3), 27.1 (CH_3), 31.0-33.0 (CH_3, ^{t}Bu), 34.8-36.1 (C, ^{t}Bu), 56.8 (m, C-3), 68.9 (m, C-5), 74.2 (C-4), 80.2 (C-2), 89.7 (m, CH allyl *trans* to P-O), 93.1 (dd, CH allyl *trans* to P-N, $J_{C\text{-}P}$ = 28.8 Hz, $J_{C\text{-}P}$ = 6.2 Hz), 103.5 (C-1), 112.5 (CMe_2), 113.1 (m, CH allyl central), 124.0-150.0 (aromatic carbons). Anal. calcd (%) for $C_{79}H_{105}BF_4NO_8P_2Pd$: C 65.35, H 7.29, N 0.96; found: C 65.13, H 7.22, N 0.91.

[Pd(η^3-1,3-diphenylallyl)(L1g)]BF_4 (28). Isomer **A** (20%): ^{31}P NMR (CD_2Cl_2, 263 K), δ: 140.5 (d, 1P, P-O, $^2J_{P\text{-}P}$ = 154.4 Hz), 146.3 (d, 1P, P-N, $^2J_{P\text{-}P}$ = 154.4 Hz). ^{1}H NMR (CD_2Cl_2, 263 K), δ: 0.51 (s, 9H, $Si(CH_3)_3$), 0.75-0.92 (m, 27H, $Si(CH_3)_3$), 1.24 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 3.02 (m, 1H, NH), 3.42 (m, 2H, H-5 and H-5'), 4.02 (m, 2H, H-2

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and H-4), 4.62 (m, 1H, H-3), 4.86 (m, 1H, CH allyl terminal), 5.18 (d, 1H, H-1, $^{3}J_{1\text{-}2}$ = 3.6 Hz), 5.61 (m, 1H, CH allyl terminal), 6.21 (m, 2H, CH=), 6.41 (m, 1H, CH allyl central), 6.5-8.5 (m, 20H, CH=). ^{13}C NMR (CD_2Cl_2, 263 K), δ: 0.8-2.4 ($Si(CH_3)_3$), 24.9 (CH_3), 26.5 (CH_3), 37.2 (C-5), 78.7 (m, C-4), 79.4 (m, C-2), 82.5 (C-3), 88.0 (dd, CH allyl *trans* to P-O, $J_{C\text{-}P}$ = 36.5 Hz, $J_{C\text{-}P}$ = 6.0 Hz), 99.8 (m, CH allyl *trans* to P-N), 105.3 (C-1), 113.0 (CMe_2), 114.0 (m, CH allyl central), 120.0-155.0 (aromatic carbons). Isomer **B** (80%): ^{31}P NMR (CD_2Cl_2, 263 K), δ: 142.8 (d, 1P, P-O, $^{2}J_{P\text{-}P}$ = 151.2 Hz), 147.2 (d, 1P, P-N, $^{2}J_{P\text{-}P}$ = 151.2 Hz). ^{1}H NMR (CD_2Cl_2, 263 K), δ: 0.44 (s, 9H, $Si(CH_3)_3$), 0.75-0.92 (m, 27H, $Si(CH_3)_3$), 1.27 (s, 3H, CH_3), 1.39 (s, 3H, CH_3), 2.85 (m, 1H, H-5), 3.02 (m, 1H, NH), 3.21 (m, 1H, H-5'), 4.02 (m, 2H, H-2 and H-4), 4.80 (m, 1H, H-3), 5.05 (m, 1H, CH allyl terminal), 5.20 (d, 1H, H-1, $^{3}J_{1\text{-}2}$ = 4.0 Hz), 5.72 (m, 1H, CH allyl terminal), 6.21 (m, 2H, CH=), 6.47 (m, 1H, CH allyl central), 6.5-8.5 (m, 20H, CH=). ^{13}C NMR (CD_2Cl_2, 263 K), δ: 0.8-2.4 ($Si(CH_3)_3$), 24.7 (CH_3), 26.6 (CH_3), 37.0 (C-5), 78.7 (m, C-4), 79.5 (m, C-2), 82.7 (C-3), 84.7 (dd, CH allyl *trans* to P-O, $J_{C\text{-}P}$ = 37.2 Hz, $J_{C\text{-}P}$ = 7.2 Hz), 102.9 (m, CH allyl *trans* to P-N), 105.7 (C-1), 112.6 (m, CH allyl central), 113.0 (CMe_2), 120.0-155.0 (aromatic carbons). Anal. calcd (%) for $C_{75}H_{81}BF_4NO_8P_2PdSi_4$: C 60.38, H 5.47, N 0.94; found: C 60.54, H 5.63, N 0.99.

[Pd(η^3-1,3-dimethylallyl)(L1g)]BF$_4$ (29). Isomer **A** (50%): ^{31}P NMR (CD_2Cl_2, 223 K), δ: 142.3 (d, 1P, P-O, $^{2}J_{P\text{-}P}$ = 122.0 Hz), 145.1 (d, 1P, P-N, $^{2}J_{P\text{-}P}$ = 122.0 Hz). ^{1}H NMR (CD_2Cl_2, 223 K), δ: 0.30-0.55 (m, 36H, $Si(CH_3)_3$), 0.85 (m, 3H, CH_3 allyl), 1.11 (s, 3H, CH_3), 1.18 (m, 3H, CH_3 allyl), 1.27 (s, 3H, CH_3), 3.18 (m, 1H, H-5), 3.23 (d, 1H, H-2, $^{3}J_{1\text{-}2}$ = 3.6 Hz), 3.62 (m, 2H, H-5' and NH), 3.95 (m, 1H, CH allyl terminal),

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4.11 (m, 1H, H-4), 4.22 (m, 1H, CH allyl terminal), 4.95 (m, 1H, H-3), 5.15 (m, 1H, CH allyl central), 5.49 (d, 1H, H-1, $^3J_{1\text{-}2}$ = 3.6 Hz), 7.2-7.8 (m, 20H, CH=). ^{13}C NMR (CD_2Cl_2, 223 K), δ: 0.4-2.0 ($Si(CH_3)_3$), 17.7 (CH_3 allyl), 18.2 (d, CH_3 allyl, $J_{C\text{-}P}$ = 7.5 Hz), 26.0 (CH_3), 26.6 (CH_3), 36.4 (m, C-5), 78.7 (m, C-4 and C-3), 83.2 (C-2), 87.0 (d, CH allyl *trans* to P-O, $J_{C\text{-}P}$ = 35.6 Hz), 100.4 (d, CH allyl *trans* to P-N, $J_{C\text{-}P}$ = 34.9 Hz), 105.5 (C-1), 113.2 (CMe_2), 118.3 (m, CH allyl central), 122.0-157.0 (aromatic carbons). Isomer **B** (50%): ^{31}P NMR (CD_2Cl_2, 223 K), δ: 142.9 (d, 1P, P-O, $^2J_{P\text{-}P}$ = 115.1 Hz), 146.4 (d, 1P, P-N, $^2J_{P\text{-}P}$ = 115.1 Hz). ^{1}H NMR (CD_2Cl_2, 223 K), δ: 0.30-0.55 (m, 36H, $Si(CH_3)_3$), 1.08 (m, 6H, CH_3 allyl and CH_3), 1.18 (m, 3H, CH_3 allyl), 1.40 (s, 3H, CH_3), 3.20 (m, 1H, H-5), 3.55 (m, 2H, H-5' and NH), 3.82 (d, 1H, H-2, $^3J_{1\text{-}2}$ = 3.6 Hz), 3.99 (m, 1H, CH allyl terminal), 4.11 (m, 1H, H-4), 4.27 (m, 1H, CH allyl terminal), 4.99 (m, 1H, H-3), 5.19 (m, 1H, CH allyl central), 5.60 (d, 1H, H-1, $^3J_{1\text{-}2}$ = 3.6 Hz), 7.2-7.8 (m, 20H, CH=). ^{13}C NMR (CD_2Cl_2, 223 K), δ: 0.4-2.0 ($Si(CH_3)_3$), 17.9 (CH_3 allyl), 18.6 (d, CH_3 allyl, $J_{C\text{-}P}$ = 7.0 Hz), 26.2 (CH_3), 29.4 (CH_3), 36.7 (m, C-5), 78.7 (m, C-4 and C-3), 83.5 (C-2), 85.1 (d, CH allyl *trans* to P-O, $J_{C\text{-}P}$ = 34.8 Hz), 97.4 (d, CH allyl *trans* to P-N, $J_{C\text{-}P}$ = 35.1 Hz), 105.8 (C-1), 113.2 (CMe_2), 118.2 (m, CH allyl central), 122.0-157.0 (aromatic carbons). Anal. calcd (%) for $C_{65}H_{77}BF_4NO_8P_2PdSi_4$: C 57.08, H 5.67, N 1.02; found: C 57.14, H 5.72, N 1.07.

[Pd(η^3-1,3-dimethylallyl)(L2g)]BF_4 (30). Isomer **A** (45%): ^{31}P NMR (CD_2Cl_2, 253 K), δ: 140.8 (d, 1P, P-O, $^2J_{P\text{-}P}$ = 144.1 Hz), 144.3 (d, 1P, P-N, $^2J_{P\text{-}P}$ = 144.1 Hz). ^{1}H NMR (CD_2Cl_2, 253 K), δ: 0.30-0.90 (m, 36H, $Si(CH_3)_3$), 1.05 (m, 3H, CH_3 allyl), 1.19 (s, 3H, CH_3), 1.25 (m, 6H, CH_3 allyl and CH_3), 3.21 (m, 1H, H-5), 3.43 (m, 2H, H-2 and NH), 3.57

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(m, 1H, H-5'), 3.86 (m, 1H, CH allyl terminal), 4.20 (m, 1H, H-4), 4.29 (m, 1H, CH allyl terminal), 4.83 (m, 1H, H-3), 5.33 (m, 1H, CH allyl central), 5.39 (d, 1H, H-1, $^{3}J_{1\text{-}2}$ = 3.6 Hz), 7.2-7.8 (m, 20H, CH=). ^{13}C NMR (CD_2Cl_2, 253 K), δ: 0.2-2.0 ($Si(CH_3)_3$), 16,8 (d, CH_3 allyl, $J_{C\text{-}P}$ = 7.5 Hz), 18.3 (d, CH_3 allyl, $J_{C\text{-}P}$ = 7.2 Hz), 26.2 (CH_3), 27.3 (CH_3), 37.2 (m, C-5), 78.9 (C-4), 80.1 (C-3), 83.5 (C-2), 86.1 (d, CH allyl *trans* to P-O, $J_{C\text{-}P}$ = 35.2 Hz), 96.9 (d, CH allyl *trans* to P-N, $J_{C\text{-}P}$ = 34.7 Hz), 105.3 (C-1), 113.9 (CMe_2), 117.9 (m, CH allyl central), 120.0-156.0 (aromatic carbons). Isomer **B** (55%): ^{31}P NMR (CD_2Cl_2, 253 K), δ: 141.5 (d, 1P, P-O, $^{2}J_{P\text{-}P}$ = 147.2 Hz), 142.6 (d, 1P, P-N, $^{2}J_{P\text{-}P}$ = 147.2 Hz). ^{1}H NMR (CD_2Cl_2, 253 K), δ: 0.30-0.90 (m, 36H, $Si(CH_3)_3$), 1.11 (m, 3H, CH_3 allyl), 1.22 (s, 3H, CH_3), 1.29 (m, 3H, CH_3), 1.33 (s, 3H, CH_3 allyl), 3.33 (m, 2H, H-5 and NH), 3.49 (m, 1H, H-2), 3.57 (m, 1H, H-5'), 3.93 (m, 1H, CH allyl terminal), 4.20 (m, 1H, H-4), 4.33 (m, 1H, CH allyl terminal), 4.89 (m, 1H, H-3), 5.29 (m, 1H, CH allyl central), 5.43 (d, 1H, H-1, $^{3}J_{1\text{-}2}$ = 3.6 Hz), 7.2-7.8 (m, 20H, CH=). ^{13}C NMR (CD_2Cl_2, 253 K), δ: 0.2-2.0 ($Si(CH_3)_3$), 17.2 (d, CH_3 allyl, $J_{C\text{-}P}$ = 7.2 Hz), 18.8 (d, CH_3 allyl, $J_{C\text{-}P}$ = 7.6 Hz), 26.5 (CH_3), 27.8 (CH_3), 37.8 (m, C-5), 78.9 (C-4), 80.5 (C-3), 83.8 (C-2), 86.4 (d, CH allyl *trans* to P-O, $J_{C\text{-}P}$ = 35.2 Hz), 101.3 (d, CH allyl *trans* to P-N, $J_{C\text{-}P}$ = 35.0 Hz), 105.3 (C-1), 114.1 (CMe_2), 117.5 (m, CH allyl central), 120.0-156.0 (aromatic carbons). Anal. calcd (%) for $C_{65}H_{77}BF_4NO_8P_2PdSi_4$: C 57.08, H 5.67, N 1.02; found: C 57.23, H 5.81, N 0.95.

[Pd(η^3-1,3-cyclohexylallyl)(L1a)]BF_4 (31). Isomer **A** (45%): ^{31}P NMR (CD_2Cl_2, 223 K), δ: 140.4 (d, 1P, P-O, $^{2}J_{P\text{-}P}$ = 79.3 Hz), 144.8 (d, 1P, P-N, $^{2}J_{P\text{-}P}$ = 79.3 Hz). ^{1}H NMR (CD_2Cl_2, 213 K), δ: 0.95 (m, 2H, CH_2), 1.15 (m, 2H, CH_2), 1.25-1.61 (m, 78 H, CH_3 and CH_3 ^{t}Bu), 1.72

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(m, 2H, CH_2), 3.41 (m, 1H, H-5), 3.85 (m, 1H, H-5'), 4.31 (m, 2H, H-3, CH allyl terminal), 4.42 (m, 2H, H-2, NH), 4.59 (m, 1H, H-4), 4.81 (m, 1H, CH allyl central), 5.78 (d, 1H, H-1, $^3J_{1\text{-}2}$ = 3.6 Hz), 5.92 (m, 1H, CH allyl terminal), 7.2-7.8 (m, 8H, CH=). ^{13}C NMR (CD_2Cl_2, 213 K), δ: 20.3 (b, CH_2), 26.5 (CH_3), 26.8 (CH_3), 27.2 (b, CH_2), 27.9 (b, CH_2), 31.4-33.5 (CH_3, ^{t}Bu), 35.2-36.0 (C, ^{t}Bu), 38.0 (m, C-5), 75.0 (m, CH allyl *trans* to P-O), 77.8 (C-4), 80.2 (C-2), 83.5 (C-3), 98.7 (m, CH allyl *trans* to P-N), 105.5 (C-1), 111.4 (m, CH allyl central), 113.6 (CMe_2), 124.0-150.0 (aromatic carbons). Isomer **B** (55%): ^{31}P NMR (CD_2Cl_2, 223 K), δ: 143.1 (d, 1P, $^2J_{P\text{-}P}$ = 72.8 Hz), 147.1 (d, 1P, $^2J_{P\text{-}P}$ = 72.8 Hz). ^{1}H NMR (CD_2Cl_2, 213 K), δ: 0.95 (m, 2H, CH_2), 1.15 (m, 2H, CH_2), 1.25-1.61 (m, 78 H, CH_3 and CH_3 ^{t}Bu), 1.72 (m, 2H, CH_2), 3.38 (m, 1H, H-5), 3.80 (m, 1H, H-5'), 4.29 (m, 1H, H-3), 4.42 (m, 2H, H-2, NH), 4.53 (m, 2H, H-4 and CH allyl terminal), 4.81 (m, 1H, CH allyl central), 5.82 (d, 1H, H-1, $^3J_{1\text{-}2}$ = 3.6 Hz), 5.87 (m, 1H, CH allyl terminal), 7.2-7.8 (m, 8H, CH=). ^{13}C NMR (CD_2Cl_2, 213 K), δ: 20.3 (b, CH_2), 26.3 (CH_3), 26.7 (CH_3), 27.2 (b, CH_2), 27.9 (b, CH_2), 31.4-33.5 (CH_3, ^{t}Bu), 35.2-36.0 (C, ^{t}Bu), 38.0 (m, C-5), 76.3 (m, CH allyl *trans* to P-O), 77.9 (C-4), 80.0 (C-2), 83.1 (C-3), 99.2 (m, CH allyl *trans* to P-N), 105.3 (C-1), 111.1 (m, CH allyl central), 113.6 (CMe_2), 124.0-150.0 (aromatic carbons). Anal. calcd (%) for $C_{70}H_{101}BF_4NO_8P_2Pd$: C 62.76, H 7.60, N 1.05; found: C 62.55, H 7.71, N 1.09.

[Pd(η^3-1,3-cyclohexylallyl)(L2a)]BF_4 (32). Isomer **A** (55%): ^{31}P NMR (CD_2Cl_2, 233 K), δ: 145.5 (d, 1P, P-O, $^2J_{P\text{-}P}$ = 80.5 Hz), 147.3 (d, 1P, P-N, $^2J_{P\text{-}P}$ = 80.5 Hz). ^{1}H NMR (CD_2Cl_2, 233 K), δ: 0.98 (m, 2H, CH_2), 1.15 (m, 2H, CH_2), 1.21 (s, 3H, CH_3), 1. 1.32 (s, 9H, CH_3, ^{t}Bu), 1.35 (s, 12H, CH_3 and CH_3 ^{t}Bu), 1.47 (s, 18H, CH_3, ^{t}Bu), 1.50 (s, 18H,

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CH_3, ^{t}Bu), 1.53 (s, 9H, CH_3, ^{t}Bu), 1.62 (s, 9H, CH_3, ^{t}Bu), 1.79 (m, 2H, CH_2), 3.52 (m, 1H, H-5), 3.73 (m, 1H, H-5'), 4.11 (m, 2H, NH, H-4), 4.41 (m, 1H, CH allyl terminal), 4.62 (m, 1H, H-3), 4.71 (m, 1H, H-2), 5.12 (m, 1H, CH allyl central), 5.81 (d, 1H, H-1, $^3J_{1\text{-}2}$ = 4.0 Hz), 5.98 (m, 1H, CH allyl terminal), 7.1-7.8 (m, 8H, CH=). ^{13}C NMR (CD_2Cl_2, 233 K), δ: 18.3 (CH_2), 26.3 (CH_3), 26.8 (CH_3), 28.2 (b, CH_2), 31.1-32.7 (CH_3, ^{t}Bu), 35.2-36.1 (C, ^{t}Bu), 38.7 (m, C-5), 74.9 (b, C-3 and CH allyl *trans* to P-O), 77.0 (C-4), 78.0 (C-2), 101.9 (d, CH allyl *trans* to P-N, $J_{C\text{-}P}$ = 37.0 Hz), 104.2 (C-1), 114.5 (m, CH allyl central), 115.3 (CMe_2), 124.0-150.0 (aromatic carbons). Minor isomer **B** (45%): ^{31}P NMR (CD_2Cl_2, 233 K), δ: 144.4 (d, 1P, P-O, $^2J_{P\text{-}P}$ = 79.3), 149.4 (d, 1P, P-N, $^2J_{P\text{-}P}$ = 79.3). ^{1}H NMR (CD_2Cl_2, 233 K), δ: 0.98 (m, 2H, CH_2), 1.15 (m, 2H, CH_2), 1.29 (s, 3H, CH_3), 1. 1.33 (s, 9H, CH_3, ^{t}Bu), 1.35 (s, 21H, CH_3 and CH_3 ^{t}Bu), 1.47 (s, 8H, CH_3, ^{t}Bu), 1.57 (s, 27H, CH_3, ^{t}Bu), 1.62 (s, 9H, CH_3, ^{t}Bu), 1.79 (m, 2H, CH_2), 3.55 (m, 1H, H-5), 3.62 (m, 1H, H-5'), 4.11 (m, 2H, NH, H-4), 4.49 (m, 1H, CH allyl terminal), 4.62 (m, 1H, H-3), 4.77 (m, 2H, H-2 and CH allyl terminal), 4.98 (m, 1H, CH allyl central), 5.85 (d, 1H, H-1, $^3J_{1\text{-}2}$ = 4.0 Hz), 7.1-7.8 (m, 8H, CH=). ^{13}C NMR (CD_2Cl_2, 233 K), δ: 18.7 (CH_2), 26.4 (CH_3), 27.0 (CH_3), 28.2 (b, CH_2), 31.1-32.7 (CH_3, ^{t}Bu), 35.2-36.1 (C, ^{t}Bu), 38.7 (m, C-5), 74.6 (b, C-3), 77.0 (C-4), 78.0 (C-2 and CH allyl *trans* to P-O), 91.9 (d, CH allyl *trans* to P-N, $J_{C\text{-}P}$ = 36.6 Hz), 104.4 (C-1), 113.8 (m, CH allyl central), 115.3 (CMe_2), 124.0-150.0 (aromatic carbons). Anal. calcd (%) for $C_{70}H_{101}BF_4NO_8P_2Pd$: C 62.76, H 7.60, N 1.05; found: C 62.89, H 7.63, N 1.01.

[Pd(η^3-1,3-cyclohexylallyl)(L3a)]BF_4 (33). Isomer **A** (57%): ^{31}P NMR (CD_2Cl_2, 223 K), δ: 140.0 (d, 1P, P-O, $^2J_{P\text{-}P}$ = 76.9), 145.7 (d, 1P, P-N, $^2J_{P\text{-}P}$ = 76.9). ^{1}H NMR (CD_2Cl_2, 213 K), δ: 0.99 (m, 2H, CH_2), 1.17

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(m, 2H, CH_2), 1.3-1.6 (m, 78 H, CH_3 and CH_3 ^{t}Bu), 1.7.5 (m, 2H, CH_2), 3.25 (m, 1H, NH), 4.05 (m, 1H, H-3), 4.42 (m, 1H, H-4), 4.55 (m, 2H, H-5 and H-5'), 4.58 (m, 1H, H-2), 4.69 (m, 1H, CH allyl terminal), 5.01 (m, 1H, CH allyl central), 5.80 (d, 1H, H-1, $^3J_{1\text{-}2}$ = 3.6 Hz), 5.94 (m, 1H, CH allyl terminal), 7.2-7.8 (m, 8H, CH=). ^{13}C NMR (CD_2Cl_2, 213 K), δ: 19.0 (b, CH_2), 26.3 (CH_3), 26.5 (CH_3), 28.2 (b, CH_2), 31.5-33.5 (CH_3, ^{t}Bu), 35.2-36.2 (C, ^{t}Bu), 56.3 (m, C-3), 63.8 (m, C-5), 77.7 (C-4), 77.7 (b, CH allyl *trans* to P-O), 85.6 (C-2), 98.9 (m, CH allyl *trans* to P-N), 104.4 (C-1), 113.3 (m, CMe_2 and CH allyl central), 124.0-150.0 (aromatic carbons). Isomer **B** (43%): ^{31}P NMR (CD_2Cl_2, 223 K), δ: 144.2 (d, 1P, $^2J_{P\text{-}P}$ = 72 Hz), 149.2 (d, 1P, $^2J_{P\text{-}P}$ = 72 Hz). ^{1}H NMR (CD_2Cl_2, 213 K), δ: 0.99 (m, 2H, CH_2), 1.17 (m, 2H, CH_2), 1.3-1.6 (m, 78 H, CH_3 and CH_3 ^{t}Bu), 1.7.5 (m, 2H, CH_2), 3.25 (m, 1H, NH), 4.11 (m, 1H, H-3), 4.38 (m, 1H, H-4), 4.42 (m, 1H, H-5), 4,52 (m ,1H, H-5'), 4.60 (m, 1H, H-2), 4.62 (m, 1H, CH allyl terminal), 4.95 (m, 1H, CH allyl central), 5.84 (d, 1H, H-1, $^3J_{1\text{-}2}$ = 3.6 Hz), 5.86 (m, 1H, CH allyl terminal), 7.2-7.8 (m, 8H, CH=). ^{13}C NMR (CD_2Cl_2, 213 K), δ: 19.0 (b, CH_2), 26.3 (CH_3), 26.7 (CH_3), 28.2 (b, CH_2), 31.5-33.5 (CH_3, ^{t}Bu), 35.2-36.2 (C, ^{t}Bu), 56.5 (m, C-3), 63.3 (m, C-5), 77.5 (C-4), 77.7 (b, CH allyl *trans* to P-O), 85.5 (C-2), 93.0 (m, CH allyl *trans* to P-N), 104.4 (C-1), 113.2 (CMe_2), 114.0 (m, CH allyl central), 124.0-150.0 (aromatic carbons). Anal. calcd (%) for $C_{70}H_{101}BF_4NO_8P_2Pd$: C 62.76, H 7.60, N 1.05; found: C 62.72, H 7.54, N 1.11.

[Pd(η^3-1,3-cyclohexylallyl)(L4a)]BF_4 (34). Isomer **A** (45%): ^{31}P NMR (CD_2Cl_2, 223 K), δ: 143.2 (d, 1P, P-O, $^2J_{P\text{-}P}$ = 72.9 Hz), 148.9 (d, 1P, P-N, $^2J_{P\text{-}P}$ = 72.9 Hz). ^{1}H NMR (CD_2Cl_2, 213 K), δ: 0.97 (m, 2H, CH_2), 1.17 (m, 2H, CH_2), 1.3-1.6 (m, 78 H, CH_3 and CH_3 ^{t}Bu), 1.84 (m,

2H, CH_2), 4.11 (m, 2H, H-3, NH), 4.38 (m, 1H, CH allyl terminal), 4.45 (m, 2H, H-5 and H-5'), 4.54 (m, 1H, H-4), 4.62 (m, 1H, H-2), 4.70 (m, 1H, CH allyl central), 5.81 (d, 1H, H-1, $^3J_{1\text{-}2}$ = 3.6 Hz), 5.98 (m, 1H, CH allyl terminal), 7.2-7.8 (m, 8H, CH=). ^{13}C NMR (CD_2Cl_2, 213 K), δ: 18.7 (CH_2), 26.2 (CH_3), 27.0 (CH_3), 28.3 (b, CH_2), 30.5-33.9 (CH_3, ^{t}Bu), 35.0-36.5 (C, ^{t}Bu), 53.3 (m, C-3), 65.2 (m, C-5), 75.9 (C-4), 77.5 (b, CH allyl *trans* to P-O), 78.1 (C-2), 92.8 (m, CH allyl *trans* to P-N), 104.9 (C-1), 112.9 (CMe_2), 113.2 (m, CH allyl central), 124.0-150.0 (aromatic carbons). Isomer **B** (55%): ^{31}P NMR (CD_2Cl_2, 223 K), δ: 145.4 (d, 1P, $^2J_{P\text{-}P}$ = 79.3 Hz), 148.2 (d, 1P, $^2J_{P\text{-}P}$ = 79.3 Hz). ^{1}H NMR (CD_2Cl_2, 213 K), δ: 0.97 (m, 2H, CH_2), 1.17 (m, 2H, CH_2), 1.3-1.6 (m, 78 H, CH_3 and CH_3 ^{t}Bu), 1.84 (m, 2H, CH_2), 4.14 (m, 2H, H-3, NH), 4.41 (m, 1H, CH allyl terminal), 4.49 (m, 2H, H-5 and H-5'), 4.56 (m, 1H, H-4), 4.62 (m, 1H, H-2), 4.73 (m, 1H, CH allyl central), 5.79 (m, 1H, CH allyl terminal), 5.83 (d, 1H, H-1, $^3J_{1\text{-}2}$ = 3.6 Hz), 7.2-7.8 (m, 8H, CH=). ^{13}C NMR (CD_2Cl_2, 213 K), δ: 18.9 (CH_2), 26.1 (CH_3), 27.3 (CH_3), 28.3 (b, CH_2), 30.5-33.9 (CH_3, ^{t}Bu), 35.0-36.5 (C, ^{t}Bu), 53.6 (m, C-3), 65.2 (m, C-5), 74.5 (C-4), 77.5 (b, CH allyl *trans* to P-O), 78.4 (C-2), 96.0 (m, CH allyl *trans* to P-N), 104.9 (C-1), 112.9 (CMe_2), 113.4 (m, CH allyl central), 124.0-150.0 (aromatic carbons). Anal. calcd (%) for $C_{70}H_{101}BF_4NO_8P_2Pd$: C 62.76, H 7.60, N 1.05; found: C 62.86, H 7.77, N 0.99.

3.2.4.5. Study of the reactivity of the [Pd(η^3-allyl)(L))]BF$_4$ with sodium malonate by in situ NMR.[37]

A solution of *in situ* prepared [Pd(η^3-allyl)(**L**)]BF_4 (**L**= phosphite-phosphoroamidite ligand, 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

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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.

3.2.4.6. Typical procedure of allylic alkylation of disubstituted linear (S1 and S2) and cyclic (S5 and S6) substrates.

A degassed solution of $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (0.9 mg, 0.0025 mmol) and the corresponding phosphite-phosphoroamidite (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), dimethyl malonate (171 μL, 1.5 mmol), *N*,*O*-bis(trimethylsilyl)-acetamide (370 μL, 1.5 mmol) and a pinch of the corresponding base 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 substrate **S1**, solvent was removed and conversion was measured by ^1H-NMR. To determine the ee by HPLC (Chiralcel OD, 0.5% 2-propanol/hexane, flow 0.5 mL/min), a sample was filtered over basic alumina using dichloromethane as the eluent.[38] For substrates **S2**, **S5** and **S6**, conversion and enantiomeric excess was determined by GC.[39]

3.2.4.7. Typical procedure of allylic alkylation of monosubstituted substrates S3 and S4.

A degassed solution of $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (1.8 mg, 0.005 mmol) and the corresponding phosphite-phosphoroamidite (0.011 mmol) in

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dichloromethane (0.5 mL) was stirred for 30 min at room temperature. Subsequently, a solution of substrate (0.5 mmol) in dichloromethane (1.5 mL), dimethyl malonate (171 μL, 1.5 mmol), *N*,*O*-bis(trimethylsilyl)-acetamide (370 μL, 1.5 mmol) and a pinch of KOAc were added. After 2 hours at room temperature, the reaction mixture was diluted with Et_2O (5 mL) and saturated NH_4Cl (aq) (25 mL) was added. The mixture was extracted with Et_2O (3 x 10 mL) and the extract dried over $MgSO_4$. Solvent was removed and conversion and regioselectivity were measured by ^{1}H-NMR. To determine the ee by HPLC (Chiralcel OJ, 13% 2-propanol/hexane, flow 0.7 mL/min), a sample was filtered over basic alumina using dichloromethane as the eluent.[40]

3.2.4.8. Typical procedure of allylic amination of disubstituted linear substates (S1 and S2).

A degassed solution of $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (0.9 mg, 0.0025 mmol) and the corresponding phosphite-phosphoroamidite (0.0055 mmol) in dichloromethane (0.5 mL) was stirred for 30 min. Subsequently, a solution of the corresponding substrate (0.5 mmol) in dichloromethane (1.5 mL) and benzylamine (131 μL, 1.5 mmol) were added. The reaction mixture was stirred at room temperature. After the desired reaction time, the reaction mixture was diluted with Et_2O (5 mL) and saturated NH_4Cl (aq) (25 mL) was added. The mixture was extracted with Et_2O (3 x 10 mL) and the extract dried over $MgSO_4$. For substrate **S1**, solvent was removed and conversion was measured by ^{1}H-NMR. To determine the ee by HPLC (Chiralcel OJ, 13% 2-propanol/hexane, flow 0.5 mL/min), a sample was filtered over silica using 10% Et_2O/hexane mixture as the

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eluent.[38] For substrate **S2**, conversion and enantiomeric excess was determined by GC.[41]

3.2.5. Acknowledgements

We thank the Spanish Government (Consolider Ingenio CSD2006-0003, CTQ2007-62288/BQU, 2008PGIR/07 to O.P. and 2008PGIR/08 to M.D.) and the Catalan Government (2005SGR007777 and Distinction to M.D.) for financial support.

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[26] The reactivity of the Pd-intermediates with sodium malonate at low temperature by *in situ* NMR indicates that isomer **28B** reacts around 20 times faster than isomer **28A**.

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3.2.7. Supporting Information

Table SI.1. Selected results for the Pd-catalyzed allylic substitution of **S1** using ligands **L1a**, **L2a**, **L3a** and **L4a**. Effect of the solvent and ligand to palladium ratio.

Table SI.2. Selected results for the Pd-catalyzed allylic substitution of **S2** using ligands **L1a**, **L2a**, **L3a** and **L4a**. Effect of the solvent and ligand to palladium ratio.

Table SI.3. Selected results for the Pd-catalyzed allylic amination of **S2** using ligands **L1-L4a-g**.

Table SI.4. Selected results for the Pd-catalyzed allylic substitution of **S5** using ligands **L1a**, **L2a**, **L3a** and **L4a**. Effect of the solvent and ligand to palladium ratio.

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Table SI.1. Selected results for the Pd-catalyzed allylic substitution of **S1** using ligands **L1a**, **L2a**, **L3a** and **L4a**. Effect of the solvent and ligand-to-palladium ratio.[a]

Entry	Ligand	Solvent	L/Pd	% Conv (t/min)[b]	% ee[c]
1	**L1a**	THF	1.1	18 (30)	48 (*S*)
2	**L1a**	CH_2Cl_2	1.1	85 (15)	62 (*S*)
3	**L1a**	Toluene	1.1	9 (30)	60 (*S*)
4	**L1a**	DMF	1.1	100 (5)	40 (*S*)
5	**L2a**	THF	1.1	12 (30)	36 (*S*)
6	**L2a**	CH_2Cl_2	1.1	64 (15)	55 (*S*)
7	**L2a**	Toluene	1.1	11 (30)	57 (*S*)
8	**L2a**	DMF	1.1	100 (5)	22 (*S*)
9	**L3a**	THF	1.1	15 (30)	38 (*R*)
10	**L3a**	CH_2Cl_2	1.1	41 (15)	42 (*R*)
11	**L3a**	Toluene	1.1	8 (30)	39 (*R*)
12	**L3a**	DMF	1.1	100 (15)	16 (*R*)
13	**L4a**	THF	1.1	11 (15)	43 (*S*)
14	**L4a**	CH_2Cl_2	1.1	72 (15)	49 (*S*)
15	**L4a**	Toluene	1.1	6 (30)	50 (*S*)
16	**L4a**	DMF	1.1	100 (15)	22 (*S*)
17	**L1a**	CH_2Cl_2	0.75	80 (15)	62 (*S*)
18	**L1a**	CH_2Cl_2	2	87 (15)	62 (*S*)
19	**L3a**	CH_2Cl_2	0.75	37 (15)	42 (*R*)
20	**L3a**	CH_2Cl_2	2	44 (15)	41 (*R*)

[a] All reactions were run at 25 ºC. 0.5 mol% $[PdCl(\eta^3\text{-}C_3H_5)]_2$. **S1** (0.5 mmol). BSA (1.5 mmol). Dimethyl malonate (1.5 mmol) [b] Conversion percentage determined by ^{1}H-NMR. [c] Enantiomeric excesses determined by HPLC on a Chiralcel-OD column. Absolute configuration drawn in parentheses.

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Table SI.2. Selected results for the Pd-catalyzed allylic substitution of **S2** using ligands **L1a**, **L2a**, **L3a** and **L4a**. Effect of the solvent and ligand-to-palladium ratio.[a]

Entry	Ligand	Solvent	L/Pd	% Conv (t/h)[b]	% ee[c]
1	**L1a**	THF	1.1	100 (0.5)	10 (*R*)
2	**L1a**	CH_2Cl_2	1.1	100 (0.5)	8 (*R*)
3	**L1a**	Toluene	1.1	17 (1)	10 (*R*)
4	**L1a**	DMF	1.1	100 (0.5)	4 (*R*)
5	**L2a**	THF	1.1	100 (0.5)	16 (*S*)
6	**L2a**	CH_2Cl_2	1.1	100 (0.5)	13 (*S*)
7	**L2a**	Toluene	1.1	12 (1)	15 (*S*)
8	**L2a**	DMF	1.1	100 (0.5)	5 (*S*)
9	**L3a**	THF	1.1	100 (0.5)	10 (*S*)
10	**L3a**	CH_2Cl_2	1.1	100 (0.5)	7 (*S*)
11	**L3a**	Toluene	1.1	19 (1)	8 (*S*)
12	**L3a**	DMF	1.1	100 (0.5)	2 (*S*)
13	**L4a**	THF	1.1	100 (0.5)	16 (*R*)
14	**L4a**	CH_2Cl_2	1.1	100 (0.5)	11 (*R*)
15	**L4a**	Toluene	1.1	14 (1)	12 (*R*)
16	**L4a**	DMF	1.1	100 (0.5)	3 (*R*)
17	**L1a**	CH_2Cl_2	0.75	100 (0.5)	10 (*R*)
18	**L1a**	CH_2Cl_2	2	100 (0.5)	10 (*R*)
19	**L3a**	CH_2Cl_2	0.75	98 (0.5)	10 (*S*)
20	**L3a**	CH_2Cl_2	2	100 (0.5)	10 (*S*)

[a] All reactions were run at 25 ºC. 0.5 mol% $[PdCl(\eta^3\text{-}C_3H_5)]_2$. **S2** (0.5 mmol). BSA (1.5 mmol). Dimethyl malonate (1.5 mmol) [b] Conversion percentage determined by ^{1}H-NMR. [c] Enantiomeric excesses determined by HPLC on a Chiralcel-OD column. Absolute configuration drawn in parentheses.

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Table SI.3. Selected results for the Pd-catalyzed allylic amination of **S2** using ligands **L1-L4a-g**.[a]

Entry	Ligand	% Conv (t/h)[b]	% ee[c]
1	**L1a**	87 (20)	9 (*R*)
2	**L2a**	96 (20)	14 (*S*)
3	**L2b**	100 (20)	7 (*S*)
4	**L2c**	25 (20)	33 (*S*)
5	**L2f**	29 (20)	24 (*S*)
6	**L2g**	74 (20)	72 (*S*)
7	**L3a**	97 (20)	10 (*S*)
8	**L4a**	89 (20)	17 (*R*)
9	**L4e**	65 (20)	71 (*R*)

[a] All reactions were run at 25 ºC. 0.5 mol% $[PdCl(\eta^3\text{-}C_3H_5)]_2$. **S2** (0.5 mmol). Benzylamine (1.5 mmol) [b] Conversion percentage determined by ^{1}H-NMR. [c] Enantiomeric excesses determined by HPLC. Absolute configuration drawn in parentheses.

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Table SI.4. Selected results for the Pd-catalyzed allylic substitution of **S5** using ligands **L1a**, **L2a**, **L3a** and **L4a**. Effect of the solvent and ligand-to-palladium ratio.[a]

Entry	Ligand	Solvent	L/Pd	% Conv (t/min)[b]	% ee[c]
1	**L1a**	THF	1.1	100 (120)	12 (*R*)
2	**L1a**	CH_2Cl_2	1.1	100 (120)	10 (*R*)
3	**L1a**	Toluene	1.1	11 (120)	13 (*R*)
4	**L1a**	DMF	1.1	100 (30)	2 (*R*)
5	**L2a**	THF	1.1	100 (120)	85 (*S*)
6	**L2a**	CH_2Cl_2	1.1	100 (120)	73 (*S*)
7	**L2a**	Toluene	1.1	9 (120)	83 (*S*)
8	**L2a**	DMF	1.1	100 (30)	43 (*S*)
9	**L3a**	THF	1.1	100 (120)	80 (*R*)
10	**L3a**	CH_2Cl_2	1.1	100 (120)	67 (*R*)
11	**L3a**	Toluene	1.1	14 (120)	79 (*R*)
12	**L3a**	DMF	1.1	100 (30)	32 (*R*)
13	**L4a**	THF	1.1	100 (120)	57 (*S*)
14	**L4a**	CH_2Cl_2	1.1	100 (120)	53 (*S*)
15	**L4a**	Toluene	1.1	16 (120)	57 (*S*)
16	**L4a**	DMF	1.1	100 (30)	23 (*S*)
17	**L1a**	CH_2Cl_2	0.75	95 (120)	12 (*R*)
18	**L1a**	CH_2Cl_2	2	100 (120)	11 (*R*)
19	**L3a**	CH_2Cl_2	0.75	96 (120)	79 (*R*)
20	**L3a**	CH_2Cl_2	2	100 (120)	80 (*R*)

[a] All reactions were run at 25 ºC. 0.5 mol% $[PdCl(\eta^3\text{-}C_3H_5)]_2$. **S5** (0.5 mmol). BSA (1.5 mmol). Dimethyl malonate (1.5 mmol) [b] Conversion percentage determined by ^{1}H-NMR. [c] Enantiomeric excesses determined by HPLC on a Chiralcel-OD column. Absolute configuration drawn in parentheses.

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3.3. Sugar-based diphosphoroamidite as a promising new class of ligands in the Pd-catalyzed asymmetric allylic alkylation reactions

Eva Raluy, Oscar Pàmies and Montserrat Diéguez in *J. Org. Chem.* **2007**, *72*, 2842.

Abstract. We have designed a new family of readily available modular diphosphoroamidite ligands from D-(+)-xylose for Pd-catalyzed asymmetric allylic alkylation reactions. This constitutes the first example of diphosphoroamidite ligands applied to this process. Good-to-excellent activities (TOF's up to 850 mol substrate x (mol Pd x h)$^{-1}$) and enantioselectivities (ee's up to 95%) have been obtained for several substrates with different electronic and steric properties. The results indicate that catalytic performance is highly affected by the substituents and the axial chirality of the biaryl moieties of the ligand. We also discuss the synthesis and characterization of the Pd-π-allyl intermediates to get more insight into the origin of enantioselectivity using these catalytic systems.

3.3.1. Introduction

The development of methods for enantioselective carbon-carbon bond formation is one of the key issues in organic synthesis. A versatile method for achieving this is the palladium-catalyzed asymmetric allylic substitution with carbon nucleophiles.[1] A large number of chiral ligands, mainly P- and N- ligands, which possess either C_2- or C_1- symmetry, have provided high enantiomeric excesses.[1] Most of the chiral ligands

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developed for asymmetric allylic substitution are mixed bidentate donor ligands (such as P-N, P-S and S-N).[1,2] The efficiency of this type of hard-soft heterodonor ligands has been mainly attributed to the different electronic effects of the donor atoms. However, homodonor ligands (e.g. diphosphine,[3] dithioether[4] and bisoxazoline[5] ligands) have, though to a lesser extent, also demonstrated their potential usefulness in this process mainly based on the chiral discrimination induced by C_2 or C_1 backbone symmetry. Recently, a group of less electron-rich phosphorus compounds–biaryl diphosphite ligands–have also demonstrated their potential utility by overcoming the most common limitations of this process, such as low reaction rates and high substrate specificity.[6] Therefore, these ligand systems have provided excellent enantioselectivities and activities in different substrate types.[6] Using biaryl phosphites was beneficial because: (1) the reaction rates increased due to the larger π-acceptor ability of the phosphite moiety,[7] and (2) enantioselectivity increased because the chiral pocket (the chiral cavity where the allyl is embedded) created is flexible enough to allow the perfect coordination of hindered and unhindered substrates (which decreases the substrate specificity).[8]

Following our interest in highly modular, versatile π-acceptor ligands, and encouraged by the success of the phosphoroamidite ligands in asymmetric catalysis,[9] we report here the synthesis of a new family of furanoside diphosphoroamidite ligands (**L5a-d**,**f-g**; Figure 1) for the enantioselective Pd-catalyzed allylic alkylation reactions. We also discuss the synthesis and characterization of the Pd-π-allyl intermediates to get more insight into the origin of the enantioselectivity using these catalytic systems.

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These diphosphoroamidite ligands are derived from natural D-(+)-xylose so they also have the advantage of carbohydrates, such as availability at a low price and facile modular construction, which makes the tedious optical resolution procedure unnecessary.[10] The modular construction of these ligands allows sufficient flexibility to fine-tune the steric and electronic properties of the biaryl moieties to explore how they affect catalytic performance (activity and selectivity). In this way, we studied how attaching different groups to the *ortho*- and *para*-positions of the biphenyl moieties affects the catalytic performance with ligands **L5a-d**. To further investigate how enantioselectivity was influenced by the configuration of the biaryl moieties, ligands **L5f-g** containing different enantiomerically pure binapthyl moieties were also tested. As a result, the optimal combination for maximum activity and selectivity for different substrates types were reached.

To the best of our knowledge this is the first example of diphosphoroamidite ligands applied to the enantioselective Pd-catalyzed allylic substitution reactions.

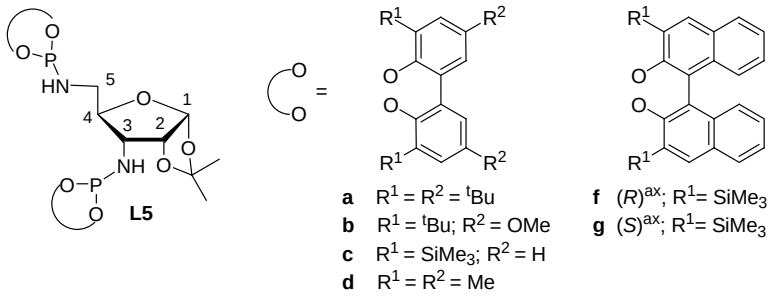

Figure 1. Diphosphoroamidite ligands **L5a-d**,**f-g**.

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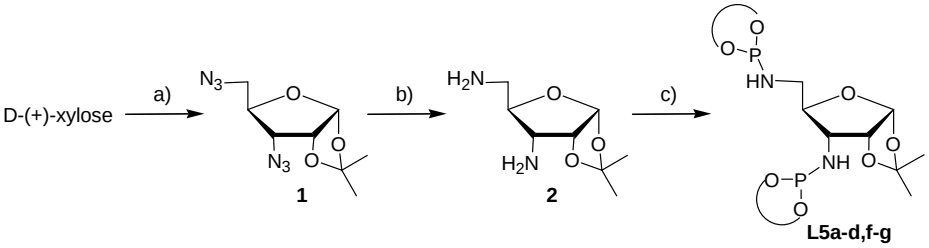
3.3.2. Results and Discussions

3.3.2.1. Synthesis of ligand library

The new diphosphoroamidite ligands **L5a-d**,**f-g** were synthesized very efficiently from diamine **2** by reacting two equiv of the desired *in situ*-formed phosphorochloridite[11] in the presence of pyridine. 3,5-Dideoxy-3,5-diamino-1,2-*O*-isopropylidene-ribofuranose **2** was easily prepared on a large scale from inexpensive D-(+)-xylose. All the ligands were stable during purification on neutral alumina under an atmosphere of argon and isolated in moderate yields as white solids. The ^{1}H, ^{31}P and ^{13}C NMR spectra were as expected for these C_1 ligands (see Experimental Section).



Scheme 1. Synthesis of the new diphosphoroamidite ligands **L5a-d**,**f-g**. a) ref. 12; b) PPh_3, THF/H_2O; c) $ClP(OR)_2$, Py, toluene.

3.3.2.2. Asymmetric Allylic Alkylation Reactions

We first investigated the Pd-catalyzed allylic substitution of *rac*-1,3-diphenyl-3-acetoxyprop-1-ene **S1**, which is widely used as a model substrate, with dimethyl malonate using the chiral diphosphoroamidite ligands **L5a-d**,**f-g** (eq. 1). The catalysts were generated *in situ* from 0.5 mol% of π-allyl-palladium chloride dimer $[PdCl(\eta^3\text{-}C_3H_5)]_2$, the corresponding ligand and a catalytic amount of KOAc. The nucleophile

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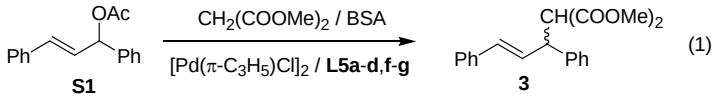
was generated from dimethyl malonate in the presence of *N,O*-bis(trimethylsilyl)acetamide (BSA).



(1)

We determined the optimal reaction conditions by conducting a series of experiments in which the solvent and the ligand-to-palladium ratio were varied. We first studied the effect of four solvents with ligand **L5a** (Table 1, entries 1-4). The best activity and enantioselectivity was achieved with dichloromethane as solvent (entry 1). We next studied the effect of varying the ligand-to-palladium ratio (Table 1, entries 1, 5 and 6). The results show that excess of ligand is not needed for good activities and enantioselectivities.

Table 1. Pd-catalyzed allylic alkylation of **S1** using ligand **L5a**. Effect of the solvent and ligand-to-palladium ratio.[a]

Entry	Solvent	Ratio **L5a**/Pd	% Conv[b] (min)	% ee[c]
1	CH_2Cl_2	1.1	100 (15)	66 (*R*)
2	DMF	1.1	90 (15)	53 (*R*)
3	Toluene	1.1	10 (15)	58 (*R*)
4	THF	1.1	20 (15)	54 (*R*)
5	CH_2Cl_2	0.8	62 (15)	67 (*R*)
6	CH_2Cl_2	2	100 (15)	62 (*R*)

[a] 0.5 mol% $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$, 30 min; 3 equiv of $CH_2(COOMe)_2$ and *N,O*-bis(trimethylsilyl)acetamide (BSA), a pinch of KOAc, room temperature. [b] Measured by ^1H NMR. Reaction time in minutes shown in parentheses. [c] Determined by HPLC (Chiralcel OD). Absolute configuration shown in parentheses.

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For comparative purposes, the rest of the ligands were tested under conditions that provided the optimum trade-off between enantioselectivities and reaction rates, i.e. a ligand-to-palladium ratio of 1.1 and dichloromethane as a solvent. The results, shown in Table 2, indicate that catalytic performance (activities and enantioselectivities) is highly affected by the substituents and the axial chirality of the biaryl moieties. In general, good activity (TOF's up to 850 mol **S1** x (mol Pd x h)$^{-1}$)[13] and enantioselectivity (ee's up to 75%) were obtained in the alkylation of **S1**.

The effect of the biphenyl substituents was investigated with ligands **L5a-d** (Table 2, entries 1-4). We found that these moieties affect both activity and enantioselectivity. Substituents in the *para* positions of the biphenyl moieties are required for good enantioselectivity (Table 2, entries 1, 2 and 4 vs 3). Thus, ligands **L5a-b** and **L5d** with substituents at *para* positions of the biphenyl moieties provided higher enantioselectivities than ligand **L5c**, without substituents in these positions. However, the type of substituents in the *para* positions is also important. Therefore, the presence of the methoxy group in the biphenyl moieties has a negative effect on both activity and enantioselectivity (Table 2, entry 1 *vs* 2). Moreover, the substituents in the *ortho* positions of the biphenyl moieties have a slight but important effect on both activity and enantioselectivity (Table 2, entries 1 *vs* 4). Activities and enantioselectitivies are therefore highest when *tert*-butyl groups are present at both *ortho* and *para* positions of the biphenyl moieties.

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Table 2. Pd-catalyzed allylic alkylation of **S1** with ligands **L5a-d**,**f-g**.[a]

Entry	Ligand	% Conv (min)[b]	% ee[c]
1	**L5a**	100 (15)	66 (*R*)
2	**L5b**	33 (15)	59 (*R*)
3	**L5c**	11 (15)	13 (*S*)
4	**L5d**	87 (15)	63 (*R*)
5	**L5f**	78 (30)	75 (*R*)
6	**L5g**	85 (30)	30 (*R*)
7[d]	**L5a**	98 (60)	66 (*R*)
8[d]	**L5f**	24 (150)	74 (*R*)

[a] 0.5 mol% $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$, 1.1 mol% ligand, room temperature. [b] Measured by ^{1}H-NMR. Reaction time in minutes shown in parentheses. [c] Determined by HPLC (Chiralcel-OD). Absolute configuration shown in parentheses. [d] Reaction carried out at 0.1 mol% of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$.

To further investigate how enantioselectivity was influenced by the groups attached to the biaryl moieties, ligands **L5f-g** containing different enantiomerically pure binapthyl moieties were also tested (Table 2, entries 5 and 6). Ligand **L5f** containing *R*-binaphtyl moieties produced the *R*-**9** product in 75% ee, while ligand **L5g** containing *S*-binaphtyls produced the *R*-**9** product in lower enantioselectivity (30% ee). These results indicate that there is a cooperative effect between the configuration of the biaryl moieties and the configurations of the ligand backbone that results in a matched combination for ligand **L5f**. Note that this cooperative effect is highly advantageous, allowing us to increase enantioselectivity up to 75% ee (entry 5).

We also performed the reaction at a low catalyst concentration (**S1**/Pd = 500) using ligands **L5a** and **L5f** (entries 7 and 8). Good

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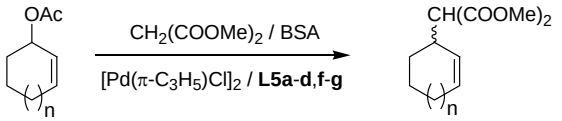
enantioselectivity (ee's up to 74% (*R*)) and high activity (TOF's up to > 560 mol **S1** x (mol Pd x h)$^{-1}$) were obtained.

We next tested this new family of ligands in the Pd-catalyzed asymmetric allylic alkylation of cyclic substrates (eq. 2). Enantioselectivity in cyclic substrates is usually more difficult to control, mainly because of the presence of less sterically demanding *syn* substituents, which play a crucial role in the enantioselection observed with acyclic substrates in the corresponding Pd-allyl intermediate.[1] Therefore, few catalytic systems have provided good enantioselectivities.[3b,3d,7b,14]

We first tested the efficiency of the chiral diphosphoroamidite ligands **L5a-d**,**f-g** in the Pd-catalyzed allylic alkylation of *rac*-3-acetoxycyclohexene **S2** (eq. 2), which is usually used as a model cyclic substrate.



(2)

S2 n = 1
S3 n = 2

4
5

The preliminary investigations into the solvent effect, and the ligand-to-palladium ratio using ligand **L5a** provided a different trend for the solvent effect than those into the previously tested substrate **S1**. Therefore, the best enantioselectivities and reaction rates were obtained when THF was used as solvent and the ligand-to-palladium ratio was 1.1 (Table 3).

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Table 3. Pd-catalyzed allylic alkylation of **S2** using ligand **L5a**. Effect of the solvent and ligand-to-palladium ratio.[a]

Entry	Solvent	Ratio **L5a**/Pd	% Conv[b] (min)	% ee[c]
1	CH_2Cl_2	1.1	100 (120)	82 (*S*)
2	DMF	1.1	100 (120)	75 (*S*)
3	Toluene	1.1	56 (120)	79 (*S*)
4	THF	1.1	100 (120)	88 (*S*)
5	THF	0.8	95 (120)	88 (*S*)
6	THF	2	100 (120)	86 (*S*)

[a] 0.5 mol% $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$, 30 min; 3 equiv of $CH_2(COOMe)_2$ and *N*,*O*-bis(trimethylsilyl)acetamide (BSA), a pinch of KOAc, room temperature. [b] Measured by GC. Reaction time in minutes shown in parentheses. [c] Determined by GC. Absolute configuration shown in parentheses.

The results of using ligands **L5a-d**,**f-g** under the optimized conditions are shown in Table 4. In general, high enantioselectivity (ee's up to 88%) with good activity were obtained in the alkylation of **S2**. Again, enantioselectivity was affected by the substituents at the biaryl moieties and the cooperative effect between stereocenters. However, the effect of these parameters was different from those observed in the alkylation of **S1**. Therefore, enantioselectivity was best with ligand **L5a** (88% (*S*) ee). These results clearly show the importance of using modular scaffolds in the ligand design.

Regarding the effect of the substituents in the biphenyl moieties, again substituents in the *para* position are necessary for high ee's (entries 1 and 2 vs 3). However, in contrast to the alkyltaion of **S1**, the effect of the type of substituent in *ortho* positions is more significant. Therefore, enantioselectivities and activities are higher when more sterically demanding substituents are present (i.e. ^{t}Bu > Me).

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Concerning the effect of the configuration of the biaryl moieties, the cooperative effect previously reported with substrate **S1** also showed a different tendency and the matched combination was therefore observed for ligand **L5g** (entries 5 and 6).

Encouraged by the excellent results obtained in the alkylation of cyclic substrate **S2**, we examined the stereoselective allylic alkylation of the 7-membered cyclic substrate **S3** using ligand **L5a** (Table 4, entry 7). Interestingly, for this sterically undemanding substrate, high enantioselectivities (ee's up to 95%) were also obtained.

In summary the results obtained with cyclic substrates are amongst the best reported so far.[3b, 3d, 7b, 14]

Table 4. Pd-catalyzed allylic alkylation of **S2** and **S3** with ligands **L5a-d**,**f-g**.[a]

Entry	Ligand	Substrate	% Conv (min)[b]	% ee[c]
1	**L5a**	**S2**	100 (120)	88 (*S*)
2	**L5b**	**S2**	100 (120)	76 (*S*)
3	**L5c**	**S2**	90 (120)	17 (*S*)
4	**L5d**	**S2**	32 (120)	5 (*S*)
5	**L5f**	**S2**	19 (120)	56 (*R*)
6	**L5g**	**S2**	42 (120)	72 (*S*)
7	**L5a**	**S3**	51 (360)	95 (*S*)

[a] 0.5 mol% $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$, 1.1 mol% ligand, room temperature. [b] Conversion percentage of acetates **4** and **5** determined by GC. Reaction time in minutes shown in parentheses. [c] Enantiomeric excesses determined by GC. Absolute configuration shown in parentheses.

To further study the potential of these readily available ligands, we also tested them in the allylic alkylation of the monosubstituted linear substrate 1-(1-naphthyl)allyl acetate **S4** (eq. 3). For this substrate, as well as controlling the enantioselectivity of the process, the regioselectivity is

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also a problem, because a mixture of regioisomers may be obtained. Most Pd-catalysts developed to date favor the formation of the achiral linear product **7** rather than the desired branched isomer **6**.[1] Therefore, the development of highly regio- and enantioselective Pd-catalysts is still a challenge.[15] The results are summarized in Table 5. Interestingly, under non-optimized conditions, the catalytic system containing ligand **L5a** produced the desired branched isomer as the major product with high activity and enantioselectivity (ee's up to 83% (*S*)). The results indicate that enantioselectivities are highly affected by the substituents in the *para* position of the biphenyl moieties (Table 5, entries 1-4). However, regioselectivity is mainly governed by the substituents at the *ortho* positions (Table 5, entries 1-4). It should be note that the cooperative effect previously observed with substrates **S1** and **S2** has the main effect on regioselectivity (Table 5, entries 5 and 6). These results are among the best reported so far[15] and it is clear that they represent a major improvement over other Pd-homodonor bidentate catalytic systems[16] that predominantly provide the linear achiral product as the major one.

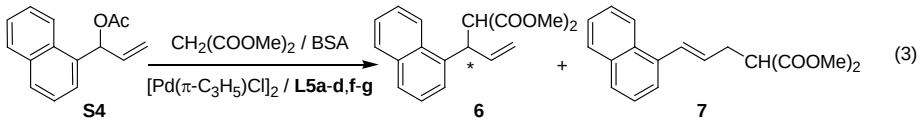

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Table 5. Selected results for the Pd-catalyzed allylic alkylation of **S4**.[a]

Entry	Ligand	% Conv[b] (min)	**6**/**7**[c]	% ee[d]
1	**L5a**	100 (30)	65/35	76 (*S*)
2	**L5b**	100 (30)	65/35	22 (*R*)
3	**L5c**	100 (30)	60/40	13 (*S*)
4	**L5d**	100 (30)	40/60	72 (*S*)
5	**L5f**	100 (30)	65/35	33 (*R*)
6	**L5g**	100 (30)	80/20	20 (*S*)
7[e]	**L5a**	100 (120)	65/35	83 (*S*)

[a] 0.5 mol% $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$, 1.1 mol% ligand, room temperature. [b] Conversion percentage measured by ^{1}H-NMR. Reaction time in minutes shown in parentheses. [c] Branched to linear ratio determined by ^{1}H-NMR. [d] Enantiomeric excesses determined by HPLC. Absolute configuration shown in parentheses. [e] T = 0 °C.

To sum up, these diphosphoroamidite ligands have provided good results in different substrates types. The high activities and enantioselectivities (ee's up to 95%) obtained for cyclic substrates are particularly noteworthy as is the combination of high regio- and enantioselectivitities (regio's up to 65% and ee's up 83%) for monosubstituted substrate **S4**. These facts, along with the promising results obtained for substrate **S1**, open up the Pd-catalyzed allylic alkylation reactions to a new class of ligands –the diphosphoroamidites-. The efficiency of the ligand design is also corroborated by the fact that these Pd-diphosphoroamidite catalysts provide higher activities, regio- and enantioselectioselectivities than their Pd-diphosphite analogues[6b] (Scheme 2). In addition, these ligands provide comparable results to those with related heterodonor phosphite-phosphoroamidite ligands (**L2** and **L4**) recently described for this process.[9i]

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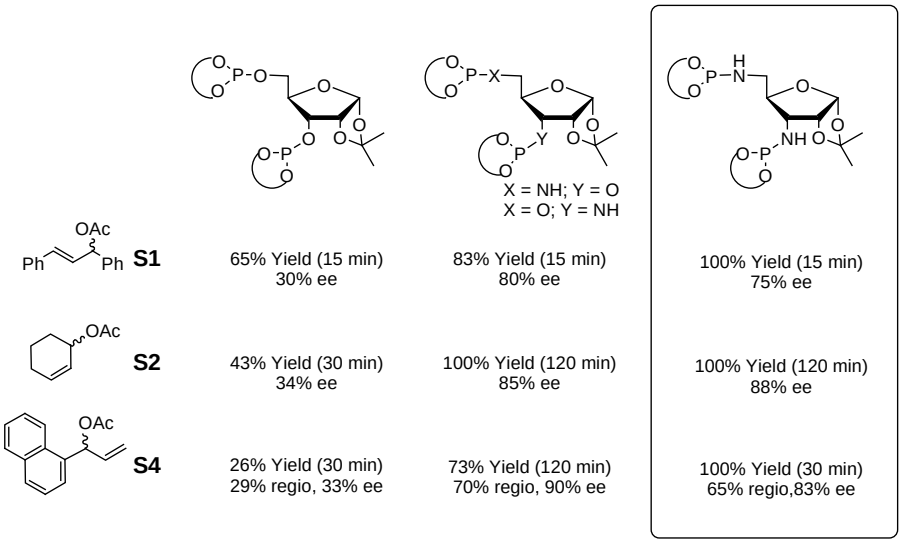

Scheme 2.

3.3.2.3. Origin of enantioselectivity. Study of the Pd-π-allyl intermediates

In order to get more insight into the effect of the ligand parameters on catalytic performance, we performed a study of the Pd-π-allyl compounds **8-11**, $[Pd(\eta^3\text{-allyl})(L)]BF_4$ (L = diphosphoroamidite ligands), since they are key intermediates in the studied allylic alkylation reactions (Scheme 3).[1] These ionic palladium complexes containing 1,3-diphenyl and cyclohexenyl groups were prepared from the corresponding palladium allyl dimer and the appropriate ligand in the presence of silver tetrafluoroborate, following the previously described methodology (Scheme 3).[17] The complexes were characterized in solution using ^1H, ^{13}C, and ^{31}P NMR spectroscopy. The spectral assignments (see Experimental Section) were based on information from ^1H–^1H, ^{31}P-^1H and ^{13}C–^1H correlation measurements in combination with ^1H-^1H NOESY experiments.

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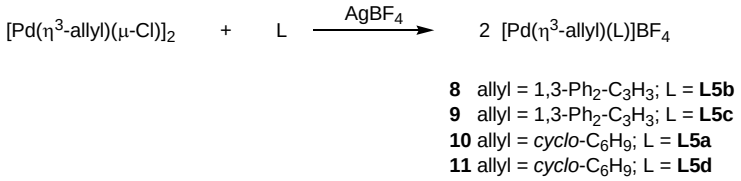

Scheme 3. Preparation of Pd-allyl intermediates **8-11**.

3.3.2.3.1. Palladium 1,3-diphenyl-allyl complexes

To understand the differences in catalytic performance observed in the alkylation of **S1** using ligands **L5a-d**,**f-g**, we decided to study the 1,3-diphenylallyl palladium-complexes containing ligand **L5b** (which provided product *R*-**9** in good enantioselectivity) and ligand **L5c** without substituents on the *para* positions of the biphenyl moieties (which provided low enantioselectivity in the reversed enantiomer). In addition, this study allowed us to explain the important effect of the *para* substituents of the biphenyl groups on catalytic performance (see above).

The NMR study of the Pd-allyl intermediate containing ligand **L5b**, [Pd(η^3-1,3-diphenylallyl)(**L5b**)]BF_4 (**8**), showed a mixture of two isomers in a ratio of 1:1 (see Experimental Section). No changes were observed down to –80 °C. Both isomers could be unambiguously assigned by NOE to the two *syn*/*syn* isomers (Scheme 4). The carbon NMR chemical shifts indicates for both isomers that the most electrophilic allylic carbon terminus is *trans* to the phosphorous at C-5 position (P_2). Assuming that the nucleophilic attack takes place at the more electrophilic carbon terminus[18] and based on the observed stereochemical outcome of the reaction, 59% (*R*) in product **3**, and the fact that enantiomeric excess of **3** is higher than the diastereoisomeric excess of the Pd-intermediates, the **B** isomer must react faster than the **A** isomer. This is consistent with the fact that for both isomers, the most

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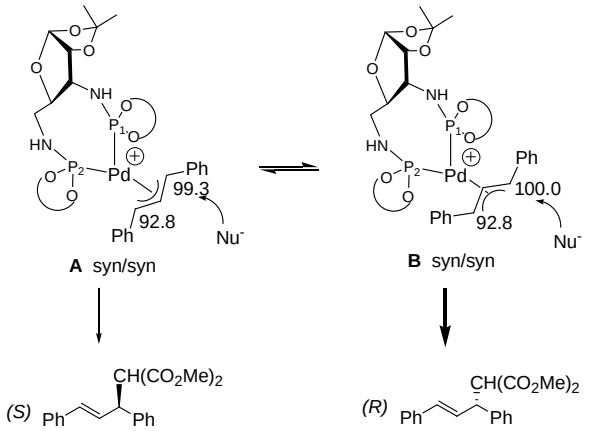
electrophilic allylic terminal carbon atom is the one *trans* to the phosphorous at C-5 (P_2) in the **B** isomer.



Scheme 4. Diastereoisomer Pd-allyl intermediates **8**. P_1 phosphorous atom next to C-3. P_2: phosphorous atom next to C-5 (assigned by ^{31}P-^{1}H HMBC correlation experiment).

The NMR study of the Pd-allyl intermediate containing ligand **L5c**, [Pd(η^3-1,3-diphenylallyl)(**L5c**)]BF_4 (**9**), showed a mixture of two isomers in a ratio of 1:1 (see Experimental Section). One of the isomers could be unambiguously assigned by NOE experiment to a *syn*/*syn* isomer **A** (Scheme 5). However, for the other isomer and in contrast to **8**, the VT-^{31}P NMR spectra indicated a fluxional behavior for the phosphorous next to C-3 (P_1) in isomer **B** (assigned by ^{31}P-^{1}H HMBC correlation experiment) that could not be frozen out until –80 C. This fluxionability can be attributted to an equilibrium between *syn*/*syn* and *syn*/*anti* isomers (Scheme 5) or to the fluxional behavior of the biphenyl moieties. However, the study of the models suggested that the absence of the *para* substituents in the biphenyl moieties in ligand **L5c** caused a different orientation of the biphenyl moieties in the Pd-π-allyl intermediate than for

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complex **8** which resulted in a new steric repulsion between one of the biphenyl moieties and one of the phenyl substituents of **S1** in this isomer (Scheme 5). The formation of the *anti* isomer minimized this new steric repulsion. It should be noted that this *syn*/*anti* isomerism is observed at the most electrophilic allylic terminal carbon (the one exhibiting the highest ^{13}C chemical shifts).

Another important difference between complexes **8** and **9** was found in the ^{13}C NMR spectra. For each isomer of complex **9** the electronic differences between both allylic terminal carbons ($\Delta(\delta^{13}C) \approx 1$ ppm) decreased considerably compared to those of isomers of **8** ($\Delta(\delta^{13}C) \approx 8$ ppm). Therefore, the electrophilicity of the allylic terminal carbons for **9** decreased.

In summary, the notable decrease in enantioselectivity observed using the Pd/**L5c** catalyst in comparison with the Pd/**L5b** catalyst system may be due to either the presence of a *syn*/*syn* and *syn*/*anti* equilibrium or the possibility that the nucleophile attacks at both allylic terminal carbons in each isomer, due to their low electronic differentiation ($\Delta(\delta^{13}C) \approx 1$ ppm), or a combination of both. However, the fact that the allylic terminal carbons in complex **8** are more electrophilic may explain the higher activities obtained with the Pd/**L5b** catalytic system (Table 2, entries 2 *vs* 3).

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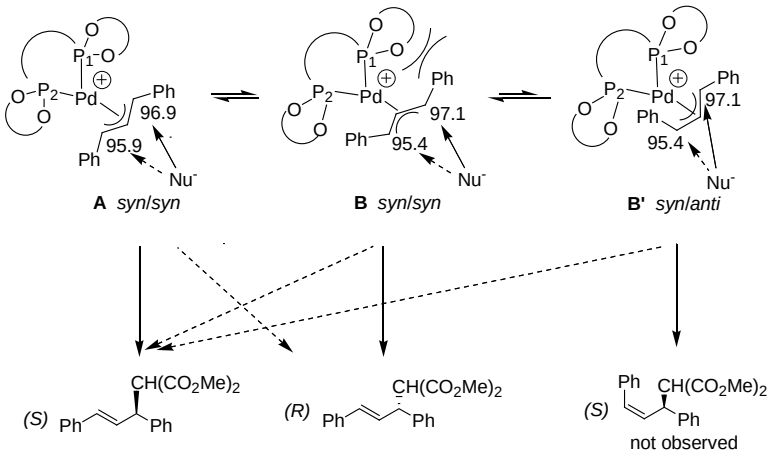

Scheme 5. Diastereoisomer Pd-allyl intermediates **9**. P_1 phosphorous atom next to C-3. P_2: phosphorous atom next to C-5 (assigned by ^{31}P-^{1}H HMBC correlation experiment).

3.3.2.3.2. Palladium 1,3- cyclohexenyl-allyl complexes

In order to elucidate the difference in catalytic performance observed with ligands **L5a-d**,**f-g** in the alkylation of cyclic substrates (**S2** and **S3**), we next studied the ionic palladium complexes containing the cyclohexenyl groups. In contrast to the alkylation of **S1**, the substituents in the *ortho* positions of the biaryl moieties also have a considerable effect on catalytic performance. For this reason, we decided to study the cyclohexenyl allyl-palladium complexes containing ligand **L5a** (which provided the best enantioselectivity) and ligand **L5d** (which provided the lowest enantioselectivity).

The NMR study of the Pd-allyl intermediate containing ligand **L5a**, [Pd(η^3-*cyclo*-C_6H_9)(**L5a**)]BF_4 (**10**), showed a mixture of two isomers in a ratio of 1:1 (see Experimental Section). Both isomers could be assigned by NOE to the two *syn*/*syn* isomers (Scheme 6). The carbon NMR chemical shifts indicated for both isomers that the most

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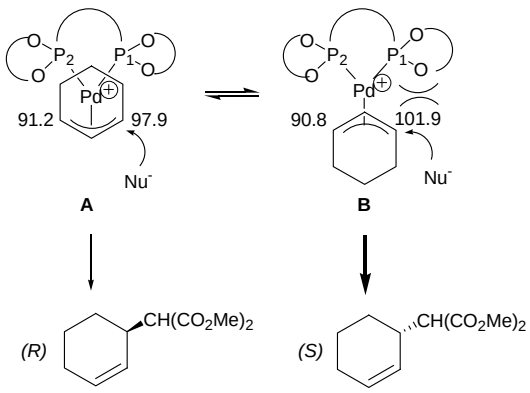
electrophilic allylic terminus carbon is *trans* to the phosphorous at C-5 position (P_2). Assuming that the nucleophilic attack takes place at the most electrophilic allylic carbon terminus and based on the observed stereochemical outcome of the reaction, 88% (*S*) in product **4**, and the fact that enantiomeric excess of **4** is higher than the diastereoisomeric excesses of the Pd-intermediates, the **B** isomer must react faster than the **A** isomer. This is consistent with the fact that for both isomers the most electrophilic allylic carbon atom is the one *trans* to the phosphorous at C-5 in the **B** isomer.



Scheme 6. Diastereoisomer Pd-allyl intermediates **10**. P_1 phosphorous atom next to C-3. P_2: phosphorous atom next to C-5 (assigned by ^{31}P-^{1}H HMBC correlation experiment).

In contrast to complex **10**, the NMR study of the Pd-allyl intermediate containing ligand **L5d**, [Pd(η^3-*cyclo*-C_3H_9)(**L5d**)]BF_4 (**11**), revealed the presence of one isomer in excess 1.8:1 (see Experimental Section). Both isomers could be assigned by NOE to the two *syn*/*syn* isomers (Scheme 7). Another important difference between complexes **10** and **11** is the lower electronic differentiation between the more electrophilic allylic terminus carbon atoms of both isomers (**A** and **B**) in

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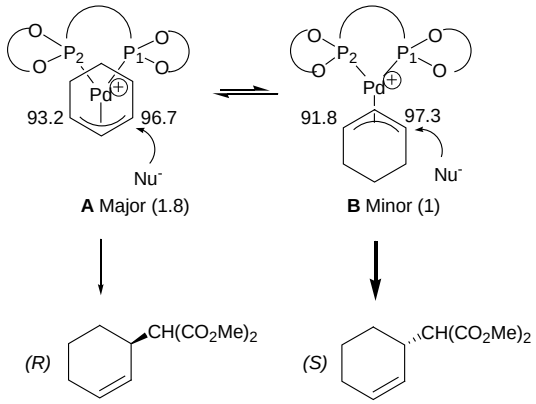
complex **11** ($\Delta(\delta^{13}C) \approx 0.6$ ppm) than in complex **10** ($\Delta(\delta^{13}C) \approx 4$ ppm). This low electronic differentiation suggests that the nucleophile can attack both isomers at a similar rate. However, the difference between the diastereoisomeric ratio and enantioselectivity observed in the alkylation of **S2** (d.e = 28% vs ee = 5%) indicates that the nucleophile reacts faster with the minor isomer, but the relative reaction rates between both isomers is much lower than in complex **10**. The lower activity observed with Pd/**L5d** catalytic system may be due to fact that the allylic terminal carbons in complex **11** are less electrophilic than with complex **10** (Table 4, entries 1 *vs* 4).



Scheme 7. Diastereoisomer Pd-allyl intermediates **11**. P_1 phosphorous atom next to C-3. P_2: phosphorous atom next to C-5 (assigned by ^{31}P-^{1}H HMBC correlation experiment).

3.3.3. Conclusions

In summary, we have described the first application of diphosphoroamidite ligands for the Pd-catalyzed asymmetric allylic substitution reactions of several substrate types. These ligands have the

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advantage of being easily prepared in a few steps from commercial D-(+)-xylose, an inexpensive natural chiral feedstock. In addition, they can be easily tuned so the effect of different substituents and configurations of the biaryl moieties on catalytic performance can be explored. By carefully selecting the ligand components, we obtained good results in different substrate types. Particularly, for the hindered disubstituted linear substrate **S1**, we found that substituents in the *para* positions of the biphenyl moieties are needed for good enantioselectivity. However for cyclic substrates **S2** and **S3**, in addition to the presence of para substituents, the presence of bulky substituents in the *ortho* positions are necessary for high enantioselectivity. For the monosubstituted linear substrate **S5**, the results indicate that enantioselectivities are highly affected by the substituents in the *para* position of the biphenyl moieties. However, regioselectivity is mainly governed by the substituents at the *ortho* positions. Therefore, the presence of substituents in the *para* positions combined with bulky substituents in the *ortho* positions of the biaryl moieties are necessary to obtain the optimum trade-off between regio- and enantioselectivities. The study of the 1,3-diphenyl and cyclohexenyl Pd-π-allyl intermediates by NMR spectroscopy allows the understanding of the catalytic behaviour observed. This study indicates that the nucleophilic attack takes place predominantly at the allylic terminal carbon atom located *trans* to the phosphoroamidite moiety attached to C-5.

The high activities and enantioselectivities (ee's up to 95%) obtained for cyclic substrates **S2** and **S3** are particularly noteworthy as is the combination of high regio- and enantioselectivitities (regio's up to 65% and ee's up 83%) for monosubstituted substrate **S4**. These facts

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together with the promising results obtained for substrate **S1** open up the Pd-catalyzed allylic alkylation reactions to a new class of ligands –the diphosphoroamidites-.

3.3.4. Experimental Section

3.3.4.1. General considerations.

All reactions were carried out using standard Schlenk techniques under an atmosphere of argon. Solvents were purified and dried by standard procedures. 3,5-Dideoxy-3,5-diazido-1,2-*O*-isopropylidene-ribofuranose **1**[12] and phosphorochloridites[11] were prepared as previously described. ^{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.

3.3.4.2. Synthesis of 3,5-dideoxy-3,5-diamino-1,2-O-isopropylidene-ribofuranose (2).

3,5-Dideoxy-3,5-diazido-1,2-*O*-isopropylidene-ribofuranose **1** (2.0 g, 4.1 mmol) was dissolved in a THF:H_2O (90 mL, 4:1), and triphenylphosphine (5.0 g, 19.1 mmol) was added. The reaction mixture was stirred overnight at room temperature, and the THF was evaporated under vacuum. The residue was extracted with ether (3 x 20 mL). Evaporation of the aqueous solution gave the product as a yellow oil Yield: 1.2 g, 77 %. ^{1}H NMR, δ: 1.34 (s, 3H; CH_3), 1.53 (s, 3H; CH_3), 1.62 (b, 4H, NH_2), 2.83 (dd, 1H, H-5', $^{2}J_{5',-5} = 13.6$ Hz, $^{3}J_{5',-4} = 6$ Hz), 3.02 (m, 1H, H-3), 3.07 (dd, 1H, H-5, $^{2}J_{5-5'} = 13.6$ Hz, $^{3}J_{5-4} = 3.2$ Hz), 3. 66 (m, 1H, H-4), 4.46 (t, 1H, H-2, $^{3}J_{2-1} = {}^{3}J_{2-3} = 4$ Hz), 5.77 (d, 1H, H-1, $^{3}J_{1-2} = 4$ Hz).

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^{13}C NMR, δ: 26.6 (CH_3), 26.8 (CH_3), 42.9 (C-5), 56.4 (C-3), 81.0 (C-2), 82.4 (C-4), 104.3 (C-1), 112.1 (CMe_2). Anal. calcd (%) for $C_8H_{16}N_2O_3$: C 51.05, H 8.57, N 14.88; found: C 51.12, H 8.64, N 14.97.

3.3.4.3. General procedure for the synthesis of diphosphoroamidite ligands L5a-d,f-g

Phosphorochloridite (2.2 mmol) produced *in situ* was dissolved in toluene (5 mL) and pyridine (0.36 mL, 4.6 mmol) was added. Diamine **2** (189 mg, 1 mmol) was azeotropically dried with toluene (3 x 1 mL) and then dissolved in toluene (10 mL), to which pyridine (0.36 mL, 4.6 mmol) was added. The phosphorochloridite solution was transferred slowly over 5 minutes at room temperature to the solution of **2**. The reaction mixture was warmed up to 80 ºC and stirred overnight, and the pyridine salts were removed by filtration. Evaporation of the solvent gave a white foam, which was purified by flash chromatography over neutral alumina (toluene/NEt_3 = 100/2) to produce the corresponding ligand as white powder.

L5a. Yield: 0.55 g, 52 %. ^{31}P NMR (C_6D_6), δ: 149.4 (d, 1P, $J_{P\text{-}P}$ = 4 Hz), 150.7 (d, 1P, $J_{P\text{-}P}$ = 4 Hz). ^{1}H NMR (C_6D_6), δ: 1.12 (s, 3H, CH_3), 1.24 (s, 9H, CH_3, ^{t}Bu), 1.25 (s, 9H, CH_3, ^{t}Bu), 1.32 (s, 18H, CH_3, ^{t}Bu), 1.48 (s, 3H, CH_3), 1.58 (s, 9H, CH_3, ^{t}Bu), 1.62 (s, 9H, CH_3, ^{t}Bu), 1.63 (s, 18H, CH_3, ^{t}Bu), 3.04 (m, 1H, H-5'), 3.26 (m, 1H, NH-C-3), 3.35 (m, 1H, H-3), 3.40 (m, 1H, NH-C-5), 3.56 (m, 1H, H-5), 3.62 (m, 1H, H-4), 3.68 (m, 1H, H-2), 5.33 (d, 1H, H-1, $^3J_{1\text{-}2}$ = 4 Hz), 7.0-7.6 (m, 8H, CH=). ^{13}C NMR (C_6D_6), δ: 26.7 (CH_3), 27.0 (CH_3), 31.9 (CH_3, ^{t}Bu), 32.0 (CH_3, ^{t}Bu), 32.1 (CH_3, ^{t}Bu), 32.3 (CH_3, ^{t}Bu), 35.0 (C, ^{t}Bu), 36.0 (C, ^{t}Bu), 36.1 (C, ^{t}Bu), 42.6 (d, CH_2, $J_{C\text{-}P}$ = 24.2 Hz), 55.7 (d, CH_2, $J_{C\text{-}P}$ = 15.9 Hz),

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80.8 (C-2), 81.9 (C-4), 104.3 (C-1), 112.2 (CMe_2), 124.4 (CH=), 124.5 (CH=), 124.7 (CH=), 124.9 (CH=), 126.9 (CH=), 127.1 (CH=), 127.2 (CH=), 127.3 (CH=), 127.6 (CH=), 134.2 (C), 134.4 (C), 134.5 (C), 134.7 (C), 141.2 (C), 141.3 (C), 146.6 (C), 146.7 (C), 146.8 (C), 147.0 (C). Anal. calcd (%) for $C_{64}H_{94}N_2O_7P_2$: C 72.15, H 8.89, N 2.63; found: C 72.45, H 8.59, N 2.49.

L5b. Yield: 0.41 g, 43 %. ^{31}P NMR (C_6D_6), δ: 148.5 (s, 1P), 151.4 (s, 1P). ^{1}H NMR (C_6D_6), δ: 1.10 (s, 3H, CH_3), 1.29 (s, 3H, CH_3), 1.52 (s, 9H, CH_3, ^{t}Bu), 1.54 (s, 9H, CH_3, ^{t}Bu), 1.55 (s, 9H, CH_3, ^{t}Bu), 1.58 (s, 9H, CH_3, ^{t}Bu), 3.15 (m, 1H, H-5'), 3.26 (s, 3H; OCH_3), 3.31 (s, 3H; OCH_3), 3.32 (b, 2H, NH), 3.34 (s, 3H; OCH_3), 3.39 (s, 3H; OCH_3), 3.40 (m, 1H, H-3), 3.50 (m, 1H, H-5), 3.63 (m, 1H, H-4), 3.86 (m, 1H, H-2), 5.39 (d, 1H, H-1, $^{3}J_{1\text{-}2}$ = 4 Hz), 6.6-7.2 (m, 8H, CH=). ^{13}C NMR (C_6D_6), δ: 26.7 (CH_3), 27.0 (CH_3), 31.7 (CH_3, ^{t}Bu), 31.9 (CH_3, ^{t}Bu), 32.0 (CH_3, ^{t}Bu), 35.9 (C, ^{t}Bu), 41.8 (d, C-5, $J_{C\text{-}P}$ = 22 Hz), 55.1 (d, C-3, $J_{C\text{-}P}$ = 15 Hz), 55.4 (OCH_3), 55.5 (OCH_3), 80.2 (C-2), 82.1 (C-4), 104.4 (C-1), 112.3 (CMe_2), 113.3 (CH=), 113.4 (CH=), 113.8 (CH=), 114.8 (CH=), 114.9 (CH=), 115.2 (CH=), 128.8 (CH=), 129.6 (CH=), 134.9 (C), 135.1 (C), 135.3 (C), 156.3 (C), 156.4 (C), 156.5 (C), 156.7 (C). Anal. calcd (%) for $C_{52}H_{70}N_2O_{11}P_2$: C 64.99, H 7.34, N 2.91; found: C 65.01, H 7.41, N 2.79.

L5c. Yield: 0.46 g, 51 %. ^{31}P NMR (C_6D_6), δ: 148.0 (s, 1P), 154.3 (s, 1P). ^{1}H NMR (C_6D_6), δ: -0.32 (s, 9H, CH_3-Si), 0.38 (s, 9H, CH_3-Si), 0.4 (s, 18H, CH_3-Si), 1.13 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 2.92 (m, 1H, H-5'), 3.06 (m, 1H, H-3), 3.14 (m, 1H, NH-C-5), 3.29 (s, 1H, NH-C-3), 3.45 (m, 1H, H-5), 3.56 (m, 1H, H-4), 3.79 (m, 1H, H-2), 5.47 (d, 1H, H-1, $^{3}J_{1\text{-}2}$ = 4 Hz), 6.9-7.4 (m, 12H, CH=). ^{13}C NMR (C_6D_6), δ: 0.56 (CH_3-Si), 0.59 (CH_3-Si), 0.63 (CH_3-Si), 0.68 (CH_3-Si), 0.82 (CH_3-Si), 0.86

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(CH_3-Si), 26.8 (CH_3), 27.1 (CH_3), 42.6 (d, C-5, $J_{C\text{-}P}$ = 20 Hz), 54.4 (C-3), 80.7 (C-2), 82.1 (C-4), 104.3 (C-1), 112.1 (CMe_2), 124.8 (CH=), 125.2 (CH=), 125.4 (CH=), 126.0 (CH=), 132.2 (C), 132.3 (C), 132.4 (CH=), 132.5 (CH=), 132.6 (CH=), 132.5 (CH=), 135.7 (CH=), 138.1 (C), 156.4 (C), 155.5 (C), 156.0 (C). Anal. calcd (%) for $C_{44}H_{62}N_2O_7P_2Si_4$: C 58.38, H 6.90, N 3.09; found: C 58.31, H 6.84, N 3.01.

L5d. Yield: 0.23 g, 32 %. ^{31}P NMR (C_6D_6), δ: 141.8 (s, 1P), 148.0 (s, 1P). ^{1}H NMR (C_6D_6), δ: 1.29 (s, 3H, CH_3), 1.48 (s, 3H, CH_3), 2.18 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 2.47 (s, 3H, CH_3), 2.49 (s, 3H, CH_3), 2.50 (s, 3H, CH_3), 3.14 (m, 1H, H-5'), 3.28 (m, 2H, NH), 3.37 (m, 1H, H-3), 3.42 (m, 2H, H-5, H-4), 4.16 (m, 1H, H-2), 5.52 (d, 1H, H-1, $^3J_{1\text{-}2}$ = 4 Hz), 6.9-7.4 (m, 8H, CH=). ^{13}C NMR (C_6D_6), δ: 16.9 (CH_3), 17.1 (CH_3), 17.3 (CH_3), 17.5 (CH_3), 20.9 (CH_3), 21.2 (CH_3), 21.3 (CH_3), 26.7 (CH_3), 27.0 (CH_3), 40.3 (d, C-5, $J_{C\text{-}P}$ = 20 Hz), 54.0 (d, C-3, $J_{C\text{-}P}$ = 12 Hz), 81.1 (C-2), 81.6 (C-4), 104.6 (C-1), 112.2 (CMe_2), 128.5 (CH=), 128.6 (CH=), 128.8 (CH=), 129.6 (CH=), 130.2 (C), 131.4 (CH=), 131.5 (CH=), 131.6 (CH=), 131.7 (CH=), 132.3 (C), 132.7 (C), 133.4 (C), 133.6 (C), 134.0 (C), 147.0 (C), 147.1 (C), 147.8 (C), 147.98 (C). Anal. calcd (%) for $C_{40}H_{46}N_2O_7P_2$: C 65.92, H 6.36, N 3.84; found: C 65.99, H 6.42, N 3.89.

L5f. Yield: 0.33 g, 30 %. ^{31}P NMR (C_6D_6), δ: 147.2 (s, 1P), 151.2 (s, 1P). ^{1}H NMR (C_6D_6), δ: 0.43 (s, 9H, CH_3-Si), 0.45 (s, 9H, CH_3-Si), 0.52 (s, 9H, CH_3-Si), 0.57 (s, 9H, CH_3-Si), 1.12 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 2.79 (m, 2H, H-5', NH-C-3), 3.08 (m, 1H, H-3), 3.23 (m, 1H, NH-C-5), 3.38 (m, 1H, H-2), 4.41 (m, 1H, H-4), 5.03 (d, 1H, H-1, $^3J_{1\text{-}2}$ = 4 Hz), 6.8-8.2 (m, 20H, CH=). ^{13}C NMR (C_6D_6), δ: 0.6 (CH_3-Si), 0.7 (CH_3-Si), 1.0 (CH_3-Si), 1.1 (CH_3-Si), 1.1 (CH_3-Si), 26.5 (CH_3), 27.1 (CH_3),

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42.7 (d, C-5, $J_{C\text{-}P}$ = 16 Hz), 54.4 (C-3), 80.5 (C-2), 81.5 (C-4), 104.1 (C-1), 111.9 (CMe_2), 125.0 (CH=), 125.1 (CH=), 125.4 (CH=), 127.1 (CH=), 127.4 (CH=), 127.5 (CH=), 127.6 (CH=), 127.8 (CH=), 128.2 (CH=), 128.6 (CH=), 128.8 (CH=), 129.1 (CH=), 129.2 (CH=), 129.6 (CH=), 131.2 (CH=), 131.8 (CH=), 132.7 (C), 133.0 (C), 133.4 (C), 133.6 (C), 134.7 (C), 135.0 (C), 136.6 (CH=), 136.9 (CH=), 137.7 (CH=), 137.9 (CH=), 153.0 (C), 153.9 (C), 154.5 (C). Anal. calcd (%) for $C_{60}H_{70}N_2O_7P_2Si_4$: C 65.19, H 6.38, N 2.53; found: C 65.25, H 6.29, N 2.39.

L5g. Yield: 0.24 g, 22 %. ^{31}P NMR (C_6D_6), δ: 153.5 (s, 1P), 154.6 (s, 1P). ^{1}H NMR (C_6D_6), δ: 0.54 (s, 9H, CH_3-Si), 0.56 (s, 9H, CH_3-Si), 0.62 (s, 9H, CH_3-Si), 0.67 (s, 9H, CH_3-Si), 1.00 (s, 3H, CH_3), 1.05 (s, 3H, CH_3), 3.32 (m, 3H, H-3, H-5', NH), 3.48 (m, 1H, NH), 3.60 (m, 1H, H-5), 3.67 (m, 1H, H-4), 4.32 (m, 1H, H-2), 5.05 (d, 1H, H-1, $^{3}J_{1\text{-}2}$ = 3.6 Hz), 6.8-8.2 (m, 20H, CH=). ^{13}C NMR (C_6D_6), δ: 0.7 (CH_3-Si), 0.8 (CH_3-Si), 0.9 (CH_3-Si), 1.1 (CH_3-Si), 1.2 (CH_3-Si), 26.7 (CH_3), 26.9 (CH_3), 43.0 (d, C-5, $J_{C\text{-}P}$ = 28 Hz), 56.3 (d, C-3, $J_{C\text{-}P}$ = 22 Hz), 80.5 (d, C-2, $J_{C\text{-}P}$ = 5.2 Hz), 82.2 (d, C-4, $J_{C\text{-}P}$ = 6.4 Hz), 104.4 (C-1), 112.3 (CMe_2), 125.1 (CH=), 125.3 (CH=), 126.0 (CH=), 127.1 (CH=), 127.2 (CH=), 127.4 (CH=), 127.5 (CH=), 127.7 (CH=), 128.2 (CH=), 128.6 (CH=), 128.8 (CH=), 129.0 (CH=), 131.4 (CH=), 131.8 (CH=), 132.4 (C), 132.7 (C), 132.9 (C), 133.1 (C), 137.0 (CH=), 137.2 (CH=), 137.7 (CH=), 137.9 (CH=), 151.8 (C), 151.9 (C), 154.3 (C), 154.4 (C). Anal. calcd (%) for $C_{60}H_{70}N_2O_7P_2Si_4$: C 65.19, H 6.38, N 2.53; found: C 65.07, H 6.42 N 2.58.

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3.3.4.4. General procedure for the preparation of [Pd(η^3-allyl)(L)]BF_4 complexes 8-11.

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, 0.5 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 adding hexane as pale yellow solids.

[Pd(η^3-1,3-diphenylallyl)(L5b)]BF_4 (8). Isomer **B**: ^{31}P NMR (CD_2Cl_2), δ: 145.0 (d, 1P, P next to C-3, $J_{P\text{-}P}$ = 116 Hz), 148.1 (d, 1P, P next to C-5, $J_{P\text{-}P}$ = 116 Hz). ^{1}H NMR (CD_2Cl_2), δ: 1.2-1.7 (m, 42H, CH_3, ^{t}Bu), 2.81 (m, 1H, NH), 3.52 (m, 2H, H-5, H-5'), 3.71 (m, 1H, H-4), 3.8-4.0 (m, 14H, H-3, N-H, OCH_3), 4.57 (m, 1H, H-2), 5.20 (m, 1H, CH terminal), 5.26 (m, 1H, CH terminal), 5.66 (d, 1H, H-1, $^3J_{1\text{-}2}$ = 3.2 Hz), 6.24 (m, 2H, CH=), 6.44 (m, 1H, CH central), 6.5-7.2 (m, 16 H, CH=). ^{13}C NMR (CD_2Cl_2), δ: 26.3 (CH_3), 26.6 (CH_3), 31-33 (m, CH_3, ^{t}Bu), 35-36 (m, C, *t*-Bu), 38.7 (m, C-5), 53.4 (m, C-3), 56.0 (OCH_3), 56.2 (OCH_3), 56.4 (OCH_3), 78.4 (m, C-2), 79.9 (m, C-4), 92.8 (m, CH terminal), 100.0 (m, CH terminal), 104.9 (C-1), 113.3 (m, CH central), 114.3 (CMe_2), 114.5- 157.0 (aromatic carbons). Isomer **A**: ^{31}P NMR (CD_2Cl_2), δ: 144.7 (d, 1P, P next to C-3, $J_{P\text{-}P}$ = 115 Hz), 148.0 (d, 1P, P next to C-5, $J_{P\text{-}P}$ = 115 Hz). ^{1}H NMR (CD_2Cl_2), δ: 1.2-1.7 (m, 42H, CH_3, CH_3, ^{t}Bu), 2.81 (m, 1H, NH), 3.52 (m, 2H, H-5, H-5'), 3.71 (m, 1H, H-4), 3.8-4.0 (m, 14H, H-3, N-H, OCH_3), 4.66 (m, 1H, H-2), 5.18 (m, 1H, CH terminal), 5.24 (m, 1H, CH terminal), 5.72 (d, 1H, H-1, $^3J_{1\text{-}2}$ = 3.6 Hz), 6.24 (m, 2H, CH=), 6.44 (m, 1H, CH central), 6.5-7.2 (m, 16 H, CH=). ^{13}C NMR (CD_2Cl_2), δ:

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26.3 (CH_3), 26.6 (CH_3), 31-33 (m, CH_3, ^tBu), 35-36 (m, C, ^tBu), 38.7 (m, C-5), 53.4 (m, C-3), 56.0 (OCH_3), 56.2 (OCH_3), 56.4 (OCH_3), 78.4 (m, C-2), 79.9 (m, C-4), 92.8 (m, CH terminal), 99.3 (m, CH terminal), 104.9 (C-1), 113.3 (m, CH central), 114.3 (CMe_2), 114.5-157.0 (aromatic carbons).

[Pd(η^3-1,3-diphenylallyl)(L5c)]BF_4 (9). Isomer **B**: ^{31}P NMR (CD_2Cl_2), δ: 145.2 (d, 1P, P next to C-3, J_{P-P} = 97 Hz), 148.5 (d, 1P, P next to C-5, J_{P-P} = 97 Hz). ^1H NMR (CD_2Cl_2), δ: 0.3-0.7 (m, 36H, CH_3-Si), 1.2-1.3 (m, 6H, CH_3), 2.9 (m, 1H, NH), 3.4-3.9 (m, 5H, H-3, H-4, H-5, H-5', NH), 4.63 (m, 1H, H-2), 5.48 (m, 1H, CH terminal), 5.52 (m, 1H, CH terminal), 5.66 (d, 1H, H-1, $^3J_{1-2}$ = 3.6 Hz), 6.52 (m, 1H, CH central), 6.7-7.7 (m, 22H, CH=). ^{13}C NMR (CD_2Cl_2), δ: 0-2.2 (CH_3-Si), 26.3 (CH_3), 39.1 (m, C-5), 53.1 (m, C-3), 78.6 (m, C-2), 79.5 (b, C-4), 95.4 (m, CH terminal), 97.1 (m, CH terminal), 104.3 (C-1), 112.2 (m, CH central), 114.1 (CMe_2), 125-155 (aromatic carbons). Isomer **A**: ^{31}P NMR (CD_2Cl_2), δ: 145.8 (d, 1P, P next to C-3, J_{P-P} = 97 Hz), 149.7 (d, 1P, P next to C-5, J_{P-P} = 97 Hz). ^1H NMR (CD_2Cl_2), δ: 0.3-0.7 (m, 36H, CH_3-Si), 1.2-1.3 (m, 6H, CH_3), 2.9 (m, 1H, NH), 3.4-3.9 (m, 5H, H-3, H-4, H-5, H-5', NH), 4.70 (m, 1H, H-2), 5.40 (m, 1H, CH terminal), 5.44 (m, 1H, CH terminal), 5.71 (d, 1H, H-1, $^3J_{1-2}$ = 4.0 Hz), 6.52 (m, 1H, CH central), 6.7-7.7 (m, 22 H, CH=). ^{13}C NMR (CD_2Cl_2), δ: 0-2.2 (CH_3-Si), 26.3 (CH_3), 39.1 (m, C-5), 53.1 (m, C-3), 78.6 (m, C-2), 79.5 (b, C-4), 95.9 (m, CH terminal), 96.9 (m, CH terminal), 104.3 (C-1), 112.2 (m, CH central), 114.1 (CMe_2), 125-155 (aromatic carbons).

[Pd(η^3-1,3-cyclohexenylallyl)(L5a)]BF_4 (10). Isomer **A**: ^{31}P NMR (CD_2Cl_2), δ: 144.5 (d, 1P, P next to C-3, J_{P-P} = 75.8 Hz), 145.7 (d, 1P, P next to C-5, J_{P-P} = 75.8 Hz). ^1H NMR (CD_2Cl_2), δ: 1.2-1.6 (m, 82H,

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CH_3, CH_3, ^{t}Bu, CH_2), 1.83 (m, 2H, CH_2), 3.49 (m, 1H, H-5'), 3.70 (m, 2H, NH), 3.78 (m, 2H, H-4, H-5), 4.07 (m, 1H, H-3), 4.38 (m, 1H, CH terminal), 4.72 (m, 1H, H-2), 5.02 (m, 1H, CH central), 5.83 (d, 1H, H-1, $^3J_{1\text{-}2}$ = 4.0 Hz), 5.93 (m, 1H, CH terminal), 7.1-7.6 (m, 8 H, CH=). ^{13}C NMR (CD_2Cl_2), δ: 18.7 (CH_2), 26.0 (CH_2), 26.4 (CH_3), 26.7 (CH_3), 28.0 (CH_2), 31.6-32.6 (CH_3, ^{t}Bu), 35.2 (C, ^{t}Bu), 35.9 (C, ^{t}Bu), 38.2 (m, C-5), 53.8 (m, C-3), 78.6 (C-2), 79.9 (C-4), 91.2 (m, CH terminal), 97.9 (m, CH terminal), 104.9 (C-1), 113.6 (m, CH central), 114.2 (CMe_2), 125-150 (aromatic carbons). Isomer **B**: ^{31}P NMR (CD_2Cl_2), δ: 140.9 (bd, 1P, P next to C-3, $J_{P\text{-}P}$ = 75.8 Hz), 148.6 (d, 1P, P next to C-5, $J_{P\text{-}P}$ = 75.8 Hz). ^{1}H NMR (CD_2Cl_2), δ: 1.2-1.6 (m, 82H, CH_3, CH_3, ^{t}Bu, CH_2), 3.49 (m, 2H, H-5, H-5'), 3.78 (m, 2H, H-4, H-3), 4.21 (m, 1H, N-H), 4.37 (m, 1H, N-H), 4.54 (m, 1H, CH terminal), 4.62 (m, 1H, H-2), 5.02 (m, 1H, CH central), 5.81 (d, 1H, H-1, $^3J_{1\text{-}2}$ = 4.0 Hz), 5.83 (m, 1H, CH terminal), 7.1-7.6 (m, 8 H, CH=). ^{13}C NMR (CD_2Cl_2), δ: 18.8 (CH_2), 26.4 (CH_3), 26.7 (CH_3), 28.2 (CH_2), 28.3 (CH_2), 31.6-32.6 (CH_3, ^{t}Bu), 35.2 (C, ^{t}Bu), 35.9 (C, ^{t}Bu), 38.2 (m, C-5), 53.8 (m, C-3), 78.7 (C-2), 80.2 (C-4), 90.8 (m, CH terminal), 101.9 (m, CH terminal), 104.9 (C-1), 113.6 (m, CH central), 114.2 (CMe_2), 125-150 (aromatic carbons).

[Pd(η^3-1,3-cyclohexenylallyl)(L5d)]BF_4 (11). Isomer **A**: ^{31}P NMR (CD_2Cl_2), δ: 148.0 (d, 1P, P next to C-3, $J_{P\text{-}P}$ = 78 Hz), 149.2 (d, 1P, P next to C-5, $J_{P\text{-}P}$ = 78 Hz). ^{1}H NMR (CD_2Cl_2), δ: 0.9-1.2 (m, 2H, CH_2), 1.59 (s, 3H, CH_3), 1.65 (s, 3H, CH_3), 1.6-2.2 (m, 4H, CH_2), 2.40 (s, 3H, CH_3-Ar), 2.60 (m, 18H, CH_3-Ar), 2.78 (s, 3H, CH_3-Ar), 3.61 (m, 2H, H-5, H-5'), 3.83 (m, 1H, H-4), 4.18 (m, 2H, H-3, N-H), 4.36 (m, 1H, NH), 4.75 (m, 1H, H-2), 5.14 (m, 1H, CH terminal), 5.24 (m, 1H, CH central), 5.83 (d, 1H, H-1, $^3J_{1\text{-}2}$ = 3.6 Hz), 6.02 (m, 1H, CH terminal), 7.2-7.5 (m, 8 H,

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CH=). ^{13}C NMR (CD_2Cl_2), δ: 16.9-17.3 (CH_3-Ar), 18.6 (CH_2), 21.1 (CH_3-Ar), 26.6 (CH_3), 28.2 (CH_2), 28.8 (CH_2), 39.2 (d, C-5, J_{C-P} = 19.2 Hz), 52.6 (d, C-3, J_{C-P} = 19.7 Hz), 79.5 (m, C-2), 80.2 (b, C-4), 93.2 (dd, CH terminal, J_{C-P} = 31.4 Hz, J_{C-P} = 5.2 Hz), 96.7 (dd, CH terminal, J_{C-P} = 33.9 Hz, J_{C-P} = 5.4 Hz), 104.7 (C-1), 113.7 (m, CH central), 114.1 (CMe_2), 128.9-138.0 (aromatic carbons). Isomer **B**: ^{31}P NMR (CD_2Cl_2), δ: 146.3 (d, 1P, P next to C-3, J_{P-P} = 79 Hz), 151.3 (d, 1P, P next to C-5, J_{P-P} = 79 Hz). ^{1}H NMR (CD_2Cl_2), δ: 0.9-1.2 (m, 2H, CH_2), 1,45 (s, 3H, CH_3), 1.65 (s, 3H, CH_3), 1.6-2.2 (m, 4H, CH_2), 2.42 (s, 3H, CH_3-Ar), 2.60 (m, 18H, CH_3-Ar), 2.76 (s, 3H, CH_3-Ar), 3.61 (m, 1H, H-5'), 3.76 (m, 1H, H-3), 3.83 (m, 1H, H-4), 3.97 (m, 1H, H-5), 4.18 (m, 2H, N-H), 4.75 (m, 1H, H-2), 5.24 (m, 1H, CH central), 5.33 (m, 1H, CH terminal), 5.83 (d, 1H, H-1, $^{3}J_{1-2}$ = 3.6 Hz), 5.88 (m, 1H, CH terminal), 7.2-7.5 (m, 8H, CH=). ^{13}C NMR (CD_2Cl_2), δ: 16.9-17.3 (CH_3-Ar), 18.7 (CH_2), 21.2 (CH_3-Ar), 26.6 (CH_3), 28.2 (CH_2), 28.8 (CH_2), 37.1 (d, C-5, J_{C-P} = 16 Hz), 53.5 (m, C-3), 79.5 (m, C-2), 80.2 (b, C-4), 91.8 (dd, CH terminal, J_{C-P} = 31.6 Hz, J_{C-P} = 8 Hz), 97.3 (m, CH terminal), 104.8 (C-1), 113.7 (m, CH central), 114.1 (CMe_2), 128.9-138.0 (aromatic carbons).

3.3.4.5. Allylic alkylation of rac-1,3-diphenyl-3-acetoxyprop-1-ene (S1).

A degassed solution of $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (0.9 mg, 0.0025 mmol) and the diphosphoroamidite ligand (0.0055 mmol) in dichloromethane (0.5 mL) was stirred for 30 min. Subsequently, a solution of *rac*-**S1** (126 mg, 0.5 mmol) in dichloromethane (1.5 mL), dimethyl malonate (171 μL, 1.5 mmol), *N*,*O*-bis(trimethylsilyl)-acetamide (370 μL, 1.5 mmol) and a pinch of KOAc were added. The reaction mixture was stirred at room temperature. After 5 min the reaction mixture was diluted with Et_2O (5

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mL) and saturated NH_4Cl (aq) (25 mL) was added. The mixture was extracted with Et_2O (3 x 10 mL) and the extract dried over $MgSO_4$. The solvent was removed and the conversion was measured by ^{1}H-NMR. To determine the ee by HPLC (Chiralcel-OD, 0.5% 2-propanol/hexane, flow 0.5 mL/min), a sample was filtered over basic alumina using dichloromethane as the eluent.

3.3.4.6. Allylic alkylation of rac-3-acetoxycyclohexene (S2) and rac-3-acetoxycycloheptene (S3).

A degassed solution of $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (0.9 mg, 0.0025 mmol) and the diphosphoroamidite ligand (0.0055 mmol) in THF (0.5 mL) was stirred for 30 min. Subsequently, a solution of substrate (0.5 mmol) in THF (1.5 mL), dimethyl malonate (171 μL, 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 30 min 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 and enantiomeric excess were determined by GC using a FS-β-Cyclodex 25 m column, internal diameter 0.2 mm, film thickness 0.33 mm, carrier gas: 100 kPa He, F.I.D. detector).

3.3.4.7. Allylic alkylation of 1-(1-naphthyl)allyl acetate (S4).

A degassed solution of $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (1.8 mg, 0.005 mmol) and the diphosphoroamidite ligand (0.011 mmol) in dichloromethane (0.5 mL) was stirred for 30 min. Subsequently, a solution of *rac*-**S4** (113 mg, 0.5 mmol) in dichloromethane (1.5 mL), dimethyl malonate (171 μL, 1.5

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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 2 hours the reaction mixture was diluted with Et_2O (5 mL) and saturated NH_4Cl (aq) (25 mL) was added. The mixture was extracted with Et_2O (3 x 10 mL) and the extract dried over $MgSO_4$. The solvent was removed and the conversion and regioselectivity were measured by ^{1}H-NMR. To determine the ee by HPLC (Chiralcel-OJ, 3% 2-propanol/hexane, flow 0.7 mL/min), a sample was filtered over basic alumina using dichloromethane as the eluent.

3.3.5. Acknowledgements

We are indebted to Prof. P. W. N. M. van Leeuwen, University of Amsterdam, for his comments and suggestions. We thank the Spanish Government (Consolider Ingenio CSD2006-0003, CTQ2004-04412/BQU and the Ramon y Cajal fellowship to O.P.) and the Generalitat de Catalunya (2005SGR007777 and Distinction to M.D.) for financial support.

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nucleophilic attack to the more electrophilic terminal carbon of the allyl ligand in the Pd(II)-intermediates such as **8**. See ref. 1.

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Chapter 4

Asymmetric Cu-catalyzed allylic alkylation

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4. Asymmetric Cu-catalyzed allylic alkylations

4.1. Background

Complementary to the asymmetric Pd-catalyzed allylic substitution reactions, copper allows non-stabilized nucleophiles to be used.[1] Despite its importance, asymmetric Cu-catalyzed allylic alkylation is underdeveloped compared to the Pd-version.[2] Although high selectivities have been recently obtained using amines, phosphorous, sulfonamides, peptide with imine core and carbene ligands, the number of ligands developed for this process is not enough to predict the right ligand type for this process.[1] More research is therefore needed to study the possibilities offered by other ligands for this transformation.

In chapter 4.2, we report the preliminary results in the application of phosphite-phosphoroamidite (**L1**-**L4**), diphosphoroamidite (**L5**) and monophosphoroamidite (**L6**-**L10**) in the asymmetric Cu-catalyzed allylic substitution reactions. To provide an uniform format throughout the thesis, in this section we also include the synthesis of the new monophosphoroamidite ligand library (**L6**-**L10**) although only few of them has been applied in this process.

4.1.1. References

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4.2. Furanoside phosphite-phosphoroamidite, di- and monophosphoroamidite ligands for asymmetric Cu-catalyzed allylic alkylations

Eva Raluy, Oscar Pàmies, Montserrat Diéguez, Stephane Rosset and Alexander Alexakis *preliminary results.*

Abstract. We described the synthesis of the monophosphoroamidite ligand library (**L6**-**L10**) derived from D-glucose, D-fructose and D-galactose. We also showed the preliminary results using these ligands and the previously described phosphite-phosphoroamidite (**L1**-**L4**) and diphosphoroamidite (**L5**) ligand libraries in the asymmetric Cu-catalyzed allylic alkylation reactions. Our results indicated that selectivity depended strongly on the ligand parameters. Excellent regioselectivities (up to 99%) combined with moderate enantioselectivities (up to 54%) were obtained with the phosphite-phosphoroamidite ligand **L2a**.

4.2.1. Introduction

The complexity of natural and pharmaceutical products currently challenging synthetic chemists provides a major incentive in the design of catalytic methods, which enable access to versatile multifunctional optically active building blocks and starting materials. Among the methods available to prepare these synthons, enantioselective catalysis is particularly attractive due to the ready accessibility of both enantiomers, the potential atom efficiency of such reactions, and the ease with which small variations in the product can be introduced.[1]

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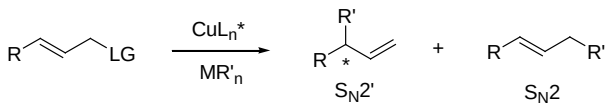
Among the enantioselective transition metal-catalyzed C-C bond forming reactions, catalytic allylic substitution has seen significant developments recently, in particular asymmetric allylic alkylations with stabilized nucleophiles (such as malonates and other stabilized carbanions) using transition metals such as Pd. These methods show impressive versatility and have seen numerous applications in total synthesis.[2]

Copper-based transition-metal catalysts offer the possibility of using non-stabilized organometallic nucleophiles, thus enabling the introduction of simple alkyl fragments at the γ-position (S_N2' product, Scheme 1).[3] This provides branched chiral products that contain a terminal olefin functionality, which can be transformed subsequently into a broad range of functional groups, from prochiral monosubstituted allylic substrates. Despite its importance, asymmetric Cu-catalyzed allylic alkylation is underdeveloped compared to the Pd-version. Although high selectivities have been recently obtained using amines, phosphorous, sulfonamides, peptide with imine core and carbene ligands,[3d] the number of ligands developed for this process is not enough to predict the right ligand type for each substrate type. More research is therefore needed to study the possibilities offered by other ligands for this transformation.



Scheme 1. Typical Cu-catalyzed asymmetric allylic alkylation.

To further expand the range of ligands and performance of this asymmetric Cu-catalyzed allylic alkylation reactions, we report here the application of the phosphite-phosphoroamidite (**L1**-**L4**) and

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diphosphoroamidite (**L5**) ligand libraries described in the previous chapter 3 and the new monophosphoroamidite (**L6**-**L10**) ligand library in this process (Figure 1). These ligands are derived from natural D-xylose, D-glucose, D-galactose and D-fructose and have the advantage of carbohydrate and phosphite/phosphoroamidite ligands, such as availability at low price from readily available alcohols and facile modular constructions.[4] With these libraries we contemplate the use of both bidentated (**L1**-**L5**) and monodentated ligands (**L6**-**L10**). More specifically, with bidentated ligands **L1**-**L5**, we fully investigated the effects of systematically varying the position of the phosphoroamidite group at both C-5 (ligands **L1** and **L2**) and C-3 (ligands **L3** and **L4**) of the furanoside backbone, as well as the effects of the configuration at C-3 of the furanoside backbone, the introduction of second phosphoroamidite moiety (ligands **L5**) and the substituents in the biaryl phosphite/phosphoroamidite moieties (**a**-**d**). With monodentated ligands (**L6**-**L10**) we investigated the effects of varying the configurations at C-3 of the ligand backbone (**L6**-**L7**), the carbohydrate ring size **(L6** and **L8**) and the flexibility of the ligand backbone (**L9**-**L10**).

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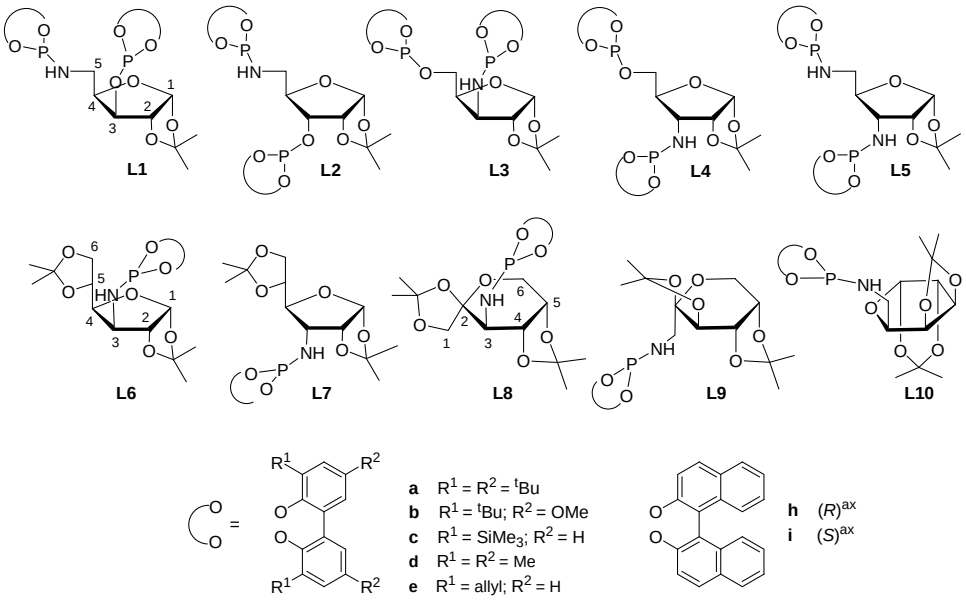

Figure 1. Phosphite-phosphoroamidite (**L1**-**L4**), diphosphoroamidite (**L5**), and monophosphoroamidite (**L6**-**L10**) ligand libraries.

4.2.2. Results and Discussions

4.2.2.1. Synthesis of monophosphoroamidite ligand library (L6-L10)

Ligands **L6**-**L10** were efficiently synthesized in one step by reaction of the corresponding sugar amines (**1**-**5**) with 1 equiv of the phosphorochloridite ($ClP(OR)_2$; $(OR)_2$ = **a**-**e**, **h**-**i**) formed *in situ* in the presence of pyridine (Scheme 1). Sugar amines **1**-**5** were easily prepared on a large scale from inexpensive D-(+)-glucose, D-(-)-fructose and D-(+)-galactose (Scheme 2). All the ligands were purified on neutral alumina under an atmosphere of argon and isolated in moderate yields as white solids or colorless liquids. The elemental analyses were in agreement with the assigned structure. The ^{1}H, ^{31}P and ^{13}C NMR spectra were as expected for these C_1 ligands (see Experimental Section). One

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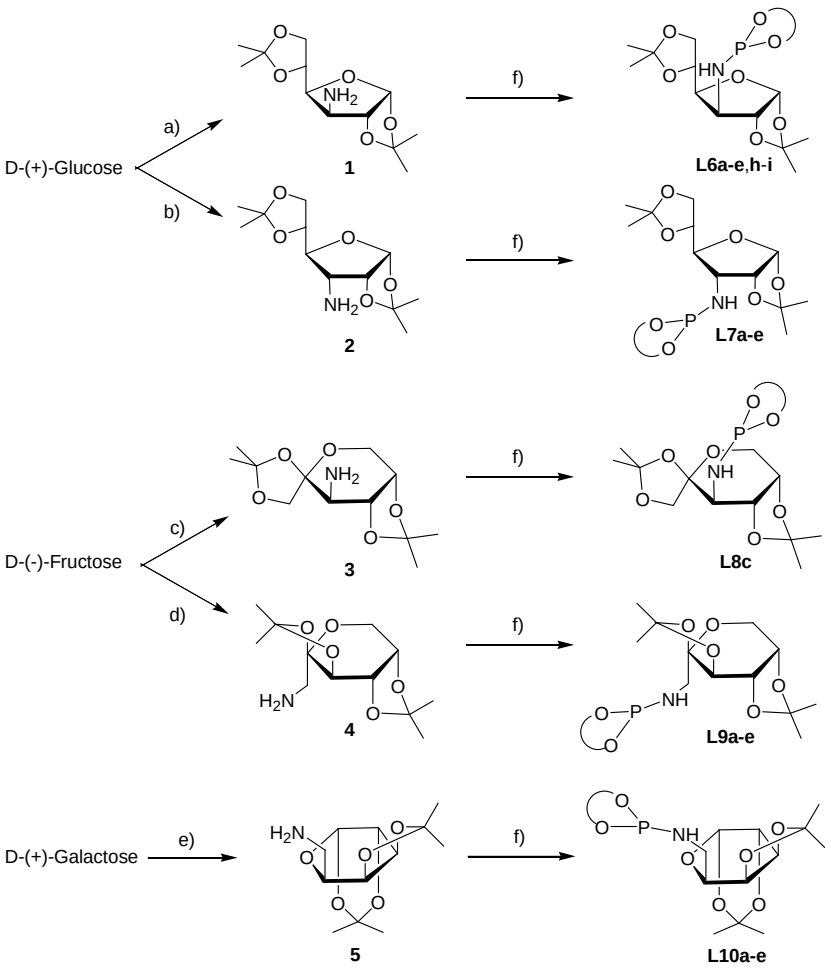
singlet for each compound was observed in the ^{31}P NMR spectrum (see Experimental Section). Rapid ring inversions (atropoisomerization) in the biphenyl-phosphorus moieties (**a**-**e**) occurred on the NMR time scale since the expected diastereoisomers were not detected by low-temperature phosphorus NMR.[5]



Scheme 2. Synthesis of monophosphoroamidite ligand library **L6**-**L10a**-**e**,**h**-**i**. a) ref 6. b) ref 7. c) ref 8. d) ref 9. e) ref 10. f) $ClP(OR)_2$; $(OR)_2$ = **a**-**e**,**h**-**i** / Py / Toluene.

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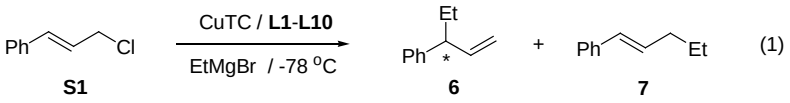
4.2.2.2. Asymmetric Cu-catalyzed allylic alkylation of cinnamyl chloride (S1)

We tested sugar-based ligands **L1-L5a-d** and **L6-L10a-b** in the copper-catalyzed allylic alkylation of ethylmagnesium bromide to cinnamyl chloride **S1**, which is used as a model substrate (Equation 1).



S1 **6** **7**

The catalytic system was generated *in situ* by adding the corresponding ligand to a suspension of catalyst precursor under standard conditions.[11] The results are shown in Table 1. In general, excellent regioselectivities towards the desired branched product **6** (up to 99%) and moderate enantioselectivities (ee's up to 54%) were obtained. The results indicated that bidentate ligands provided higher enantioselectivities than monodentated ligands (Table 1, entries 1-9 vs 10-14).

For bidentated ligands, we found that enantioselectivity is highly affected by the position of the phosphoroamidite group at either C-5 or C-3 of the furanoside backbone, the configuration of C-3, the introduction of second phosphoroamidite moiety and the substituents in the biaryl phosphite/phosphoroamidite moieties (**a-d**). Regarding the effect of the configuration of C-3 and the position of the phosphoroamidite, we observed a cooperative effect between them. The results therefore indicated that the matched combination is achieved with ligands **L2**, whose phosphoroamidite moiety is attached to C-3 and which have an *R* configuration of carbon atom C-3 on the tetrahydrofuran ring (Table 1, entries 3-6). Concerning the effect of the substituents in the biaryl

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phosphite/phosphoroamidite moieties, we found that the presence of bulky substituents at the *ortho* positions are necessary for high enantioselectivities (Table 1, entries 1 vs 2 and 3-5 vs 6). Finally, the replacement of the phosphite moiety by a phosphoroamidite group has a negative effect on enantioselectivity (Table 1, entries 3 and 8 vs 9).

Surprisingly, for monosubstituted ligands, the use of the most flexible ligands **L9a-b** provided much higher enantioselectivity than more rigid furanoside ligands **L6** and **L7** (Table 1, entries 12 and 13 vs 10 and 11).

Table 1. Cu-catalyzed asymmetric allylic alkylation of **S1** using ligands **L1-L5a-e** and **L6-L10a-b**.[a]

Entry	L	% Yield[b]	**6**/**7**[c]	% ee[d]
1	**L1a**	81	99/1	38 (*S*)
2	**L1d**	60	97/3	16 (*S*)
3	**L2a**	85	99/1	54 (*S*)
4	**L2b**	78	98/2	42 (*S*)
5	**L2c**	28	97/3	52 (*S*)
6	**L2d**	84	99/1	4 (*S*)
7	**L3a**	76	93/7	2 (*S*)
8	**L4a**	66	96/4	38 (*S*)
9	**L5a**	82	99/1	8 (*S*)
10	**L6a**	84	97/3	12 (*S*)
11	**L7a**	84	92/8	6 (*R*)
12	**L9a**	95	98/2	40 (*R*)
13	**L9b**	95	99/1	38 (*R*)
14	**L10a**	94	98/2	14 (*S*)

[a] CuTC (1 mol%), ligand (1 mol%), EtMgBr (1.2 eq, 1.2 mmol), **S1** (1 mmol), CH_2Cl_2 (2 mL). [b] Yields determined after 16 hours. [c] Percentage of branched (**6**) and linear (**7**) isomers. [d] Enantiomeric excess measured using Supercritical Fluid Chromatography (SFC).

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4.2.3. Conclusions

Modular carbohydrate-based phosphite-phosphoroamiditie **L1-L4a-d**, diphosphoroamidite **L5a-d** and monophosphoroamidite **L6-L10a-b** ligand libraries were tested to determine its effects on the asymmetric Cu-catalyzed allylic alkylation of cinnamyl chloride. Our results indicated that selectivity depended strongly on the lignad parameters. Excellent regioselectivities (up to 99%) combined with moderate enantioselectivities (up to 54%) were obtained with the phosphite-phosphoroamidite ligand **L2a**.

4.2.4. Experimental Section

4.2.4.1. General considerations.

All syntheses were performed by using standard Schlenk techniques under an argon atmosphere. Solvents were purified by standard procedures. The synthesis of ligands **L1-L5a-d** has been previously described in Chapter 3. Compounds **1-5** were prepared by previously described methods.[6-10] Phosphorochloridites were easily prepared in one step from the corresponding biaryls.[12] All other reagents were used as commercially available.

4.2.4.2. Genreal procedure for the preparation of monophosphoroamidite ligands L6-L10a-e,h-i.

Phosphorochloridite (1.1 mmol) produced *in situ* was dissolved in toluene (5 mL) and pyridine (0.18 mL, 2.3 mmol) was added. Amine (1

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mmol) was azeotropically dried with toluene (3 x 1 mL) and then dissolved in toluene (10 mL), to which pyridine (0.18 mL, 2.3 mmol) was added. The amine solution was transferred slowly at 0 ºC to the solution of phosphorochloridite. The reaction mixture was warmed to 80 ºC and stirred overnight, and the pyridine salts were removed by filtration. Evaporation of the solvent gave a white foam, which was purified in a short path of alumina (toluene/NEt_3 = 100/1) to produce the corresponding ligand as white powder or colorless liquid.

L6a.Yield: 271 mg (39 %). ^{31}P NMR (C_6D_6), δ: 148.7 (s, 1P). ^{1}H NMR (C_6D_6), δ: 1.09 (s, 3H, CH_3), 1.19 (s, 3H, CH_3), 1.21 (s, 9H, CH_3, ^{t}Bu), 1.29 (s, 9H, CH_3, ^{t}Bu), 1.32 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 1.47 (s, 9H, CH_3, ^{t}Bu), 1.51 (s, 9H, CH_3, ^{t}Bu), 3.23 (m, 1H, NH), 4.08 (m, 2H, H-6´ and H-6), 4.13 (m, 1H, H-3), 4.19 (m, 1H, H-4), 4.27 (m, 1H, H-5), 4.33 (d, 1H, H-2, $^{3}J_{2\text{-}1}$ = 4.0 Hz), 5.79 (d, 1H, H-1, $^{3}J_{1\text{-}2}$ = 4.0 Hz), 6.79 (m, 2H, CH=), 7.21 (m, 2H, CH=). ^{13}C NMR (C_6D_6), δ: 25.9 (CH_3), 26.1 (CH_3), 26.4 (CH_3), 27.2 (CH_3), 31.3 (CH_3, ^{t}Bu), 31.5 (CH_3, ^{t}Bu), 31.8 (CH_3, ^{t}Bu), 35.6 (C, ^{t}Bu), 35.7 (C, ^{t}Bu), 36.0 (C, ^{t}Bu), 58.0 (d, C-3, $J_{C\text{-}P}$ = 12.0 Hz), 68.3 (C-6), 73.0 (C-5), 81.7 (d, C-4, $J_{C\text{-}P}$ = 3.2 Hz), 86.3 (d, C-2, $J_{C\text{-}P}$ = 9.2 Hz), 105.8 (C-1), 109.9 (CMe_2), 112.3 (CMe_2), 124.5 (CH=), 124.7 (CH=), 127.1 (CH=), 127.6 (CH=), 133.9 (C), 134.2 (C), 144.9 (C), 145.6 (C), 150.2 (C). Anal. Calc (%) for $C_{40}H_{60}NO_7P$: C 68.84, H 8.67, N 2.01; found: C 68.88, H 8.69, N 2.03.

L6b. Yield: 277 mg (43 %). ^{31}P NMR (C_6D_6), δ: 149.8 (s, 1P). ^{1}H NMR (C_6D_6), δ: 1.08 (s, 3H, CH_3), 1.22 (s, 3H, CH_3), 1.31 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 1.49 (s, 9H, CH_3, ^{t}Bu), 1.54 (s, 9H, CH_3, ^{t}Bu), 3.18 (m, 1H, NH), 3.27 (s, 3H, CH_3-O), 3.36 (s, 3H, CH_3-O), 4.03 (m, 1H, H-6´), 4.09 (m, 1H, H-6), 4.17 (m, 1H, H-3), 4.24 (m, 1H, H-4), 4.30 (m,

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1H, H-5), 4.47 (d, 1H, H-2, $^{3}J_{2\text{-}1}$ = 3.6 Hz), 5.70 (d, 1H, H-1, $^{3}J_{1\text{-}2}$ = 3.6 Hz), 6.69 (m, 2H, CH=), 7.15 (m, 2H, CH=). ^{13}C NMR (C_6D_6), δ: 25.6 (CH_3), 26.2 (CH_3), 26.9 (CH_3), 27.3 (CH_3), 31.3 (CH_3, ^{t}Bu), 31.5 (CH_3, ^{t}Bu), 35.6 (C, ^{t}Bu), 35.7 (C, ^{t}Bu), 55.3 (CH_3-O), 58.2 (d, C-3, $J_{C\text{-}P}$ = 9.8 Hz), 68.1 (C-6), 73.2 (C-5), 81.3 (d, C-4, $J_{C\text{-}P}$ = 3.0 Hz), 85.8 (d, C-2, $J_{C\text{-}P}$ = 9.8 Hz), 105.2 (C-1), 109.7 (CMe_2), 111.6 (CMe_2), 113.2 (CH=), 113.5 (CH=), 114.8 (CH=), 115.2 (CH=), 134.8 (C), 134.9 (C), 143.2 (C), 143.5 (C), 156.4 (C), 156.5 (C). Anal. Calc (%) for $C_{34}H_{48}NO_9P$: C 63.24, H 7.49, N 2.17; found: C 63.28, H 7.46, N 2.15.

L6c. Yield: 276 mg (45 %). ^{31}P NMR (C_6D_6), δ: 151.6 (s, 1P). ^{1}H NMR (C_6D_6), δ: 0.35 (s, 3H, CH_3-Si), 0.39 (s, 3H, CH_3-Si), 1.01 (s, 3H, CH_3), 1.15 (s, 3H, CH_3), 1.26 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 3.19 (m, 1H, NH), 3.96 (m, 1H, H-6´), 4.03 (m, 1H, H-6), 4.12 (m, 1H, H-3), 4.19 (m, 1H, H-4), 4.26 (m, 1H, H-5), 4.54 (d, 1H, H-2, $^{3}J_{2\text{-}1}$ = 4.0 Hz), 5.71 (d, 1H, H-1, $^{3}J_{1\text{-}2}$ = 4.0 Hz), 6.7-7.4 (m, 6H, CH=). ^{13}C NMR (C_6D_6), δ: 0.5 (CH_3-Si), 0.6 (CH_3-Si), 25.8 (CH_3), 26.4 (CH_3), 26.9 (CH_3), 27.4 (CH_3), 58.5 (d, C-3, $J_{C\text{-}P}$ = 8.4 Hz), 68.0 (C-6), 73.4 (C-5), 81.3 (C-4), 86.2 (d, C-2, $J_{C\text{-}P}$ = 11.4 Hz), 105.3 (C-1), 109.9 (CMe_2), 111.9 (CMe_2), 121.8 (CH=), 125.2 (CH=), 132.3 (C), 132.5 (C), 133.0 (CH=), 133.7 (C), 135.7 (CH=), 136.5 (C), 136.9 (C), 154.9 (C). Anal. Calc (%) for $C_{30}H_{44}NO_7PSi_2$: C 58.32, H 7.18, N 2.27; found: C 58.34, H 7.17, N 2.26.

L6d.Yield: 206 mg (39 %). ^{31}P NMR (C_6D_6), δ: 145.4 (s, 1P). ^{1}H NMR (C_6D_6), δ: 1.12 (s, 3H, CH_3), 1.20 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 1.37 (s, 3H, CH_3), 2.12 (s, 3H, CH_3), 2.23 (s, 3H, CH_3), 2.33 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 3.21 (m, 1H, NH), 4.01 (m, 1H, H-6´), 4.12 (m, 1H, H-6), 4.21 (m, 1H, H-3), 4.26 (m, 1H, H-4), 4.32 (m, 1H, H-5), 4.42 (d, 1H, H-2, $^{3}J_{2\text{-}1}$ = 3.6 Hz), 5.71 (d, 1H, H-1, $^{3}J_{1\text{-}2}$ = 3.6 Hz), 6.7-7.3 (m, 4H,

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CH=). ^{13}C NMR (C_6D_6), δ: 16.9 (CH_3), 17.3 (CH_3), 19.9 (CH_3), 21.1 (CH_3), 25.2 (CH_3), 26.1 (CH_3), 26.6 (CH_3), 27.2 (CH_3), 58.1 (d, C-3, $J_{C\text{-}P}$ = 7.0 Hz), 68.0 (C-6), 73.1 (C-5), 81.1 (C-4), 85.3 (d, C-2, $J_{C\text{-}P}$ = 8.2 Hz), 105.0 (C-1), 109.9 (CMe_2), 111.2 (CMe_2), 128.3 (CH=), 128.5 (CH=), 130.1 (CH=), 134.8 (C), 134.9 (C), 143.2 (C), 143.4 (C), 152.1 (C), 152.5 (C). Anal. Calc (%) for $C_{28}H_{36}NO_7P$: C 63.51, H 6.85, N 2.64; found: C 63.54, H 6.87, N 2.61.

L6e. Yield: 265 mg (48 %). ^{31}P NMR (C_6D_6), δ: 150.6 (s, 1P). ^{1}H NMR (C_6D_6), δ: 1.04 (s, 3H, CH_3), 1.26 (s, 3H, CH_3), 1.29 (s, 3H, CH_3), 1.33 (s, 3H, CH_3), 3.08 (m, 1H, NH), 3.57 (CH_2 allyl), 3.98 (m, 1H, H-6´), 4.02 (m, 1H, H-6), 4.11 (m, 1H, H-3), 4.20 (m, 2H, H-4, H-5), 4.43 (d, 1H, H-2, $^3J_{2\text{-}1}$ = 3.2 Hz), 5.03 (m, 4H, CH_2= allyl), 5.46 (d, 1H, H-1, $^3J_{1\text{-}2}$ = 3.2 Hz), 5.98 (m, 2H, CH= allyl), 6.9-7.2 (m, 6H, CH=). ^{13}C NMR (C_6D_6), δ: 25.9 (CH_3), 26.4 (CH_3), 27.1 (CH_3), 27.5 (CH_3), 35.2 (CH_2 allyl), 35.3 (CH_2 allyl), 58.4 (d, C-3, $J_{C\text{-}P}$ = 24.0 Hz), 67.9 (C-6), 73.4 (C-5), 81.1 (d, C-4, $J_{C\text{-}P}$ = 4.6 Hz), 86.7 (d, C-2, $J_{C\text{-}P}$ = 6.1 Hz), 105.1 (C-1), 109.8 (CMe_2), 112.1 (CMe_2), 116.6 (CH_2 allyl), 116.7 (CH_2 allyl), 125.1 (CH=), 125.4 (CH=), 126.0 (C), 128.9 (CH=), 129.0 (CH=), 129.6 (C), 130.3 (CH=), 132.9 (C), 133.0 (C), 133.2 (C), 137.3 (CH= allyl), 137.4 (CH= allyl). Anal. Calc (%) for $C_{30}H_{36}NO_7P$: C 65.09, H 6.55, N 2.53; found: C 65.13, H 6.59, N 2.49.

L6h.Yield: 199 mg (35 %). ^{31}P NMR (C_6D_6), δ: 152.2 (s, 1P). ^{1}H NMR (C_6D_6), δ: 1.09 (s, 3H, CH_3), 1.18 (s, 3H, CH_3), 1.25 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 3.13 (m, 1H, NH), 4.03 (m, 1H, H-6), 4.06 (m, 1H, H-6´), 4.18 (m, 1H, H-3), 4.24 (m, 2H, H-4, H-5), 4.54 (d, 1H, H-2, $^3J_{2\text{-}1}$ = 4.0 Hz), 5.29 (d, 1H, H-1, $^3J_{1\text{-}2}$ = 4.0 Hz), 6.9-7.8 (m, 12H, CH=). ^{13}C NMR (C_6D_6), δ: 25.3 (CH_3), 26.2 (CH_3), 26.7 (CH_3), 27.2 (CH_3), 57.8 (d,

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C-3, J_{C-P} = 7.8 Hz), 67.8 (C-6), 73.9 (C-5), 80.8 (C-4), 86.3 (d, C-2, J_{C-P} = 6.8 Hz), 105.8 (C-1), 109.3 (CMe_2), 111.6 (CMe_2), 121.9 (CH=), 122.8 (CH=), 125.0 (CH=), 125.4 (C), 126.1 (CH=), 126.7 (CH=), 127.0 (CH=), 128.4 (CH=), 129.6 (CH=), 131.5 (C), 131.9 (C), 133.3 (C). Anal. Calc (%) for $C_{32}H_{32}NO_7P$: C 67.01, H 5.62, N 2.44; found: C 67.09, H 5.66, N 2.41.

L6i. Yield: 223 mg (39 %). ^{31}P NMR (C_6D_6), δ: 154.4 (s, 1P). ^{1}H NMR (C_6D_6), δ: 1.04 (s, 3H, CH_3), 1.19 (s, 3H, CH_3), 1.22 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 3.03 (m, 1H, NH), 4.05 (m, 2H, H-6, H-6'), 4.13 (m, 1H, H-3), 4.25 (m, 2H, H-4, H-5), 4.57 (d, 1H, H-2, $^{3}J_{2-1}$ = 3.6 Hz), 5.39 (d, 1H, H-1, $^{3}J_{1-2}$ = 3.6 Hz), 6.9-7.8 (m, 12H, CH=). ^{13}C NMR (C_6D_6), δ: 25.4 (CH_3), 26.0 (CH_3), 26.3 (CH_3), 27.0 (CH_3), 57.8 (d, C-3, J_{C-P} = 26.3 Hz), 67.6 (C-6), 73.6 (C-5), 80.6 (C-4), 86.8 (d, C-2, J_{C-P} = 12.0 Hz), 106.3 (C-1), 109.6 (CMe_2), 111.7 (CMe_2), 121.8 (CH=), 122.6 (CH=), 125.0 (CH=), 125.6 (C), 126.5 (CH=), 127.1 (CH=), 127.2 (CH=), 128.5 (CH=), 129.1 (CH=), 130.8 (CH=), 131.4 (C), 131.8 (C), 133.3 (C). Anal. Calc (%) for $C_{32}H_{32}NO_7P$: C 67.01, H 5.62, N 2.44; found: C 66.98, H 5.63, N 2.42.

L7a. Yield: 334 mg (48 %). ^{31}P NMR (C_6D_6), δ: 149.4 (s, 1P). ^{1}H NMR (C_6D_6), δ: 1.11 (s, 3H, CH_3), 1.24 (s, 9H, CH_3, ^{t}Bu), 1.26 (s, 9H, CH_3, ^{t}Bu), 1.29 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 1.47 (s, 3H, CH_3), 1.57 (s, 9H, CH_3, ^{t}Bu), 1.63 (s, 9H, CH_3, ^{t}Bu), 3.11 (m, 1H, H-3), 3.22 (m, 1H, NH), 3.56 (m, 1H, H-2), 3.91 (m, 2H, H-6´, H-6), 4.02 (m, 1H, H-4), 4.51 (m, 1H, H-5), 5.45 (d, 1H, H-1, $^{3}J_{1-2}$ = 4.0 Hz), 6.8-7.2 (m, 4H, CH=). ^{13}C NMR (C_6D_6), δ: 26.3 (CH_3), 26.7 (CH_3), 27.0 (CH_3), 31.8 (CH_3, ^{t}Bu), 31.9 (CH_3, ^{t}Bu), 32.0 (CH_3, ^{t}Bu), 34.8 (C, ^{t}Bu), 35.0 (C, ^{t}Bu), 35.8 (C, ^{t}Bu), 56.1 (d, C-3, J_{C-P} = 9.2 Hz), 64.4 (C-6), 76.0 (C-5), 79.9 (C-4), 80.5

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(C-2), 104.4 (C-1), 109.8 (CMe_2), 112.4 (CMe_2), 124.4 (CH=), 124.8 (CH=), 125.3 (CH=), 125.5 (C), 125.6 (C), 128.9 (CH=), 138.2 (C), 146.8 (C), 147.3 (C). Anal. Calc (%) for $C_{40}H_{60}NO_7P$: C 68.84, H 8.67, N 2.01; found: C 68.91, H 8.71, N 1.99.

L7b. Yield: 284 mg (44 %). ^{31}P NMR (C_6D_6), δ: 148.7 (s, 1P). ^{1}H NMR (C_6D_6), δ: 1.02 (s, 3H, CH_3), 1.23 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 1.48 (s, 9H, CH_3, ^{t}Bu), 1.52 (s, 9H, CH_3, ^{t}Bu), 3.04 (m, 1H, H-3), 3.24 (m, 1H, NH), 3.27 (s, 3H, OCH_3), 3.29 (s, 3H, OCH_3), 3.76 (m, 1H, H-2), 3.89 (m, 1H, H-6´), 3.92 (m, 1H, H-6), 4.00 (m, 1H, H-4), 4.52 (m, 1H, H-5), 5.33 (d, 1H, H-1, $^{3}J_{1\text{-}2}$ = 3.6 Hz), 6.62 (m, 1H, CH=), 6.70 (m, 1H, CH=), 7.11 (m, 2H, CH=). ^{13}C NMR (C_6D_6), δ: 26.2 (CH_3), 26.4 (CH_3), 28.8 (CH_3), 28.9 (CH_3), 31.4 (CH_3, ^{t}Bu), 31.6 (CH_3, ^{t}Bu), 35.7 (C, ^{t}Bu), 35.8 (C, ^{t}Bu), 55.2 (OCH_3), 55.4 (OCH_3), 55.8 (d, C-3, $J_{C\text{-}P}$ = 6.8 Hz), 64.0 (C-6), 75.7 (C-5), 79.8 (C-4), 80.3 (C-2), 104.3 (C-1), 109.6 (CMe_2), 112.2 (CMe_2), 112.5 (CH=), 113.8 (CH=), 114.9 (CH=), 115.0 (CH=), 134.8 (C), 134.9 (C), 143.0 (C), 143.2 (C), 156.4 (C), 156.7 (C). Anal. Calc (%) for $C_{34}H_{48}NO_9P$: C 63.24, H 7.49, N 2.17; found: C 63.21, H 7.52, N 2.15.

L7c. Yield: 315 mg (51 %). ^{31}P NMR (C_6D_6), δ: 149.7 (s, 1P). ^{1}H NMR (C_6D_6), δ: 0.35 (s, 3H, CH_3-Si), 0.42 (s, 3H, CH_3-Si), 1.04 (s, 3H, CH_3), 1.26 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 2.87 (m, 1H, H-3), 3.12 (m, 1H, NH), 3.62 (m, 1H, H-2), 3.69 (m, 1H, H-6), 3.75 (m, 1H, H-6'), 3.97 (m, 1H, H-4), 4.65 (m, 1H, H-5), 5.26 (d, 1H, H-1, $^{3}J_{1\text{-}2}$ = 4.0 Hz), 6.7-7.4 (m, 6H, CH=). ^{13}C NMR (C_6D_6), δ: 0.5 (CH_3-Si), 0.7 (CH_3-Si), 26.5 (CH_3), 26.7 (CH_3), 26.9 (CH_3), 27.0 (CH_3), 55.4 (d, C-3, $J_{C\text{-}P}$ = 1.6 Hz), 63.8 (C-6), 75.8 (C-5), 79.9 (d, C-4, $J_{C\text{-}P}$ = 1.6 Hz), 80.6 (C-2), 104.3 (C-1), 109.8 (CMe_2), 112.4 (CMe_2), 125.2 (CH=), 126.0

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(CH=), 131.9 (C), 132.0 (C), 132.2 (CH=), 132.3 (C), 132.4 (C), 133.2 (CH=), 135.4 (CH=), 136.0 (CH=), 136.5 (C), 138.2 (C), 155.7 (C), 155.9 (C). Anal. Calc (%) for $C_{30}H_{44}NO_7PSi_2$: C 58.32, H 7.18, N 2.27; found: C 58.36, H 7.20, N 2.24.

L7d. Yield: 280 mg (53 %). ^{31}P NMR (C_6D_6), δ: 150.2 (s, 1P). ^{1}H NMR (C_6D_6), δ: 1.05 (s, 3H, CH_3), 1.24 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 2.11 (s, 3H, CH_3), 2.16 (s, 6H, CH_3), 2.24 (s, 3H, CH_3), 2.29 (s, 3H, CH_3), 2.89 (m, 1H, H-3), 3.11 (m, 1H, NH), 3.64 (m, 1H, H-2), 3.72 (m, 1H, H-6), 3.78 (m, 1H, H-6'), 3.99 (m, 1H, H-4), 4.66 (m, 1H, H-5), 5.32 (d, 1H, H-1, $^{3}J_{1\text{-}2}$ = 4.0 Hz), 6.7-7.4 (m, 4H, CH=). ^{13}C NMR (C_6D_6), δ: 17.1 (CH_3), 17.7 (CH_3), 25.8 (CH_3), 26.5 (CH_3), 26.7 (CH_3), 26.9 (CH_3), 27.0 (CH_3), 55.8 (d, C-3, $J_{C\text{-}P}$ = 6.4 Hz), 63.9 (C-6), 74.7 (C-5), 79.7 (d, C-4, $J_{C\text{-}P}$ = 3.2 Hz), 81.1 (C-2), 104.2 (C-1), 109.2 (CMe_2), 112.2 (CMe_2), 125.2 (CH=), 126.0 (CH=), 131.9 (C), 132.0 (C), 132.2 (CH=), 132.3 (C), 132.4 (C), 133.2 (CH=), 135.4 (CH=), 138.2 (C), 139.7 (C). Anal. Calc (%) for $C_{28}H_{36}NO_7P$: C 63.51, H 6.85, N 2.64; found: C 63.48, H 6.82, N 2.65.

L7e. Yield: 237 mg (42 %). ^{31}P NMR (C_6D_6), δ: 146.9 (s, 1P). ^{1}H NMR (C_6D_6), δ: 1.09 (s, 3H, CH_3), 1.25 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 1.52 (s, 3H, CH_3), 3.37 (m, 2H, NH, H-3), 3.69 (m, 5H, H-2, CH_2 allyl), 3.82 (m, 2H, H-6, H-6'), 3.91 (m, 1H, H-4), 4.34 (m, 1H, H-5), 5.13 (m, 4H, CH_2= allyl), 5.32 (d, 1H, H-1, $^{3}J_{1\text{-}2}$ = 4.0 Hz), 6.07 (m, 2H, CH= allyl), 6.9-7.2 (m, 6H, CH=). ^{13}C NMR (C_6D_6), δ: 25.5 (CH_3), 26.6 (CH_3), 26.9 (CH_3), 27.0 (CH_3), 35.7 (CH_2 allyl), 58.6 (C-3), 68.0 (C-6), 78.0 (C-5), 80.9 (C-4), 81.6 (C-2), 104.8 (C-1), 109.9 (CMe_2), 112.6 (CMe_2), 115.8 (CH_2 allyl), 120.8 (CH=), 126.0 (C), 129.7 (C), 129.9 (CH=),

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130.2 (CH=), 135.4 (C), 136.1 (C), 138.2 (CH= allyl). Anal. Calc (%) for $C_{30}H_{36}NO_7P$: C 65.09, H 6.55, N 2.53; found: C 65.10, H 6.53, N 2.51.

L8c. Yield: 234 mg (38 %). ^{31}P NMR (C_6D_6), δ: 154.3 (s, 1P). ^{1}H NMR (C_6D_6), δ: 0.31 (s, 9H, CH_3-Si), 0.42 (s, 9H, CH_3-Si), 1.09 (s, 3H, CH_3), 1.23 (s, 3H, CH_3), 1.60 (s, 3H, CH_3), 1.67 (s, 3H, CH_3), 3.82 (m, 1H, H-2), 3.98 (m, 2H, H-1, H-1'), 4.21 (d, 1H, H-6', $^{2}J_{6'-6}$ = 12.0 Hz), 4.51 (m, 1H, H-3), 4.54 (m, 1H, H-4), 5.59 (d, 1H, H-6, $^{2}J_{6-6'}$ = 12.0 Hz), 7.28 (m, 1H, CH=), 7.32 (m, 1H, CH=), 7.54 (m, 2H, CH=). ^{13}C NMR (C_6D_6), δ: 0.5 (CH_3-Si), 0.6 (CH_3-Si), 26.0 (CH_3), 26.5 (CH_3), 28.2 (CH_3), 28.8 (CH_3), 60.9 (C-1), 71.3 (C-6), 72.4 (C-4), 74.7 (C-2), 77.1 (C-3), 104.9 (C-5), 109.6 (CMe_2), 112.5 (CMe_2), 124.8 (CH=), 124.9 (CH=), 126.2 (C), 127.3 (CH=), 127.9 (CH=), 133.7 (C), 134.9 (C), 140.9 (C), 141.0 (C), 146.8 (C). Anal. Calc (%) for $C_{30}H_{44}NO_7PSi_2$: C 58.32, H 7.18, N 2.27; found: C 58.26, H 7.21, N 2.31.

L9a. Yield: 237 mg (34 %). ^{31}P NMR (C_6D_6), δ: 147.1 (s, 1P). ^{1}H NMR (C_6D_6), δ: 1.02 (s, 3H, CH_3), 1.06 (s, 3H, CH_3), 1.24 (s, 18H, CH_3, ^{t}Bu), 1.26 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 1.56 (s, 9H, CH_3, ^{t}Bu), 1.59 (s, 9H, CH_3, ^{t}Bu), 3.27 (m, 1H, H-6), 3.37 (m, 1H, H-6'), 3.56 (d, 1H, H-1, $^{2}J_{1-1'}$ = 9.2 Hz), 3.64 (d, 1H, H-1', $^{2}J_{1-1'}$ = 9.2 Hz), 3.72 (m, 1H, H-4), 3.75 (m, 1H, NH), 4.31 (m, 1H, H-3), 4.37 (m, 1H, H-2), 7.0-7.2 (m, 4H, CH=). ^{13}C NMR (C_6D_6), δ: 24.5 (CH_3), 25.7 (CH_3), 26.6 (CH_3), 30.5 (CH_3), 31.7 (CH_3, ^{t}Bu), 31.8 (CH_3, ^{t}Bu), 32.0 (CH_3, ^{t}Bu), 35.0 (C, ^{t}Bu), 35.8 (C, ^{t}Bu), 36.0 (C, ^{t}Bu), 47.5 (C-6), 61.8 (C-1), 71.1 (C-3), 71.5 (C-4), 72.2 (C-2), 108.2 (CMe_2), 109.3 (CMe_2), 124.5 (CH=), 125.3 (CH=), 126.2 (CH=), 127.0 (CH=), 137.2 (C), 143.8 (C), 146.6 (C). Anal. Calc (%) for $C_{40}H_{60}NO_7P$: C 68.84, H 8.67, N 2.01; found: C 68.87, H 8.69, N 1.98.

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L9b. Yield: 245 mg (38 %). ^{31}P NMR (C_6D_6), δ: 147.8 (s, 1P). ^{1}H NMR (C_6D_6), δ: 1.04 (s, 3H, CH_3), 1.11 (s, 3H, CH_3), 1.27 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 1.49 (s, 9H, CH_3, ^{t}Bu), 1.51 (s, 9H, CH_3, ^{t}Bu), 3.28 (s, 3H, OCH_3), 3.30 (s, 3H, OCH_3), 3.43 (m, 1H, H-6), 3.57 (m, 1H, H-6'), 3.59 (m, 1H, H-1), 3.65 (m, 1H, H-1'), 3.72 (m, 1H, NH), 3.75 (m, 1H, H-4), 4.40 (m, 1H, H-3), 4.42 (m, 1H, H-2), 7.0-7.2 (m, 4H, CH=). ^{13}C NMR (C_6D_6), δ: 24.4 (CH_3), 25.7 (CH_3), 26.5 (CH_3), 26.8 (CH_3), 31.6 (CH_3, ^{t}Bu), 31.7 (CH_3, ^{t}Bu), 35.0 (C, ^{t}Bu), 35.3 (C, ^{t}Bu), 47.5 (d, C-6, $J_{C\text{-}P}$ = 12.1 Hz), 55.2 (OCH_3), 55.3 (OCH_3), 61.9 (C-1), 71.1 (C-3), 71.5 (C-4), 72.1 (C-2), 108.3 (CMe_2), 109.3 (CMe_2), 115.0 (CH=), 116.3 (CH=), 135.0 (C), 143.1 (C), 156.6 (C). Anal. Calc (%) for $C_{34}H_{48}NO_9P$: C 63.24, H 7.49, N 2.17; found: C 63.19, H 7.50, N 2.14.

L9c. Yield: 228 mg (37 %). ^{31}P NMR (C_6D_6), δ: 149.5 (s, 1P). ^{1}H NMR (C_6D_6), δ: 0.40 (s, 9H, CH_3-Si), 0.45 (s, 9H, CH_3-Si), 1.06 (s, 3H, CH_3), 1.09 (s, 3H, CH_3), 1.29 (s, 3H, CH_3), 1.39 (s, 3H, CH_3), 3.27 (m, 1H, H-6), 3.38 (m, 1H, H-6'), 3.60 (m, 1H, H-1), 3.67 (m, 1H, H-1'), 3.73 (m, 1H, NH), 3.79 (m, 1H, H-4), 4.34 (m, 1H, H-3), 4.41 (m, 1H, H-2), 6.8-7.4 (m, 6H, CH=). ^{13}C NMR (C_6D_6), δ: 0.4 (CH_3-Si), 0.5 (CH_3-Si), 24.3 (CH_3), 25.5 (CH_3), 26.5 (CH_3), 26.7 (CH_3), 47.9 (d, C-6, $J_{C\text{-}P}$ = 8.2 Hz), 61.8 (C-1), 71.0 (C-3), 71.4 (C-4), 72.2 (C-2), 108.3 (CMe_2), 109.2 (CMe_2), 124.9 (CH=), 126.0 (C), 129.6 (CH=), 131.9 (C), 132.0 (C), 135.8 (CH=), 135.9 (CH=), 136.5 (C), 138.2 (C), 155.7 (C). Anal. Calc (%) for $C_{30}H_{44}NO_7PSi_2$: C 58.32, H 7.18, N 2.27; found: C 58.29, H 7.16, N 2.26.

L9d. Yield: 216 mg (41 %). ^{31}P NMR (C_6D_6), δ: 144.4 (s, 1P). ^{1}H NMR (C_6D_6), δ: 1.42 (s, 3H, CH_3), 1.49 (s, 3H, CH_3), 1.68 (s, 3H, CH_3), 1.73 (s, 3H, CH_3), 2.49 (s, 6H, CH_3), 2.73 (s, 6H, CH_3), 3.74 (m, 1H, H-

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6), 3.94 (m, 1H, H-6'), 4.03 (m, 1H, H-1), 4.05 (m, 1H, H-1'), 4.08 (m, 1H, NH), 4.13 (m, 1H, H-4), 4.76 (m, 1H, H-3), 4.80 (m, 1H, H-2), 7.3-7.5 (m, 4H, CH=). ^{13}C NMR (C_6D_6), δ: 17.1 (CH_3), 21.1 (CH_3), 24.3 (CH_3), 25.6 (CH_3), 26.4 (CH_3), 26.8 (CH_3), 46.7 (d, C-6, J_{C-P} = 11.4 Hz), 61.9 (C-1), 71.1 (C-3), 71.4 (C-4), 71.8 (C-2), 108.4 (CMe_2), 109.3 (CMe_2), 128.3 (CH=), 128.6 (CH=), 131.6 (C), 131.7 (C), 133.6 (C). Anal. Calc (%) for $C_{28}H_{36}NO_7P$: C 63.51, H 6.85, N 2.64; found: C 63.46, H 6.81, N 2.63.

L9e. Yield: 265 mg (48 %). ^{31}P NMR (C_6D_6), δ: 146.3 (s, 1P). ^{1}H NMR (C_6D_6), δ: 1.06 (s, 3H, CH_3), 1.09 (s, 3H, CH_3), 1.32 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 3.30 (m, 1H, H-6), 3.44 (m, 1H, H-6'), 3.47 (m, 1H, H-1), 3.50 (m, 1H, H-1'), 3.57 (m, 5H, NH, CH_2 allyl), 4.41 (m, 2H, H-4, H-3), 5.07 (m, 5H, H-2, CH= allyl), 6.02 (m, 2H, CH= allyl), 6.9-7.4 (m, 6H, CH=). ^{13}C NMR (C_6D_6), δ: 24.3 (CH_3), 25.6 (CH_3), 26.5 (CH_3), 26.8 (CH_3), 35.2 (CH_2 allyl), 35.4 (CH_2 allyl), 47.0 (d, C-6, J_{C-P} = 4.2 Hz), 61.8 (C-1), 71.0 (C-3), 71.4 (C-4), 71.9 (C-2), 108.3 (CMe_2), 109.2 (CMe_2), 116.4 (CH_2= allyl), 116.6 (CH_2= allyl), 124.9 (CH=), 125.0 (CH=), 126.3 (C), 128.8 (CH=), 130.3 (CH=), 133.1 (C), 133.2 (C), 137.3 (CH= allyl), 137.5 (CH= allyl). Anal. Calc (%) for $C_{30}H_{36}NO_7P$: C 65.09, H 6.55, N 2.53; found: C 65.12, H 6.58, N 2.56.

L10a. Yield: 306 mg (44 %). ^{31}P NMR (C_6D_6), δ: 148.5 (s, 1P). ^{1}H NMR (C_6D_6), δ: 1.03 (s, 3H, CH_3), 1.08 (s, 3H, CH_3), 1.26 (s, 3H, CH_3), 1.31 (s, 18H, CH_3, ^{t}Bu), 1.42 (s, 3H, CH_3), 1.60 (s, 18H, CH_3, ^{t}Bu), 3.17 (m, 2H, H-6, H-6'), 3.42 (m, 1H, NH), 3.79 (m, 1H, H-1), 3.81 (m, 1H, H-5), 4.12 (m, 1H, H-3), 4.40 (m, 1H, H-2), 5.41 (m, 1H, H-4), 7.2-7.6 (m, 4H, CH=). ^{13}C NMR (C_6D_6), δ: 24.7 (CH_3), 25.2 (CH_3), 26.5 (CH_3), 26.6 (CH_3), 30.2 (CH_3, ^{t}Bu), 31.8 (CH_3, ^{t}Bu), 35.6 (C, ^{t}Bu), 35.9

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(C, ^{t}Bu), 41.4 (d, C-2, $J_{C\text{-}P}$ = 12.0 Hz), 69.5 (C-5), 71.3 (C-3), 71.5 (C-2), 71.8 (C-1), 96.9 (C-4), 108.7 (CMe_2), 109.4 (CMe_2), 124.4 (CH=), 124.5 (CH=), 125.3 (C), 127.0 (CH=), 127.2 (CH=), 134.3 (C), 140.9 (C), 146.5 (C), 148.2 (C). Anal. Calc (%) for $C_{40}H_{60}NO_7P$: C 68.84, H 8.67, N 2.01; found: C 68.90, H 8.65, N 2.03.

L10b. Yield: 309 mg (48 %). ^{31}P NMR (C_6D_6), δ: 147.6 (s, 1P). ^{1}H NMR (C_6D_6), δ: 1.03 (s, 3H, CH_3), 1.06 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 1.54 (s, 9H, CH_3, ^{t}Bu), 1.56 (s, 18H, CH_3, ^{t}Bu), 3.29 (m, 2H, H-6, H-6'), 3.33 (s, 3H, OCH_3), 3.35 (s, 3H, OCH_3), 3.49 (m, 1H, NH), 3.82 (m, 1H, H-1), 3.89 (m, 1H, H-5), 4.13 (m, 1H, H-3), 4.41 (m, 1H, H-2), 5.44 (m, 1H, H-4), 7.0-7.2 (m, 4H, CH=). ^{13}C NMR (C_6D_6), δ: 24.7 (CH_3), 25.2 (CH_3), 26.5 (CH_3), 26.7 (CH_3), 31,6 (CH_3, ^{t}Bu), 34.8 (C, ^{t}Bu), 41.4 (d, C-2, $J_{C\text{-}P}$ = 12.1 Hz), 55.4 (OCH_3), 69.5 (C-5), 71.3 (C-3), 71.5 (C-2), 71.8 (C-1), 97.0 (C-4), 108.7 (CMe_2), 109.5 (CMe_2), 115.2 (CH=), 115.5 (CH=), 129.6 (C), 135.0 (C), 135.1 (C), 142.9 (C), 156.4 (C). Anal. Calc (%) for $C_{34}H_{48}NO_9P$: C 63.24, H 7.49, N 2.17; found: C 63.26, H 7.50, N 2.19.

L10c. Yield: 234 mg (38 %). ^{31}P NMR (C_6D_6), δ: 149.7 (s, 1P). ^{1}H NMR (C_6D_6), δ: 0.31 (s, 3H, CH_3-Si), 0.40 (s, 3H, CH_3-Si), 1.05 (s, 3H, CH_3), 1.23 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 3.28 (m, 1H, H-6), 3.31 (m, 1H, H-6'), 3.42 (m, 1H, NH), 3.86 (m, 1H, H-1), 3.92 (m, 1H, H-5), 4.11 (m, 1H, H-3), 4.40 (m, 1H, H-2), 5.42 (m, 1H, H-4), 7.0-7.2 (m, 6H, CH=). ^{13}C NMR (C_6D_6), δ: 0.5 (CH_3-Si), 0.7 (CH_3-Si), 24.7 (CH_3), 25.2 (CH_3), 26.5 (CH_3), 26.9 (CH_3), 69.9 (C-5), 71.2 (C-3), 71.9 (C-2), 72.4 (C-1), 97.3 (C-4), 108.7 (CMe_2), 109.9 (CMe_2), 125.1 (CH=), 125.8 (CH=), 131.9 (C), 132.1 (C), 132.2 (CH=), 132.3 (C), 132.8 (C), 133.1 (CH=), 135.5 (CH=), 136.0 (CH=), 136.5 (C), 138.2 (C), 155.7

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(C). Anal. Calc (%) for $C_{30}H_{44}NO_7PSi_2$: C 58.32, H 7.18, N 2.27; found: C 58.33, H 7.22, N 2.25.

L10d. Yield: 269 mg (51 %). ^{31}P NMR (C_6D_6), δ: 145.3 (s, 1P). ^{1}H NMR (C_6D_6), δ: 0.99 (s, 3H, CH_3), 1.04 (s, 3H, CH_3), 1.37 (s, 3H, CH_3), 1.47 (s, 3H, CH_3), 2.11 (s, 3H, CH_3), 2.13 (s, 3H, CH_3), 2.36 (s, 6H, CH_3), 3.32 (m, 2H, H-6, H-6'), 3.50 (m, 1H, NH), 3.61 (m, 1H, H-1), 3.88 (m, 1H, H-5), 4.12 (m, 1H, H-3), 4.34 (m, 1H, H-2), 5.44 (m, 1H, H-4), 7.0-7.2 (m, 4H, CH=). ^{13}C NMR (C_6D_6), δ: 17.2 (CH_3), 17.3 (CH_3), 21.2 (CH_3), 24.5 (CH_3), 25.3 (CH_3), 26.5 (CH_3), 26.6 (CH_3), 40.9 (d, C-2, $J_{C\text{-}P}$ = 7.6 Hz), 69.7 (C-5), 71.4 (C-3), 71.5 (C-2), 71.7 (C-1), 97.0 (C-4), 108.8 (CMe_2), 109.5 (CMe_2), 128.3 (CH=), 128.7 (CH=), 129.2 (CH=), 131.6 (C), 131.7 (C), 133.6 (C). Anal. Calc (%) for $C_{28}H_{36}NO_7P$: C 63.51, H 6.85, N 2.64; found: C 63.53, H 6.87, N 2.62.

L10e. Yield: 260 mg (47 %). ^{31}P NMR (C_6D_6), δ: 147.8 (s, 1P). ^{1}H NMR (C_6D_6), δ: 0.98 (s, 3H, CH_3), 0.99 (s, 3H, CH_3), 1.33 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 3.18 (m, 2H, H-6, H-6'), 3.44 (m, 1H, NH), 3.48 (m, 1H, H-1), 3.57 (m, 4H, CH_2 allyl), 3.76 (m, 1H, H-5), 4.07 (m, 1H, H-3), 4.32 (m, 1H, H-2), 5.01 (m, 4H, CH_2= allyl), 5.38 (m, 1H, H-4), 5.97 (m, 2H, CH= allyl), 6.9-7.2 (m, 6H, CH=). ^{13}C NMR (C_6D_6), δ: 24.6 (CH_3), 25.3 (CH_3), 26.5 (CH_3), 26.7 (CH_3), 35.2 (CH_2 allyl), 35.3 (CH_2 allyl), 41.1 (d, C-2, $J_{C\text{-}P}$ = 9.2 Hz), 69.6 (C-5), 71.3 (C-3), 71.5 (C-2), 71.8 (C-1), 97.0 (C-4), 108.8 (CMe_2), 109.5 (CMe_2), 116.5 (CH_2= allyl), 116.7 (CH_2= allyl), 124.8 (CH=), 125.0 (CH=), 126.0 (C), 129.6 (C), 130.2 (CH=), 132.5 (C), 133.0 (C), 137.4 (CH= allyl). Anal. Calc (%) for $C_{30}H_{36}NO_7P$: C 65.09, H 6.55, N 2.53; found: C 65.12, H 6.57, N 2.54.

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4.2.4.3. Typical procedure for the catalytic allylic alkylation of S1.

A dried Schlenk tube was charged with copper salt (1 mol%) and the corresponding ligand (1 mol% for bidentated ligands or 2 mol% for monodentated ligands). Dichloromethane (2 mL) was added and the mixture was stirred at room temperature for 30 min. Cinnamyl chloride (1 mmol) was introduced dropwise and the reaction mixture was stirred at room temperature for a further 5 min before being cooled to -78 °C in an ethanol-dry cold bath. EtMgBr (2 M in diethyl ether, 1.2 eq) in dichloromethane (0.5 mL) was added over 4 hours via syringe pump. Once the addition was complete the reaction mixture was left at –78°C for a further 16 hour at which point gas chromatography of an aliquot showed that all the starting material had been converted. The reaction was quenched by addition of aqueous hydrochloric acid (1 N, 2 mL). Diethyl ether (10 mL) was added and the aqueous phase was separated and extracted further with diethyl ether (3 x 3mL). The combined organic fractions were washed with brine (5 mL), dried over anhydrous sodium sulfate, filtered and reduced in vacuo. The oily residue was purified by flash column chromatography (eluent = pentane) to yield the product as a mixture of S_N2' and S_N2 regioisomers. Gas Supercritical Fluid Chromatography on a Chiralcel OJ column (1% MeOH, flow rate 2 mL/min) showed the enantiomeric excess of S_N2' product **6**.[11]

4.2.5. Acknowledgements

We would like to thank the Spanish Government (Consolider Ingenio CSD2006-0003, CTQ2007-62288/BQU, 2008PGIR/07 to O.P. and 2008PGIR/08 to M.D.), the Catalan Government (2005SGR007777),

ISBN:978-84-692-9762-9/DL:T-202-2010

the Swiss National Research Foundation (grant N° 200020-113332) and COST action D40 (SER contract N° C07.0097) for their financial support.

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Chapter 5

Asymmetric Cu-catalyzed 1,4-conjugate addition

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5. Asymmetric Cu-catalyzed 1,4-conjugate addition

5.1. Background

The last decade has seen important breakthroughs in what is possible in the area of catalytic asymmetric 1,4-addition of alkyl organometallic nucleophiles to enones. Most of the successful asymmetric versions of this chemistry have made use of diorganozinc reagents, specially $ZnEt_2$, a trend started by Alexakis (Cu-catalysis) and Soai (Ni-catalysis). Viable ligand classes affording > 90% ee for the addition of diorganozinc to several types of cyclic and chalcone substrates are now available.[1] However, relatively few publications describing highly enantioselective addition of organometallics to linear aliphatic and cyclic β-trisubstituted enones and using trialkylaluminum reagents as alternative to organozinc have appeared.[1] This justify to expand the range of ligands for the Cu-catalyzed addition of organoaluminum reagents to enones and more specifically to the linear aliphatic and cyclic β-trisubstituted ones. For this purpose, carbohydrates are particularly advantageous because they are available at low price and because their modular constructions are easy.

In this chapter, we report the application of the four carbohydrate-based ligand libraries described in Chapters 3 and 4 (phosphite-phosphoroamidite (**L1**-**L4**), diphosphoroamidite (**L5**), monophosphoroamidite (**L6**-**L10**) and monophosphite (**L11**-**L14**) in the asymmetric Cu-catalyzed 1,4-addition of organometallic reagents (ZnR_2 and AlR_3) to enones. More specifically, in section 5.2 we report the application of the furanoside phosphite-phosphoroamidite (**L1**-**L4**) and

ISBN:978-84-692-9762-9/DL:T-202-2010

diphosphoroamidite (**L5**) ligand libraries. Our results indicated that selectivity depended strongly on the ligand parameters and on the substrate structure. Moderate-to-good enantioselectivities (ee's up to 84%) were obtained in the 1,4-addition of several types of β-substituted cyclic and linear substrates. Of particular note is the high enantioselectivity (ee's up to 90%) obtained for the more challenging β,β'-disubstituted 3-methyl-cyclohexenone. In section 5.3, we report the application of the modular sugar-based monophosphoroamidite ligand library (**L6**-**L10**) for this process. We also compare the effectiveness of this phosphoroamidite ligand library with the results obtained using related monophosphite ligands (**L11**-**L14**). To do so, we have also expanded our previous work on monophosphite ligands (**L11**-**L14**)[2] to other challenging classes of substrates (i.e. nitro-olefins and β,β'-disubstituted enones). By carefully selecting the ligand parameters we achieved enantioselectivities of up to 60% for cyclic substrates and 72% for linear ones.

5.1.1. References

[1] Alexakis, A.; Bäckvall, J. E.; Krause, N.; Pàmies, O.; Diéguez, M. *Chem. Rev.* **2008**, *108*, 2796.

[2] Mata, Y.; Diéguez, M.; Pàmies, O.; Woodward, S. *J. Oganomet. Chem.* **2007**, *692*, 4315.

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5.2. Furanoside phosphite-phosphoroamidite and diphosphoroamidite ligands for Cu-catalyzed asymmetric 1,4-addition reactions

Eva Raluy, Oscar Pàmies, Montserrat Diéguez, Stephane Rosset and Alexander Alexakis in *Tetrahedron: Asymmetry* **2009**, *20*, 1930.

Abstract. We have also tested the previously described phosphite-phosphoroamidite and diphosphoroamidite ligand libraries **L1**-**L4a**-**g** and **L5a**-**g** in the asymmetric Cu-catalyzed 1,4-conjugate addition reactions of β-substituted and β,β'disubstituted enones. Our results indicated that selectivity depended strongly on the ligand parameters and on the substrate structure. Moderate-to-good enantioselectivities (ee's up to 84%) were obtained in the 1,4-addition of several types of β-substituted cyclic and linear substrates. Of particular note is the high enantioselectivity (ee's up to 90%) obtained for the more challenging β,β'-disubstituted 3-methyl-cyclohexenone.

5.2.1. Introduction

The enantioselective conjugate addition of organometallic reagents to α,β-unsaturated substrates catalyzed by chiral transition metal complexes is a useful synthetic process for asymmetric carbon-carbon bond formation.[1] The design of the chiral ligands together with the reaction conditions is perhaps the key to attaining high asymmetric induction in this process. Subtle changes in the conformational, steric, and/or electronic properties of the chiral ligand have led to dramatic

variation in the reactivity and enantioselectivity. Because in most cases there is a strong substrate dependence, tunable and readily synthesized ligand series are desirable if high enantioselectivities are to be obtained for a wide range of substrates.[1] Among the most efficient ligands, phosphite and phosphoroamidites based on biaryl moieties have played a prominent role.[1f-h,j,2] Although Michael additions of organolithium, Grignard and diorganozinc reagents to enones have been widely studied in the last decade,[1] less attention has been paid to trialkylaluminum reagents.[3] Trialkylaluminum reagents have recently appeared as an interesting alternative to organozinc reagents because their range can be more easily extended by technically simple hydro- and carboalumination reactions. Additionally, Cu-catalyzed 1,4-addition of trialkylaluminum reagents can be carried out on very challenging substrates (i.e. β-trisubstituted enones) which are inert to organozinc methodologies.[1] On the other hand, linear aliphatic enones is another class of substrate for which more active and enantioselective catalysts still need to be developed.[1]

Following our interest in modular ligands and encouraged by the success of phosphite and phosphoroamidite ligands in this process, we report here the application of sugar-based phosphite-phosphoroamidite[4] and diphosphoroamidite[5] ligand libraries described in Chapter 3 (**L1-L5a-g**; Figure 1) to the Cu-catalyzed asymmetric 1,4-addition of organometallic reagents to the cyclic and aliphatic linear enones. These ligands have the same advantages as carbohydrate and phosphite/phosphoroamidite ligands, that is, they are available at a low price from readily available feedstocks, they have high resistance to oxidation and have facile modular constructions.[6] Therefore, with this

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library we fully investigated the effects of systematically varying the position of the phosphoroamidite group at both C-5 (ligands **L1** and **L2**) and C-3 (ligands **L3** and **L4**) of the furanoside backbone, as well as the effects of the configuration at C-3 of the furanoside backbone, the introduction of second phosphoroamidite moiety (ligands **L5**) and the substituents/configurations in the biaryl phosphite/phosphoroamidite moieties (**a**-**g**).

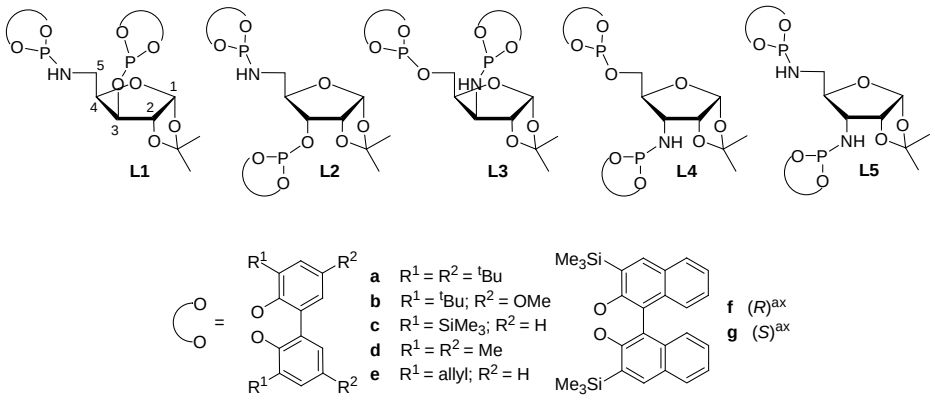

Figure 1. Phosphite-phosphoroamidite and diphosphoroamidite ligands (**L1-L5a-g**).

5.2.2. Results and Discussions

5.2.2.1. Asymmetric conjugate 1,4-addition to β-substituted enones

5.2.2.1.1. Asymmetric conjugate 1,4-addition of $ZnEt_2$ and $AlEt_3$ to cyclohexenone S1

In the first set of experiments, we tested furanoside ligands **L1-L5a-g** in the Cu-catalyzed conjugate addition of diethylzinc to 2-cyclohexenone **S1** (Equation 1). The latter was chosen as a substrate

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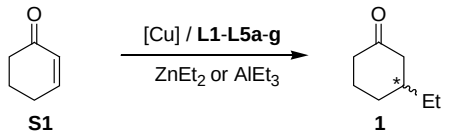
because this reaction has been performed with a wide range of ligands with several donor groups, thus enabling the efficiency of the various ligand systems to be compared directly.[1]



(1)

The catalytic system was generated *in situ* by adding the corresponding ligand to a suspension of catalyst precursor under standard conditions.[7] The results are shown in Table 1. They indicate that enantioselectivity is highly affected by the position of the phosphoroamidite group at either C-5 or C-3 of the furanoside backbone, and by the configuration of C-3, the introduction of second phosphoroamidite moiety and the substituents and configurations in the biaryl phosphite/phosphoroamidite moieties (**a**-**g**).

We first studied the configuration of C-3 and the effect of the position of the phosphoroamidite group at either C-5 (ligands **L1** and **L2**) or C-3 (ligands **L3** and **L4**) of the furanoside backbone. We observed a cooperative effect between the position of the phosphoroamidite group and the configuration of carbon atom C-3 of the furanoside backbone. The results indicate that the matched combination is achieved with ligands **L4**, whose phosphoroamidite moiety is attached to C-3 and which have an *R*-configuration of carbon atom C-3 on the tetrahydrofuran ring (Table 1, entries 16-22).

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Table 1. Cu-catalyzed asymmetric 1,4-addition of diethylzinc to **S1** using ligands **L1-L5a-g**.[a]

Entry	L	% Conv[b]	% Yield[b]	% ee[c]
1	**L1a**	100	95	10 (*R*)
2	**L1b**	84	80	2 (*R*)
3	**L1c**	99	92	1 (*R*)
4	**L1d**	95	93	51 (*S*)
5	**L1e**	100	96	41 (*S*)
6	**L2a**	100	92	20 (*S*)
7	**L2b**	99	90	10 (*S*)
8	**L2c**	96	88	11 (*S*)
9	**L2d**	100	93	55 (*R*)
10	**L2e**	100	91	37 (*R*)
11	**L3a**	97	89	28 (*S*)
12	**L3b**	97	93	18 (*S*)
13	**L3c**	100	96	18 (*S*)
14	**L3d**	100	92	12 (*R*)
15	**L3e**	100	90	6 (*R*)
16	**L4a**	99	94	38 (*S*)
17	**L4b**	97	90	28 (*S*)
18	**L4c**	100	91	15 (*S*)
19	**L4d**	100	89	53 (*R*)
20	**L4e**	100	84	30 (*R*)
21	**L4f**	100	86	16 (*R*)
22	**L4g**	100	90	64 (*S*)
23	**L5a**	100	92	12 (*S*)
24	**L5b**	100	87	29 (*S*)
25	**L5d**	100	96	32 (*R*)

[a] CuTC (2 mol%), ligand (2 mol%), $ZnEt_2$ (1.5 eq, 0.62 mmol), **S1** (0.415 mmol), Et_2O (2.5 mL). [b] Conversion and yields determined by GC using undecane as internal standard after 18 hours. [c] Enantiomeric excess measured by GC.

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We next studied the effects of the biaryl phosphite/phosphoroamidite moieties using ligands **L1**-**L4a-g** (Table 1). We found that enantioselectivity was negatively affected by the presence of sterically hindered substituents at the *ortho* positions and either methoxy or hydrogen substituents at the *para* position of the biphenyl moieties (Table 1, entries 16-20). We also observed a cooperative effect between the configuration of the biaryl moieties and the configuration of carbon atom C-3. The results indicated that the matched combination is achieved with ligand **L4g**, which has an *R*-configuration at carbon atom C-3 and an *S*-configuration in the binaphthyl phosphite/phosphoroamidite moieties (Table 1, entry 22).

We then used ligands **L5** to study how replacing the phosphite moiety with a phosphoroamidite group affected catalytic performance. The results indicated that the presence of a second phosphoroamidite moiety in the ligands had a negative effect on enantioselectivity (Table 1, entries 9 and 19 vs 25).

In summary, the best result was obtained with ligand **L4g** (Table 1, entry 22), which contains the optimal combination of ligand parameters (position of the phosphoroamidite group, configuration at C-3 of the furanoside backbone and the substituents and configurations in the biaryl phosphite/phosphoroamidite moieties).

In addition to control the effect of the structural parameters on catalytic performance, the reaction parameters can also be controlled to further improve yields and selectivities. Therefore, the effect of several reaction parameters, such as catalyst precursor, solvent, alkylating reagent and temperature, were studied using ligands **L4f** and **L4g** (Table 2). In this case, enantioselectivity was further improved (ee's up to 84%) with

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ligand **L4g** by using copper ditriflate and diethylzinc in dichloromethane at 0 ºC (Table 2, entry 6).[8]

Table 2. Selected results for the Cu-catalyzed asymmetric 1,4-addition of **S1** using ligands **L4f** and **L4g**. Effect of the reaction parameters.[a]

Entry	L	Precursor	Solvent	T	% Conv (h)[b]	% Yield[b]	% ee[c]
1	**L4f**	CuTC	Et_2O	-30	100 (18)	86	16 (*R*)
2	**L4g**	CuTC	Et_2O	-30	100 (18)	90	64 (*S*)
3[d]	**L4f**	CuTC	Et_2O	-30	100 (18)	85	9 (*R*)
4[d]	**L4g**	CuTC	Et_2O	-30	100 (18)	81	36 (*S*)
5	**L4f**	$Cu(OTf)_2$	CH_2Cl_2	0	100 (0.5)	92	60 (*R*)
6	**L4g**	$Cu(OTf)_2$	CH_2Cl_2	0	100 (0.5)	94	84 (*S*)

[a] Cu-precursor (2 mol%), ligand (2 mol%), $ZnEt_2$ (1.5 eq, 0.62 mmol), **S1** (0.415 mmol), solvent (2.5 mL). [b] Conversion and yields determined by GC using undecane as internal standard. [c] Enantiomeric excess measured by GC. [d] Using $AlEt_3$ (1.5 eq, 0.62 mmol).

5.2.2.1.2. Asymmetric conjugate 1,4-addition of $ZnEt_2$, $AlEt_3$ and $AlMe_3$ to trans-3-nonen-2-one S2

We have also screened the use of ligands **L1-L5a-g** in the Cu-catalyzed conjugate addition of several alkylating reagents to the linear substrate: *trans*-3-nonen-2-one **S2** (Equation 2). This enone, possessing only aliphatic substituents, is a more demanding substrate class for asymmetric conjugate addition than **S1**. The high conformational mobility of this substrate together with the presence of only subtle substrate-catalyst steric interactions makes designing effective enantioselective systems very challenging.[3e,h,9]

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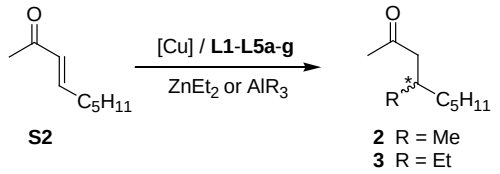

(2)

Table 3. Selected results for the Cu-catalyzed asymmetric 1,4-addition of **S2** using ligands **L1**-**L5a-g**.[a]

Entry	L	Precursor	Alkylating reagent	% Conv[b]	% Yield[b]	% ee
1	**L1a**	CuTC	$AlMe_3$	90	76	7 (*R*)
2	**L2a**	CuTC	$AlMe_3$	100	74	11 (*S*)
3	**L3a**	CuTC	$AlMe_3$	92	81	14 (*R*)
4	**L4a**	CuTC	$AlMe_3$	95	74	23 (*S*)
5	**L4b**	CuTC	$AlMe_3$	91	69	14 (*S*)
6	**L4c**	CuTC	$AlMe_3$	87	67	17 (*S*)
7	**L4d**	CuTC	$AlMe_3$	75	68	44 (*R*)
8	**L4e**	CuTC	$AlMe_3$	83	71	5 (*R*)
9	**L4f**	CuTC	$AlMe_3$	88	74	32 (*R*)
10	**L4g**	CuTC	$AlMe_3$	91	79	51 (*S*)
11	**L5d**	CuTC	$AlMe_3$	81	72	39 (*R*)
12	**L4g**	$Cu(OTf)_2$	$AlMe_3$	91	83	35 (*S*)
13	**L4g**	$[Cu(CH_3CN)_4]BF_4$	$AlMe_3$	90	78	18 (*S*)
14	**L4g**	CuTC	$AlEt_3$	96	85	40 (*S*)
15	**L4g**	CuTC	$ZnEt_2$	66	59	5 (*S*)

[a] Cu-precursor (2 mol%), ligand (2 mol%), alkylating reagent (1.5 eq, 0.62 mmol), **S2** (0.415 mmol), Et_2O (2.5 mL), T = -30 °C. [b] Conversion and yields determined by GC using undecane as internal standard after 18 h. [c] Enantiomeric excess measured by GC.

Table 3 shows the most representative results. In general the ligand requirements were the same as for the 1,4-addition of **S1**. Again, the best enantioselectivity (ee's up to 51%) was obtained with ligand **L4g**

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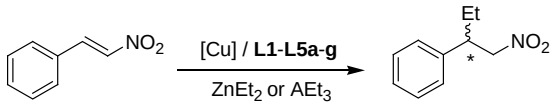
(Table 3, entry 10). However the effect of the reaction parameters (catalyst precursor, solvent, alkylating reagent and temperature) were different than those observed for **S1**. Therefore, the best enantioselectivities were obtained using CuTC and trimethylaluminum in diethylether at -30 ºC (Table 3, entries 10 vs 12-15).

5.2.2.1.3. Asymmetric conjugate 1,4-addition of $ZnEt_2$ and $AlEt_3$ to trans-nitrostyrene S3

We next applied the ligand library **L1**-**L5a**-**g** to the Cu-catalyzed conjugate addition of several alkylating reagents to the linear nitrolefin *trans*-nitrostyrene **S3** (Equation 3). The nitro group is very important synthetically because it can be transformed into a variety of valuable organic compounds such as aldehydes, carboxylic acids, nitriles, nitro oxides and amines.[10]



S3 **4** (3)

The results are summarized in Table 4. Again, activities and enantioselectivities were affected by the position of the phosphoroamidite group at either C-5 or C-3 of the furanoside backbone, and by the configuration of C-3, the introduction of second phosphoroamidite moiety and the substituents and configurations in the biaryl phosphite/phosphoroamidite moieties (**a**-**g**). However, these parameters had a different effect on the conjugate addition of substrates **S1** and **S2**. Thus, the configuration of C-3 controls the sense of enantioselectivity. In this respect, whereas ligands **L1** and **L3** with an *S*-configuration at C-3

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provide *S*-**4**, ligands **L2**, **L4** and **L5** with an opposite configuration at C-3 predominantly provide *R*-**4** (Table 4, entries 1 and 3 vs 2, 4 and 9). We also found that diphosphoroamidite ligands provide higher enantioselectivities than the phosphite-phosphoroamidite ligands (Table 4, entries 7 vs 1-6). The effect of the substituents and configurations of the biaryl phosphite/phosphoroamidite moieties (**a**-**g**) on enantioselectivity depends on the type of ligand. Thus, in the case of phosphite-phosphoroamidite ligands, enantioselectivities are best when methyl substituents at both *ortho* and *para* positions of the biphenyl moieties are present, whereas in the case of diphosphoroamidites, the best ee's are obtained when bulky *tert*-butyl groups are present at the *ortho* positions of the biphenyl moiety (Table 4, entries 7 and 8 vs 9). In summary, and in contrast to the substrates **S1** and **S2**, the best ee's (up to 66%) were obtained with homodonor ligands **L5a**-**b** (Table 4, entries 7 and 8).

The effect of the reaction parameters (catalyst precursor, solvent, alkylating reagent and temperature) were the same as for the 1,4-addition of **S2**.

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Table 4. Selected results for the Cu-catalyzed asymmetric 1,4-addition of **S3** using ligands **L1**-**L5a**-**g**.[a]

Entry	L	Precursor	Alkylating reagent	% Conv[b]	% Yield[b]	% ee[c]
1	**L1d**	CuTC	$AlEt_3$	100	93	12 (*S*)
2	**L2d**	CuTC	$AlEt_3$	95	90	50 (*R*)
3	**L3d**	CuTC	$AlEt_3$	100	94	60 (*S*)
4	**L4d**	CuTC	$AlEt_3$	100	93	55 (*R*)
5	**L4f**	CuTC	$AlEt_3$	100	86	15 (*S*)
6	**L4g**	CuTC	$AlEt_3$	100	90	29 (*R*)
7	**L5a**	CuTC	$AlEt_3$	100	90	66 (*R*)
8	**L5b**	CuTC	$AlEt_3$	100	88	66 (*R*)
9	**L5d**	CuTC	$AlEt_3$	100	89	6 (*R*)
10[d]	**L5a**	CuTC	$AlEt_3$	80	74	40 (*R*)
11	**L4d**	CuTC	$ZnEt_2$	100	91	42 (*R*)
12	**L5a**	CuTC	$ZnEt_2$	98	87	24 (*R*)
13	**L5a**	$Cu(OTf)_2$	$ZnEt_2$	100	94	5 (*S*)

[a] Cu-precursor (2 mol%), ligand (2 mol%), alkylating reagent (1.5 eq, 0.62 mmol), **S3** (0.415 mmol), Et_2O (2.5 mL), T = -30 °C. [b] Conversion and yields determined by GC using undecane as internal standard after 18 hours. [c] Enantiomeric excess measured by GC. [d] T = -78 °C.

5.2.2.2. Asymmetric conjugate 1,4-addition of β,β'-disubstituted enones

To further study the potential of ligands **L1**-**L5a**-**g**, we tested their effect on the Cu-catalyzed conjugate addition of triethylaluminum to 3-methyl-cyclohexenone **S4** (Equation 4). The conjugate addition of this type of substrates provides an efficient way to build chiral quaternary centers into a compound.[1]

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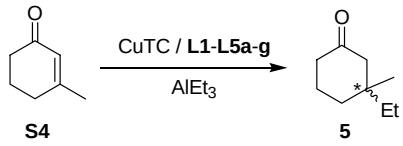

S4 **5** (4)

For a long time, the 1,4-addition of β,β'-disubstituted enones was unsuccessful because of the low reactivity of these substrates with dialkylzinc reagents. Recently, Alexakis and co-workers have disclosed that the combination of more reactive trialkylaluminum reagents together with an appropriate choice of the reaction parameters could be efficiently used for the 1,4-addition of this type of challenging substrates.[11] These latter conditions were used to test the effects of our ligand libraries on the Cu-conjugate addition of substrate **S4**. The results are summarized in Table 5. The position of the phosphoroamidite and the configuration at C-3 followed the same trends as for the 1,4-addition of substrates **S1** and **S2** (Table 5, entries 1, 6, 7 and 11). However, the effect of the substituents and configurations on the biaryl phosphite/phosphoroamidite moieties (**a-g**) was different (Table 5, entries 2-6 and 8-13). Therefore, the best enantioselectivites (ee's up to 90%) were obtained with ligand **L4e**, which has the phosphoroamidite attached to C-3, an *R*-configuration at carbon atom C-3 and allyl substituents at the *ortho* positions of the biphenyl phosphite/phosphoroamidite moieties (Table 5, entry 11).

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Table 5. Selected results for the Cu-catalyzed asymmetric 1,4-addition of **S4** using ligands **L1**-**L5a**-**g**.[a]

Entry	L	% Conv[b]	% Yield[b]	% ee[c]
1	**L1e**	6	5	10 (*S*)
2	**L2a**	51	45	30 (*S*)
3	**L2b**	35	29	18 (*S*)
4	**L2c**	<5	-[d]	-[d]
5	**L2d**	<5	-[d]	-[d]
6	**L2e**	15	13	40 (*S*)
7	**L3e**	15	11	56 (*S*)
8	**L4a**	40	34	40 (*S*)
9	**L4b**	20	18	4 (*S*)
10	**L4c**	26	21	14 (*S*)
11[e]	**L4e**	60	52	90 (*S*)
12	**L4f**	18	14	18 (*R*)
13	**L4g**	15	11	33 (*S*)
14	**L5a**	20	15	32 (*S*)

[a] CuTC (4 mol%), ligand (4 mol%), $AlEt_3$ (1.5 eq, 0.62 mmol), **S4** (0.415 mmol), Et_2O (2.5 mL), T = -30 °C. [b] Conversion and yields determined by GC using undecane as internal standard after 18 hours. [c] Enantiomeric excess measured by GC. [d] not determined. [e] t = 40 h.

5.2.3. Conclusions

A modular based-phosphite-phosphoroamidite **L1**-**L4a**-**g** and diphosphoroamidite **L5a**-**g** ligand library was tested to determine its effects on the asymmetric Cu-catalyzed 1,4-conjugate addition reactions of cyclic and acyclic enones. Our results indicated that selectivity depended strongly on the position of the phosphoroamidite group at either C-5 or C-3 of the furanoside backbone, as well as the configuration of

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C-3, the introduction of a second phosphoroamidite moiety, the substituents and configurations in the biaryl phosphite/phosphoroamidite moieties (**a**-**g**) and on the substrate structure. For β-susbtituted cyclic **S1** and linear **S2** substrates, enantioselectivities (ee's up to 84%) were best with ligand **L4g**, whereas for β-substituted nitro substrate **S3**, the best enantioselectivities (ee's up to 66%) were obtained with ligands **L5a-b**. Note the high enantioselectivity (ee's up to 90%) obtained for the more challenging β,β'-disubstituted enone **S4** using the CuTC/**L4e** catalytic system.

5.2.4. Experimental Section

5.2.4.1. General considerations.

All syntheses were performed by using standard Schlenk techniques under an argon atmosphere. Solvents were purified by standard procedures. The synthesis of ligands **L1**-**L5a**-**g** has been previously described in Chapter 3. All other reagents were used as commercially available.

5.2.4.2. Typical procedure for the catalytic conjugate addition of alkylating reagents to enones

In a typical procedure, a solution of Cu-catalyst precursor (8.3 μmol) and furanoside ligand (8.3 μmol) in the appropriate solvent (2 mL) was stirred for 30 minutes at room temperature. After cooling to the desired temperature, the alkylating reagent (0.62 mmol) was added. A solution of the desired enone (0.415 mmol) and undecane as GC internal standard (0.25 mL) in dichloromethane (0.5 mL), and was then added at

the corresponding reaction temperature. The reaction was monitored by GC. The reaction was quenched with HCl (2 M) and filtered twice through flash silica. Conversion, chemoselectivity and enantioselectivity were obtained by GC (for **S1,** Lipodex A column; for **S2**, 6-Me-2,3-pe-γ-CD column; for **S3** and **S4**, Lipodex E column).[3i]

5.2.5. Acknowledgements

We would like to thank the Spanish Government (Consolider Ingenio CSD2006-0003, CTQ2007-62288/BQU, 2008PGIR/07 to O.P. and 2008PGIR/08 to M.D.), the Catalan Government (2005SGR007777), the Swiss National Research Foundation (grant N° 200020-113332) and COST action D40 (SER contract N° C07.0097) for their financial support.

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5.3. Sugar-based phosphite and phosphoroamidite ligands for the Cu-catalyzed asymmetric 1,4-addition to enones

Eva Raluy, Oscar Pàmies, Montserrat Diéguez, Stephane Rosset and Alexander Alexakis in *Tetrahedron: Asymmetry* **2009**, *20*, 2167.

Abstract. We have also tested the previously described phosphoroamidite **L6-L10a-e**,**h-i** and phosphite **L11-L14a-e**,**h-i** ligand libraries in the asymmetric Cu-catalyzed 1,4-conjugate addition reactions of β-substituted (cyclic and linear) and β,β'disubstituted (cyclic) enones. Our results indicated that selectivity depended strongly on the configuration of carbon atom C-3, the size of the sugar backbone ring, the flexibility of the ligand backbone, the substituents and configurations in the biaryl phosphoroamidite moiety (**a-e**,**h-i**), the type of functional group attached to the ligand backbone and the substrate structure. Therefore, by carefully selecting the ligand parameters we achieved enantioselectivities of up to 60% for cyclic substrates and 72% for linear ones.

5.3.1. Introduction

Nowadays, the addition of asymmetric Cu-catalyzed conjugate is a well-developed methodology for creating chiral C-C bonds.[1] The last decade has seen important breakthroughs in what is possible in the area of catalytic asymmetric 1,4-addition of alkyl organometallic nucleophiles to enones. Most of the successful asymmetric versions of this chemistry have made use of diorganozinc reagents, especially $ZnEt_2$, a trend started by Alexakis (Cu-catalysis) and Soai (Ni-catalysis).[2] Viable ligand classes

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are now available that give > 90% ee for the addition of diorganozinc to several types of cyclic and chalcone substrates.[1] Phosphites and phosphoroamidites based on biaryl moieties are among the most efficient ligands.[1j-k,3] Despite all these advances, there have been relatively few publications describing the highly enantioselective addition of organometallics to linear aliphatic enones or the use of trialkylaluminum reagents as an alternative to organozincs.[4] Additionally, trialkylaluminum reagents allow Cu-catalyzed 1,4-addition to very challenging substrates (i.e. β,β'disubstituted enones) which are inert to organozinc methodologies.[1j,4h,k] This justifies expanding the range of ligands for the Cu-catalyzed addition of organoaluminum reagents to enones, in particularly to linear aliphatic and β,β'disubstituted enones. Carbohydrates are particularly useful for this purpose because they are available at a low price and because their modular constructions are easy.[5] In this context and encouraged by the success of monophosphoroamidite ligands in this process, we report here the use of a highly modular sugar-based monophosphoroamidite ligand library (Figure 1, **L6**-**L10a-e**,**h-i**) in the Cu-catalyzed asymmetric 1,4-addition of organometallic reagents to cyclic and linear enones. We also compare the effectiveness of this phosphoroamidite ligand library with the results obtained using related monophosphite ligands (Figure 1, **L11**-**L14a-e**,**h-i**).[6] To do so, we have also expanded our previous work on monophosphite ligands (**L11**-**L14a-e**,**h-i**) to other challenging classes of substrates (i.e. nitrolefins and β,β'disubstituted enones). Using these ligands, we fully investigated the effects of systematically varying the configuration of carbon atom C-3 (ligands **L6**, **L7**, **L11** and **L12**), the size of the sugar backbone ring (ligands **L8** and **L13**), the flexibility of the

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ligand backbone (ligands **L9**, **L10** and **L14**), the substituents and configurations in the biaryl phosphoroamidite moiety (**a-e**,**h-i**) and the type of functional group attached to the ligand backbone (X = O or NH).

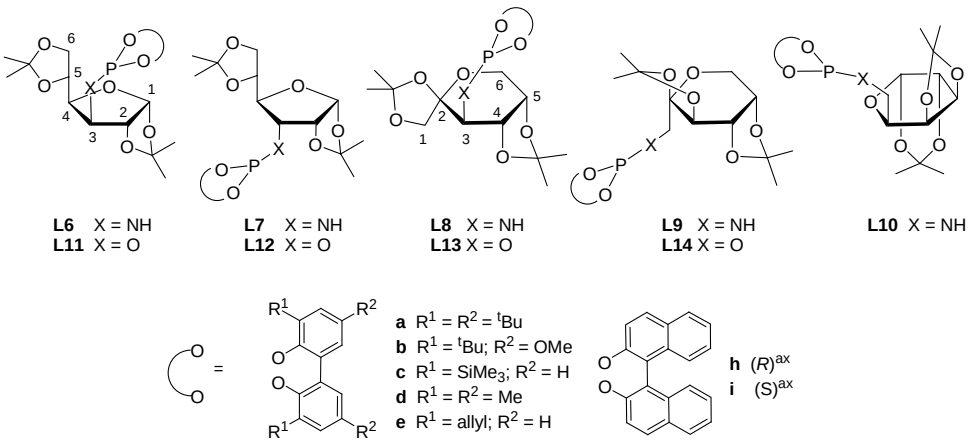

Figure 1. Phosphite and phosphoroamidite ligands (**L6**-**L14a**-**e**,**h**-**i**).

5.3.2. Results and Discussions

5.3.2.1. Asymmetric conjugate 1,4-addition to cyclic enones

5.3.2.1.1. Asymmetric conjugate 1,4-addition of $ZnEt_2$ and $AlEt_3$ to cyclohexenone S1

In the first set of experiments, we tested the phosphoroamidite ligands **L6**-**L10a**-**e**,**h**-**i** in the Cu-catalyzed conjugate addition of diethylzinc to 2-cyclohexenone **S1** (Equation 1). The latter was chosen as a substrate because this reaction has been performed with a wide range of ligands with several donor groups, thus enabling the efficiency of the various ligands systems to be directly compared.[1]

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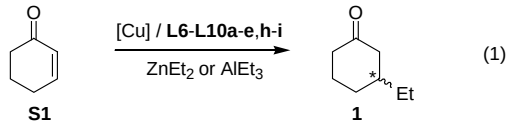

(1)

The catalytic system was generated *in situ* by adding the corresponding ligand to a suspension of catalyst precursor under standard conditions.[7] The results are shown in Table 1. They indicated that enantioselectivity is highly affected by the configuration of carbon atom C-3, the size of the sugar backbone ring, the flexibility of the ligand backbone and the substituents and configurations in the biaryl phosphoroamidite moiety (**a-e**,**h-i**). The best enantioselectivity (ee's up to 56%; Table 1, entry 7) were obtained using ligand **L6i** which has the appropriate combination of ligand parameter.

With ligands **L6a-e**,**h-i** we studied the effects of the biaryl phosphoroamidite moiety on enantioselectivity. We found that the presence of bulky substituents at the *ortho* positions of the biphenyl phosphite moiety has a positive effect on enantioselectivity (Table 1, entries 1-3 vs 4-5). We also observed a cooperative effect between the configuration of the biaryl moieties and the configuration of carbon atom C-3 in the sugar backbone (Table 1, entries 6-7). The results indicated that the matched combination is achieved with ligand **L6i**, which has an *S*-configuration in both the carbon atom C-3 and in the binaphthyl phosphoroamidite moiety (Table 1, entry 7).

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Table 1. Selected results for the Cu-catalyzed asymmetric 1,4-addition to **S1** using ligands **L6-L14a-e**,**h-i**. [a]

Entry	L	% Conv (h)[b]	% Yield[b]	% ee[c]
1	**L6a**	100 (18)	85	26 (*R*)
2	**L6b**	100 (18)	79	24 (*S*)
3	**L6c**	100 (18)	82	32 (*S*)
4	**L6d**	99 (18)	77	10 (*R*)
5	**L6e**	100 (18)	85	4 (*S*)
6	**L6h**	100 (18)	89	14 (*R*)
7	**L6i**	100 (18)	88	56 (*S*)
8	**L7a**	95 (18)	75	18 (*S*)
9	**L7b**	100 (18)	89	9 (*S*)
10	**L7c**	100 (18)	76	5 (*S*)
11	**L8c**	100 (18)	87	21 (*S*)
12	**L9a**	100 (18)	92	20 (*R*)
13	**L9b**	100 (18)	95	22 (*R*)
14	**L9d**	100 (18)	87	10 (*R*)
15	**L10a**	100 (18)	78	11 (*S*)
16	**L10b**	100 (18)	89	10 (*S*)
17	**L10d**	100 (18)	85	8 (*R*)
18	**L10e**	100 (18)	67	8 (*S*)
19[d]	**L11g**	98 (2)	24	20 (*S*)
20[d]	**L12a**	99 (2)	28	23 (*S*)
21[d]	**L13a**	94 (2)	8	4 (*S*)
22[d]	**L14a**	99 (2)	18	8 (*S*)
23[e]	**L6i**	100 (18)	69	35 (*S*)
24[f]	**L6i**	100 (18)	74	20 (*S*)

[a] CuTC (2 mol%), ligand (4 mol%), $ZnEt_2$ (1.5 eq, 0.62 mmol), **S1** (0.415 mmol), Et_2O (2.5 mL) at -30 ºC. [b] Conversion and yields determined by GC using undecane as internal standard after 18 hours. [c] Enantiomeric excess measured by GC. [d] Reported in the literature, see ref. 6. [e] Using $AlEt_3$ (1.5 eq, 0.62 mmol). [f] Using $Cu(OTf)_2$ in CH_2Cl_2 at 0 ºC.

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With ligands **L7**, whose configuration at C-3 is the opposite of that of ligands **L6**, we studied the effect of this configuration in the product outcome. The results indicated that this configuration influences enantioselectivity (Table 1, entries 8-10 vs 1-3). Therefore, ligands **L7** with an *R* configuration at C-3 provided lower enantioselectivities than ligands **L6**.

Ligands **L8**, which have a pyranoside backbone, provided lower enantioselectivitities than the related furanoside ligands **L6** (Table 1, entry 3 vs 11).

Using the most flexible ligands **L9** and **L10**, which has the phosphoroamidite moiety attached to a primary carbon, provided lower enantioselectivities than ligands **L6**. (Table 1, entries 12-18).

Finally, after comparing these results with those from the related phosphite ligands **L6**-**L9**, we found that replacing the phosphite moiety with a phosphoroamidite group has a positive effect on enantioselectivity (Table 1, entries 7, 8, 11 and 12 vs 19-22).[6]

We next used the ligand that provided the best results (ligand **L1g**) to study the effect of several reaction parameters (i.e. catalyst precursor, solvent, alkylating reagent and temperature) in enantioselectivity. However, enantioselectivities did not improve (Table 1, entries 7, 23 and 24).

5.3.2.1.2. Asymmetric conjugate 1,4-addition of 3-methyl-cyclohexenone S2

To further study the potential of ligands **L6**-**L14a-e**,**h-i**, we tested them in the Cu-catalyzed conjugate addition of triethylaluminum to 3-methyl-cyclohexenone **S2** (Equation 2). The conjugate addition of this

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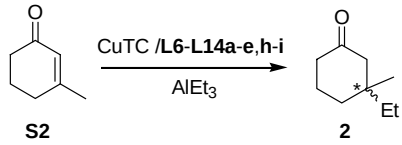
type of substrate provides an efficient way to build chiral quaternary centres into a compound.[1]



(2)

For a long time, the 1,4-addition of β,β'-disubstituted enones (as **S2**) was unsuccessful because of the low reactivity of these substrates with dialkylzinc reagents. Recently, Alexakis and co-workers have disclosed that the combination of more reactive trialkylaluminum reagents and appropriately chosen reaction parameters would be efficient in the 1,4-addition to this type of challenging substrate.[8] These latter conditions were used for testing our ligand library in the Cu-conjugate addition of substrate **S2**. The results are summarized in Table 2. We found that enantioselectivity is highly affected by the configuration of carbon atom C-3, the size of the sugar backbone ring, the flexibility of the ligand backbone, the substituents and configurations in the biaryl phosphoroamidite moiety (**a**-**e**,**h**-**i**) and the type of functional group attached to the ligand backbone. However, the effect of these parameters on the conjugate addition of substrate **S2** was different from their effect on the conjugate addition of substrate **S1**. As for substrate **S1**, the presence of bulky substitutents at the *otho* position of the biphenyl moiety usually has a positive effect on enantioselectivity (Table 2, entries 7 vs 8-9); however, ee's are negatively affected by replacing the phosphite moiety with a phosphoroamidite group (Table 2, entries 15 and 18 vs 1 and 7). Also, in contrast to **S1**, enantioselectivity in phosphoroamidite ligands **L6**-**L10a** is hardly affected by the flexibility of the ligand

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backbone (Table 2, entries 1, 7, 11 and 14), whereas for phosphite ligands **L11**-**L14**, increasing the flexibility of the ligand negatively affected ee's (Table 2, entries 15, 18, 21 and 22).

In summary, the best result (ee's up to 60%) was obtained with phosphite ligand **L12a** (Table 1, entry 18), which has bulky *tert*-butyl groups at both the *ortho* and *para* positions of the biphenyl moiety and a furanoside sugar-backbone.

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Table 2. Selected results for the Cu-catalyzed asymmetric 1,4-addition to **S2** using ligands **L6-L14a-e**,**h-i**.[a]

Entry	L	% Conv (h)[b]	% Yield[b]	% ee[c]
1	**L6a**	40 (18)	31	9 (*S*)
2	**L6b**	23 (18)	19	5 (*S*)
3	**L6c**	12 (18)	8	4 (*S*)
4	**L6d**	48 (18)	32	15(*S*)
5	**L6e**	22 (18)	14	25 (*S*)
6	**L6i**	32 (18)	22	41 (*S*)
7	**L7a**	25 (18)	19	49 (*S*)
8	**L7d**	25 (18)	18	23 (*S*)
9	**L7e**	18 (18)	11	6 (*S*)
10	**L8c**	15 (18)	13	2 (*S*)
11	**L9a**	8 (18)	7	43 (*S*)
12	**L9d**	20 (18)	11	15(*S*)
13	**L9e**	5 (18)	3	4(*S*)
14	**L10a**	12 (18)	9	35(*S*)
15	**L11a**	12 (18)	9	50 (*R*)
16	**L11h**	12 (18)	10	8 (*S*)
17	**L11i**	18 (18)	13	30 (*S*)
18	**L12a**	51 (48)	49	60 (*S*)
19	**L12h**	18 (18)	12	20 (*S*)
20	**L12i**	40 (18)	33	42 (*S*)
21	**L13a**	10 (18)	7	5 (*S*)
22	**L14a**	12 (18)	8	3 (*S*)

[a] CuTC (4 mol%), ligand (8 mol%), $AlEt_3$ (1.5 eq, 0.62 mmol), **S2** (0.415 mmol), Et_2O (2.5 mL), T = -30 °C. [b] Conversion and yields determined by GC using undecane as internal standard after 18 hours. [c] Enantiomeric excess measured by GC.

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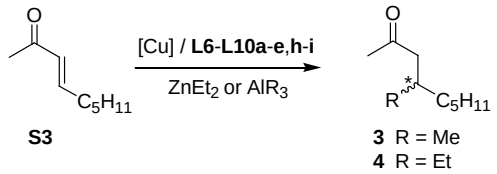
IN ASYMMETRIC METAL-CATALYZED REACTIONS
Eva Raluy González
ISBN:978-84-692-9762-9/DL:T-202-2010

5.3.2.2. Asymmetric conjugate 1,4-addition to linear enones

5.3.2.2.1. Asymmetric conjugate 1,4-addition of $ZnEt_2$ and $AlEt_3$ to trans-3-nonen-2-one S3

We have also screened the phosphoroamidite ligands **L6-L10a-e**,**h-i** in the Cu-catalyzed conjugate addition of several alkylating reagents to the linear substrate: *trans*-3-nonen-2-one **S3** (Equation 3). This enone, possessing only aliphatic substituents, is a more demanding substrate class for asymmetric conjugate addition than **S1**. The high conformational mobility of this substrate together with the presence of only subtle substrate-catalyst steric interactions makes the design of effective enantioselective systems a real challenge.[4e,h,9]



(3)

The most representative results are shown in Table 3. In general the ligand requirements were the same as for the 1,4-addition to **S1** except for those regarding the substituents and configurations in the biaryl phosphoroamidite moiety (**a-e**,**h-i**). Therefore, enantioselectivities were best (ee's up to 49%) using ligand **L6b**, which has *tert*-butyl groups at the *ortho* positions and methoxy substitutents at the *para* positions of the biphenyl moiety (Table 3, entry 2). We also studied the effect of several reaction parameters (i.e. catalyst precursor, solvent, alkylating reagent and temperature) in enantioselectivity. However, enantioselectivities did not improve (Table 3, entries 2 vs 13-16).

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Table 3. Selected results for the Cu-catalyzed asymmetric 1,4-addition to **S3** using ligands **L6-L14a-e**,**h-i**.[a]

Entry	L	Precursor	Alkylating reagent	% Conv (h)[b]	% Yield[b]	% ee[c]
1	**L6a**	CuTC	$AlMe_3$	85 (18)	72	38 (*R*)
2	**L6b**	CuTC	$AlMe_3$	97 (18)	83	49 (*R*)
3	**L6c**	CuTC	$AlMe_3$	78 (18)	65	23 (*R*)
4	**L6d**	CuTC	$AlMe_3$	78 (18)	61	14 (*R*)
5	**L6e**	CuTC	$AlMe_3$	36 (18)	26	8 (*R*)
6	**L6i**	CuTC	$AlMe_3$	45 (18)	33	26 (*S*)
7	**L7a**	CuTC	$AlMe_3$	91 (18)	76	23 (*S*)
8	**L8c**	CuTC	$AlMe_3$	84 (18)	77	14(*S*)
9	**L9a**	CuTC	$AlMe_3$	90 (18)	79	4 (*S*)
10	**L10a**	CuTC	$AlMe_3$	94 (18)	81	6 (*S*)
11[d]	**L11a**	CuTC	$AlMe_3$	99 (2)	79	18 (*R*)
12[d]	**L12a**	CuTC	$AlMe_3$	72 (2)	65	8 (*S*)
13	**L6d**	$Cu(OTf)_2$	$AlMe_3$	87 (18)	80	12 (*R*)
14	**L6d**	$[Cu(CH_3CN)_4]BF_4$	$AlMe_3$	84 (18)	79	6 (*R*)
15	**L6d**	CuTC	$AlEt_3$	99 (18)	84	4 (*R*)
16	**L6d**	CuTC	$ZnEt_2$	97 (18)	89	8 (*R*)

[a] Cu-precursor (2 mol%), ligand (4 mol%), alkylating reagent (1.5 eq, 0.62 mmol), **S3** (0.415 mmol), Et_2O (2.5 mL), T = -30 °C. [b] Conversion and yields determined by GC using undecane as internal standard after 18 h. [c] Enantiomeric excess measured by GC. [d] Reported in the literature, see ref. 6.

5.3.2.2.2. Asymmetric conjugate 1,4-addition of $ZnEt_2$ and $AlEt_3$ to trans-nitrostyrene S4

Finally, we applied monophosphoroamidite and monophosphite ligands **L6-L14a-e**,**h-i** in the Cu-catalyzed conjugate addition of several alkylating reagents to the linear nitro-olefin *trans*-nitrostyrene **S4** (Equation 4). The nitro group is of particular synthetic importance, as it

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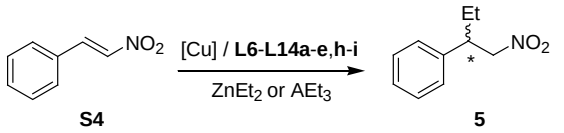
can be transformed to a variety of valuable organic compounds such as aldehydes, carboxylic acids, nitriles, nitrooxides and amines.[1j,10]



S4 **5** (4)

The results are summarized in Table 4. We found that the presence of bulky substituents at the biaryl moiety has a negative effect on enantioselectivity (Table 4, entries 1-6). However, for the most flexible ligands **L10**, enantioselectivities are better with bulky substituents at these positions (Table 4, entries 13-15). We also found that phosphite ligands provide better enantioselectivivies than their phosphoroamidite counterparts. Therefore the best result (ee's up to 72%) was obtained with ligand **L11i** (Table 4, entry 18). The reaction parameters (i.e. catalyst precursor, solvent, alkylating reagent and temperature) also indicated that diethylzinc can also be successfully used and that it provides the same enantioselectivities as when triethylaluminum is used (Table 4, entries 18 and 22), whereas the use of trimethylaluminum reduces ee's (Table 4, entry 24).

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Table 4. Selected results for the Cu-catalyzed asymmetric 1,4-addition to **S4** using ligands **L6-L14a-e**,**h-i**.[a]

Entry	L	Precursor	Alkylating reagent	% Conv (h)[b]	% Yield[b]	% ee
1	**L6a**	CuTC	$AlEt_3$	100 (18)	87	20 (*S*)
2	**L6b**	CuTC	$AlEt_3$	100 (18)	79	13 (*S*)
3	**L6c**	CuTC	$AlEt_3$	100 (18)	93	18(*S*)
4	**L6d**	CuTC	$AlEt_3$	100 (18)	89	26 (*S*)
5	**L6e**	CuTC	$AlEt_3$	100 (18)	90	35 (*S*)
6	**L6i**	CuTC	$AlEt_3$	100 (18)	86	30 (*S*)
7	**L7a**	CuTC	$AlEt_3$	100 (18)	78	14 (*R*)
8	**L7d**	CuTC	$AlEt_3$	100 (18)	91	32 (*R*)
9	**L7e**	CuTC	$AlEt_3$	100 (18)	86	45 (*R*)
10	**L8c**	CuTC	$AlEt_3$	100 (18)	91	13(*S*)
11	**L9d**	CuTC	$AlEt_3$	100 (18)	84	6 (*R*)
12	**L9e**	CuTC	$AlEt_3$	100 (18)	90	4 (*R*)
13	**L10a**	CuTC	$AlEt_3$	100 (18)	93	32 (*R*)
14	**L10d**	CuTC	$AlEt_3$	100 (18)	90	8 (*R*)
15	**L10e**	CuTC	$AlEt_3$	100 (18)	89	6 (*R*)
16	**L11a**	CuTC	$AlEt_3$	100 (18)	85	2 (*S*)
17	**L11h**	CuTC	$AlEt_3$	100 (18)	90	10 (*R*)
18	**L11i**	CuTC	$AlEt_3$	100 (18)	88	72 (*R*)
19	**L12i**	CuTC	$AlEt_3$	100 (18)	89	24 (*S*)
20	**L13h**	CuTC	$AlEt_3$	100 (18)	84	56 (*R*)
21	**L14h**	CuTC	$AlEt_3$	100 (18)	84	10 (*S*)
22	**L11i**	CuTC	$ZnEt_2$	100 (18)	93	72 (*R*)
23[d]	**L11i**	$Cu(OTf)_2$	$ZnEt_2$	100 (18)	92	0
24	**L11i**	CuTC	$AlMe_3$	98 (18)	57	56 (*R*)

[a] Cu-precursor (2 mol%), ligand (4 mol%), alkylating reagent (1.5 eq, 0.62 mmol), **S4** (0.415 mmol), Et_2O (2.5 mL), T = -30 °C. [b] Conversion and yields determined by GC using undecane as internal standard after 18 hours. [c] Enantiomeric excess measured by GC. [d] T = 0 °C.

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5.3.3. Conclusions

A carbohydrate-based phosphoroamidite **L6-L10a-e**,**h-i** and phosphite **L11-L14a-e**,**h-i** ligand libraries were tested in the asymmetric Cu-catalyzed 1,4-conjugate addition reactions of cyclic and acyclic enones. Our results indicated that selectivity depended strongly on the configuration of carbon atom C-3, the size of the sugar backbone ring, the flexibility of the ligand backbone, the substituents and configurations in the biaryl phosphoroamidite moiety (**a-e**,**h-i**), the type of functional group attached to the ligand backbone and the substrate structure. Therefore, by carefully selecting the ligand parameters we achieved enantioselectivities of up to 60% for cyclic substrates and 72% for linear substrates.

5.3.4. Experimental Section

5.3.4.1. 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 **L11-L14a-e**,**h-i** has been previously described in Chapter 4. All other reagents were used as commercially available.

5.3.4.2. Typical procedure for the catalytic conjugate addition of alkylating reagents to enones

In a typical procedure, a solution of Cu-catalyst precursor (8.3 μmol) and ligand (16.6 μmol) in the appropriate solvent (2 mL) was stirred for 30 minutes at room temperature. After cooling to the desired

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temperature, the alkylating reagent (0.62 mmol) was added. A solution of the desired enone (0.415 mmol) and undecane as GC internal standard (0.25 mL) in dichloromethane (0.5 mL), and was then added at the corresponding reaction temperature. The reaction was monitored by GC. The reaction was quenched with HCl (2 M) and filtered twice through flash silica. Conversion, chemoselectivity and enantioselectivity were obtained by GC (for **S1**, Lipodex A column; for **S2**, 6-Me-2,3-pe-γ-CD column; for **S3** and **S4**, Lipodex E column).[4i]

5.3.5. Acknowledgements

We would like to thank the Spanish Government (Consolider Ingenio CSD2006-0003, CTQ2007-62288/BQU, 2008PGIR/07 to O.P. and 2008PGIR/08 to M.D.), the Catalan Government (2005SGR007777), the Swiss National Research Foundation (grant N° 200020-113332) and COST action D40 (SER contract N° C07.0097) for their financial support.

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Chapter 6

Asymmetric Ni-catalyzed 1,2-addition

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6. Asymmetric Ni-catalyzed 1,2-addition

6.1. Background

The catalytic addition of organoaluminum reagents to aldehydes as a route to chiral alcohols has attracted much attention, since many chiral alcohols are highly valuable intermediates for preparing chiral pharmaceutical and agricultural products. Despite the organoaluminum reagents are economically obtained in industrial scale, their use is rare. In this respect, the few successful catalysts developed for the enantioselective addition of trialkylaluminum to aldehydes can be grouped in two types. The first group are the titanium complexes that usually afford high enantioselectivities, but the high catalyst loadings (10-20 mol%) and the slow turnover rate hamper their potential utility. The second ones are the recently studied nickel complexes that provide enantioselectivities similar to those using titanium complexes but with low catalyst loadings (1 mol%). For the latter nickel catalysts, only two types of ligands have been successfully applied. The first application was reported by Woodward and co-workers using monophosphoroamidite ligands as the chiral source (ee's up to 95%).[1] The second successful application used a series of carbohydrate-based monophosphite ligands (ligands **L11**-**L14**; ee's up to 94%; Chapter 2, Figure 1).[2]

Based on these excellent results and with the aim to expand the range of successful ligands for this process, in this chapter, we report the application of the three carbohydrate-based ligand libraries described in Chapters 3 and 4 (phosphite-phosphoroamidite (**L1**-**L4**), diphosphoroamidite (**L5**) and monophosphoroamidite (**L6**-**L10**) in the

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asymmetric Ni-catalyzed 1,2-addition of trialkylaluminum reagents to aldehydes. More specifically, in section 6.2 we report the application of the furanoside phosphite-phosphoroamidite (**L1**-**L4**) and diphosphoroamidite (**L5**) ligand libraries. These ligands combine a priori the advantage of both types of successful ligands (phosphites and phosphoroamidites) for this process. To the best of our knowledge this is the first successful application of a bidentate ligand in this process (ee's up to 84%). In section 6.3, we report the application of the modular sugar-based monophosphoroamidite ligand library **L6**-**L10** for the Ni-catalyzed 1,2-addition of trialkylaluminum reagents to aldehydes. This ligands are based on the successful sugar-based monophosphite ligands **L11**-**L14**, in which the phosphite group was replaced by a phosphoroamidite moiety. Therefore, this ligand library also combines advantages of both types of successful ligands (phosphoroamidite and monodentated sugar). Enantioselectivities up to 78% were obtained.

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6.2. Furanoside phosphite-phosphoroamidite and diphosphoroamidite: new ligand classes for the asymmetric nickel-catalyzed trialkylaluminum addition to aldehydes

Eva Raluy, Oscar Pàmies, Montserrat Diéguez, in *Tetrahedron Lett.* **2009**, *50*, 4495.

Abstract. We have also tested the previously described phosphite-phosphoroamidite **L1**-**L4a**-**e** and diphosphoroamidite **L5a**-**e** ligand libraries in the asymmetric Ni-catalyzed trialkylaluminum addition to several aldehydes. This represents the first successful application of bidentate ligands for this process. The ligands are prepared from inexpensive D-(+)-xylose and D-(+)-glucose and have the advantatge of carbohydrate and phosphite/phosphoroamidite moieties. After systematic variation of the position of the phosphoroamidite group at either C-5 or C-3, the configuration of C-3 and the substituents in the biaryl phosphite/phosphoroamidite moieties, enantioselectivities up to 84% and high yields were obtained in the Ni-catalyzed trialkylaluminum addition to several aldehydes.

6.2.1. Introduction

One of the main goals of modern synthetic organic chemistry is the catalytic enantioselective formation of carbon-carbon bonds. In this context, the catalytic addition of dialkylzincs to aldehydes as a route to chiral alcohols has attracted much attention, since many chiral alcohols are highly valuable intermediates for preparing chiral pharmaceutical and

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agricultural products.[1] For alkylation reagents, trialkylaluminum compounds are more interesting than other organometallic reagents because they can be economically obtained on an industrial scale from aluminum hydride and olefins.[2] Despite this advantage they are little used.[3,4] In this respect, the few successful catalysts developed for the enantioselective addition of trialkylaluminum to aldehydes can be grouped in two types. The first type are the titanium complexes. Although they usually afford high enantioselectivities, they have slow turnover rates that restrict their potential utility and also require high catalyst loadings (10-20 mol%).[3] The second type are the recently studied nickel complexes that provide enantioselectivities similar to those that are obtained with titanium complexes but with low catalyst loadings (0.05 - 1 mol%).[4] For the latter nickel catalysts, only two types of ligands have been successfully applied. The first application was reported by Woodward and co-workers using monophosphoroamidite ligands as the chiral source.[4a-b] The second application used a series of sugar-based monophosphite ligands.[4c] To further expand the range of ligands and encouraged by the success of phosphite and phosphoroamidite ligands in this process, we report here the application of phosphite-phosphoroamidite and diphosphoroamidite ligands (**L1**-**L5a**-**e**, Figure 1) in the Ni-catalyzed 1,2-addition of trialkylaluminum to aldehydes.[5] These ligands combine a priori the advantage of both types of successful ligands. They also have the advantages of carbohydrates and phosphite/phosphoroamidite ligands: they are cheap, easily constructed with modules and highly resistant to oxidation.[6] With these ligands, then, we investigated the effect of systematically varying the position of the phosphoroamidite group at either C-5 (ligands **L1** and **L2**) or C-3 (ligands

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L3 and **L4**) of the furanoside backbone, the configuration at C-3 of the furanoside backbone and the substituents in the biaryl phosphite/phosphoroamidite moieties (**a**-**e**). By carefully selecting the ligand parameters, we achieved high enantioselectivities. To the best of our knowledge this is the first successful application of a bidentate ligand in this process.

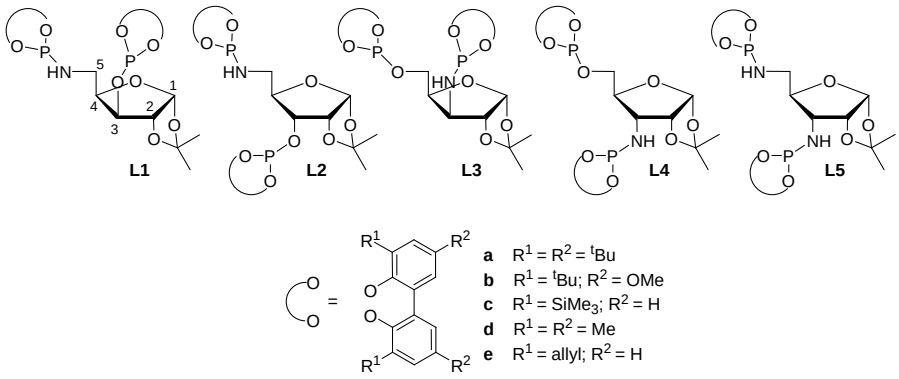

Figure 1. Carbohydrate-based phosphite-phosphoroamidite and diphosphoroamidite ligands **L1**-**L5a-e**.

6.2.2. Results and Discussions

6.2.2.1. Asymmetric addition of AlR_3 to aldehydes

To make the initial evaluation of these new types of ligands (**L1**-**L5a**-**e**), we chose the Ni-catalyzed asymmetric addition of trimethylaluminum to benzaldehyde, which is used as a model substrate (Table 1). The catalytic system was generated *in situ* by adding the corresponding ligand to a suspension of the catalyst precursor $[Ni(acac)_2]$ (acac = acetylacetonate). The results indicate that enantioselectivity is affected by the position of the phosphoroamidite group at either C-5 or C-3 of the furanoside backbone, the configuration of C-3, the introduction

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of second phosphoroamidite moiety and the substituents in the biaryl phosphite/phosphoroamidite moieties (**a**-**e**).

We first studied the effect of the position of the phosphoroamidite group at either C-5 (ligands **L1** and **L2**) or C-3 (ligands **L3** and **L4**) of the furanoside backbone and the configuration of C-3. We observed a cooperative effect between the position of the phosphoroamidite group and the configuration of carbon atom C-3 of the furanoside backbone (Table 1, entries 1, 3, 5 and 10). Therefore, the matched combination is achieved with ligands **L3**, the phosphoroamidite moiety of which is attached to C-3 and an *S* configuration of carbon atom C-3 in the tetrahydrofuran ring (Table 1, entry 5).

We then used ligands **L5** to study how replacing the phosphite moiety with a phosphoroamidite group affected catalytic performance. The results indicated that the presence of a second phosphoroamidite moiety in the ligands had a negative effect on enantioselectivity (Table 1, entries 3 vs 13).

The effect of the substituents in the biaryl phosphite/phosphoroamidite moieties was studied using ligands **L1-L4a-e** (Table 1). The results indicate that bulky substituents need to be present at both *ortho* and *para* positions of the biaryl moieties if enantioselectivities are to be high. Therefore, ligands **L1**-**L4a** provide higher enantioselectivites than ligands **L1**-**L4b**-**e** (Table 1, entries 1, 3, 5 and 10 vs 2, 4, 6-9, 11 and 12).

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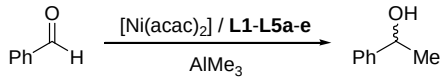
Table 1. Selected results for the Ni-catalyzed asymmetric addition of $AlMe_3$ to benzaldehyde using ligands **L1**-**L5a-e**.[a]



Entry	Ligand	L/Ni	% Conv[b]	% Yield[c]	% ee[d]
1	**L1a**	1	53	52	4 (R)
2	**L1b**	1	67	67	15 (R)
3	**L2a**	1	66	66	56 (R)
4	**L2b**	1	98	95	20 (R)
5	**L3a**	1	100	99	84 (R)
6	**L3b**	1	95	95	6 (S)
7	**L3c**	1	34	30	11 (R)
8	**L3d**	1	68	64	11 (S)
9	**L3e**	1	15	15	4 (S)
10	**L4a**	1	100	98	25 (S)
11	**L4b**	1	90	90	36 (S)
12	**L4c**	1	86	84	17 (S)
13	**L5a**	1	75	70	6 (*R*)
14	**L3a**	2	100	100	84 (R)
15	**L3a**	0.5	100	100	76 (R)

[a] T = -20 ^{o}C, $[Ni(acac)_2]$ (1 mol%), $AlMe_3$ (2 equiv.), substrate (0.25 mmol), THF (2 mL). [b] % Conversion determined by GC. [c] % Yield determined by GC using dodecane as internal standard. [d] Enantiomeric excess measured by GC.

We also used ligand **L3a** to study the effect of the ligand-to-nickel ratio on the product outcome. Our results show that no excess of ligand is needed for yields and enantioselectivities to be high (Table 1, entries 5 vs 14 and 15).

In summary, the result was best with ligand **L3a** (Table 1, entry 5, ee's up to 84%), which contains the optimal combination of ligand

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parameters (position of the phosphoroamidite group, configuration at C-3 of the furanoside backbone and the substituents in the biaryl phosphite/phosphoroamidite moieties). These results clearly show the efficiency of using highly modular scaffolds in the ligand design.

To further investigate the catalytic efficiency of these Ni/**L1-L5a-e** systems, we tested them in the Ni-catalyzed addition of several trialkylaluminum sources (AlR'_3, R' = Me or Et; and DABAL-Me_3) to other benchmark aldehydes with different steric and electronic properties. The results are summarized in Table 2.

We found that enantioselectivity for $AlMe_3$ addition is negatively affected by the presence of electron-donating groups at the *para* position of the phenyl group (Table 2, entry 1 vs 3, 5 and 8). However, the presence of electron-withdrawing groups at the *para* position has little effect on enantioselectivity (Table 2, entry 6). The enantioselectivity of the reaction is also negatively influenced by steric factors (Table 2, entries 9 and 10).

The results of using triethylaluminum as alkylating reagent indicated that the catalytic performance follows the same trend as for the trimethylaluminum addition. The enantioselectivities, however, were lower (Table 2, entries 2, 4 and 7).

Recently, Woodward and co-workers reported for the first time the advantages of using DABAL-Me_3 as an air-stable methylating reagent in Ni-catalyzed additions to aldehydes.[4a] Our results using this reagent indicate that the catalytic performance follows the same trend as for the trimethylaluminum addition to aldehydes, which is not unexpected because the reactions have a similar mechanism. However, the yields were lower than in trimethylaluminum addition (Table 2, entries 11-13).

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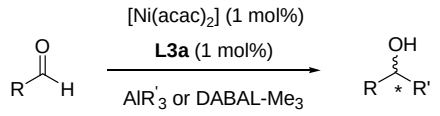
Table 2. Selected results for the Ni-catalyzed asymmetric addition of AlR'_3 (R' Me or Et) and DABAL-Me_3 to aldehydes using ligand **L3a**.[a]



Entry	R	R'	% Conv.[b]	Yield[c]	% ee[d]
1	C_6H_5	Me	100	99	84 (R)
2	C_6H_5	Et	95	92	69 (R)
3	4-CH_3-C_6H_4	Me	100	98	79 (R)
4	4- CH_3-C_6H_4	Et	98	94	53 (R)
5	4-OMe-C_6H_4	Me	98	93	67 (R)
6	4-CF_3-C_6H_4	Me	100	96	82 (R)
7	4-CF_3-C_6H_4	Et	100	93	68 (R)
8	4-F-C_6H_4	Me	99	94	67 (R)
9	3-OMe-C_6H_4	Me	100	96	53 (R)
10	2-OMe-C_6H_4	Me	65	63	0
11[e]	C_6H_5	Me	86	79	82 (R)
12[e]	4-CH_3-C_6H_4	Me	82	80	76 (R)
13[e]	4-CF_3-C_6H_4	Me	92	85	80 (R)

[a] T = -20 °C, $[Ni(acac)_2]$ (1 mol%), **L3a** (1 mol%), AlR'_3 (2 equiv.), substrate (0.25 mmol), THF (2 mL). [b] % Conversion determined by GC after 1 hour. [c] % Yield determined by GC using dodecane as internal standard. [d] Enantiomeric excess measured by GC. [e] DABAL-Me_3 (1.3 equiv), T = 5 °C.

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6.2.3. Conclusions

In summary, we have described the first successful application of bidentate ligands in the asymmetric Ni-catalyzed trialkylaluminum addition to several aldehydes. These phosphite-phosphoroamidite and diphosphoroamidite ligands have the advantage that they are easily prepared in a few steps from commercial D-xylose and D-glucose, inexpensive natural chiral feedstocks. In addition, their furanoside backbone and biaryl moieties can be easily tuned so that their effect on catalytic performance can be explored. By carefully selecting the ligand components, we obtained high activities and enantioselectivities. These results open up a new class of ligands (bidentated phosphite-phosphoroamidite) for the Ni-catalyzed trialkylaluminum addition to aldehydes. Mechanistic studies and further modifications in both the sugar backbone and the functional groups are currently being made.

6.2.4. Experimental Section

6.2.4.1. General considerations.

All syntheses were performed by using standard Schlenk techniques under an argon atmosphere. Solvents were purified by standard procedures. The synthesis of ligands **L1**-**L5a**-**e** has been previously described in Chapter 3. All other reagents were used as commercially available.

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6.2.4.2. General procedure for the Ni-catalyzed enantioselective 1,2-addition of trialkylaluminum reagents to aldehydes

[$Ni(acac)_2$] (0.6 mg, 2.33 μmol, 1 mol %) and ligand (2.33 μmol, 1 mol %) were stirred in dry THF (2 mL) under argon atmosphere at -20 ^oC for 10 min. Neat aldehyde (0.25 mmol) was then added and trialkylaluminum (0.5 mmol) was added dropwise after a further 10 min. After the desired reaction time, the reaction was quenched with 2M HCl (2 mL). Then dodecane (20 μL) was added and the mixture was extracted with Et_2O (10 mL). The organic layer was dried over $MgSO_4$ and analyzed by GC using a Cyclodex-B column.[4a]

6.2.4.2. General procedure for the Ni-catalyzed enantioselective 1,2-addition of DABAL-Me_3 to aldehydes

[$Ni(acac)_2$] (0.6 mg, 2.33 μmol, 1 mol %) and ligand (2.33 μmol, 1 mol %) were stirred in dry THF (2 mL) under argon atmosphere at 5 ^oC for 10 min. Neat aldehyde (0.25 mmol) was then added and DABAL-Me_3 (84 mg, 0.325 mmol, 1.3 equiv) was added after a further 10 min. After the desired reaction time, the reaction was quenched with 2M HCl (2 mL). Then dodecane (20 μL) was added and the mixture was extracted with Et_2O (10 mL). The organic layer was dried over $MgSO_4$ and analyzed by GC using a Cyclodex-B column.[4a]

6.2.5. Acknowledgements

We thank the Spanish Government (Consolider Ingenio CSD2006-0003, CTQ2007-62288/BQU, 2008PGIR/07 to O.P. and 2008PGIR/08 to

M.D.) and the Catalan Government (2005SGR007777) for financial support.

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[6] 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) Diéguez, M.; Pàmies, O.; Ruiz, A.; Díaz, Y.; Castillón, S.; Claver, C. *Coord. Chem. Rev.* **2004**, *248*, 2165. d) Diéguez, M.; Ruiz, A.; Claver, C. *Dalton Trans.* **2003**, 2957. e) Pàmies, O.; Diéguez, M.; Ruiz, A.; Claver, C. *Chemistry Today* **2004**, 12. f) Diéguez, M.; Pàmies, O.; Ruiz, A.; Claver, C. in *Methodologies in Asymmetric Catalysis* (Ed. Malhotra, S. V.); American Chemical Society, Washington DC, 2004. g) Diéguez, M.; Pàmies, O.; Claver, C. *Tetrahedron: Asymmetry* **2004**, *15*, 2113. h) Diéguez, M.; Claver, C.; Pàmies, O. *Eur. J. Org. Chem*. **2007**, 4621. i) Minnaard, A. J.; Feringa, B. L.; Lefort, L.; de Vries, J. G. *Acc. Chem.. Res.* **2007**, *40*, 1267. j) Börner, A. *Phosphorous Ligands in Asymmetric Catalysis* **2008**, Wiley-VCH, Weinheim.

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6.3. Screening of a modular sugar-based phosphoroamidite ligand library in the asymmetric nickel-catalyzed trialkylaluminum addition to aldehydes

Eva Raluy, Oscar Pàmies, Montserrat Diéguez, in *Tetrahedron: Asymmetry* **2009**, *20*, 1575.

Abstract. We screened the previously described modular sugar-based monophosphoroamidite ligand library (**L6-L10a-e**,**h-i**; Chapter 4) for the Ni-catalyzed trialkylaluminum addition to aldehydes. After systematic variation of the sugar backbone, the substituents at the phosphoroamidite moieties and the flexibility of the ligand backbone, the monophosphoroamidite ligand 3-amine-3-deoxy-1,2:5,6-di-*O*-isopropylidene-((3,3'-di-trimethylsilyl-1,1'-biphenyl-2,2'-diyl)phosphite) -α-D-glucofuranose **L6d** was found to be optimal. Activities were high and enantioselectivities good (ee's up to 78 %) for several aryl aldehydes.

6.3.1. Introduction

The catalytic addition of organoaluminum reagents to aldehydes as a route to chiral alcohols has attracted considerable attention, since many chiral alcohols are highly valuable intermediates for preparing chiral pharmaceutical and agricultural products.[1] Although organoaluminum reagents can be economically obtained on an industrial scale,[2] they are rarely used.[3,4,5] In this respect, the few successful catalysts developed for the enantioselective addition of trialkylaluminum to aldehydes can be grouped in two types. The first type are the titanium

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complexes. Although they usually afford high enantioselectivities, they have slow turnover rates that restrict their potential utility and also require high catalyst loadings (10-20 mol%).[3a-d] The second type are the recently studied nickel complexes that provide enantioselectivities similar to those that are obtained with titanium complexes but with low catalyst loadings (0.05 - 1 mol%).[3e,4,5a] For the latter nickel catalysts, only two types of ligands have been successfully applied. The first application was reported by Woodward and co-workers using monophosphoroamidite ligands as the chiral source.[3e,4] The second application used a series of sugar-based monophosphite ligands.[5a] On the basis of this structure and in an attempt to expand the range of ligands for this process, in this chapter we have used a ligand library in which the phosphite group is replaced by a phosphoroamidite group (Figure 1). Therefore, this ligand library combines the advantages of both types of successful ligands (phosphoroamidite and monodentated sugar).

We report, then, application of 35 potential chiral monophosphoroamidite ligands **L6-L10a-e**,**h-i** (Figure 1) in the asymmetric Ni-catalyzed 1,2-addition of trialkylaluminum to several aldehyde types. These ligands, derived from D-glucose, D-fructose and D-galactose, also have the advantages of carbohydrates and phosphoroamidite ligands: they are cheap, easily constructed with modules and highly resistant to oxidation.[6] All these features enable series of chiral ligands to be synthetized and screened in the search for high activity and selectivity. With this library we fully investigated the effects of systematically varying the configurations of the ligand backbone at C-3 (**L6-L7**), the substituents/configurations in the biaryl phosphite moiety (**a-e**,**h-i**), the carbohydrate ring size **(L6-L8**) and the

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flexibility of the ligand backbone (**L8-L10**). By carefully selecting these elements, we achieved good enantioselectivities and activities in several aryl aldehydes.

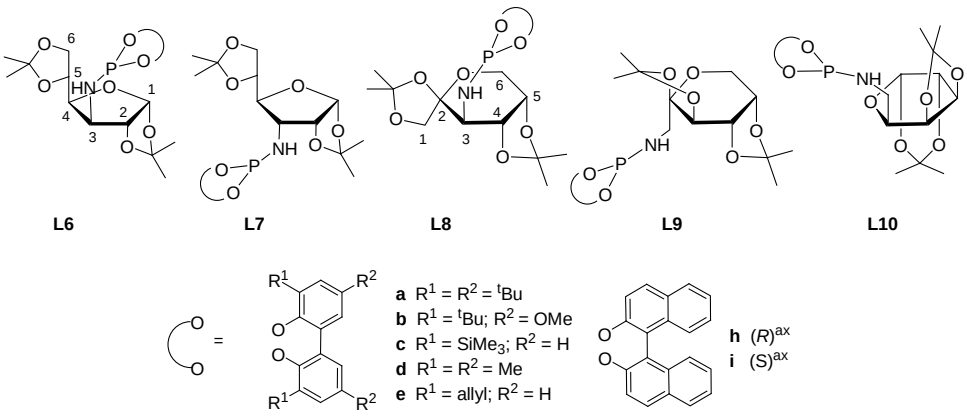
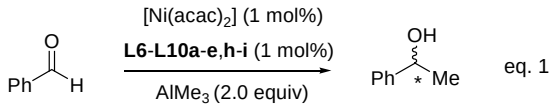


Figure 1. Phosphite and phosphoroamidite ligands (**L6-L10a-e**,**h-i**).

6.3.2. Results and Discussions

6.3.2.1. Asymmetric addition of AlR_3 to aldehydes

In the first set of experiments, we evaluated the phosphoroamidite ligand library **L6-L10a-e**,**h-i** (Figure 1) in the Ni-catalyzed asymmetric addition of trimethylaluminum to benzaldehyde, which is used as a model substrate (eq. 1). The catalytic system was generated *in situ* by adding the corresponding phosphoroamidite ligand to a suspension of the catalyst precursor [$Ni(acac)_2$] (acac = acetylacetonate).



The results, which are summarized in Table 1, indicate that the catalytic performance (activities and enantioselectivities) is highly

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affected by the configuration of carbon atom C-3, the size of the ring of the sugar backbone and the substituents of the biaryl moieties.

With ligands **L6a-e** we studied how the substituents of the biaryl phosphoroamidite moiety affect the product outcome. The results indicated that the substituents at the *ortho* positions of the biphenyl moiety mainly affected activities, while enantioselectivitites are affected by the substituents at both *ortho* and *para* positions. Activities were controlled by the steric properties of the *ortho* substituents (Table 1, entries 1-5). They were higher when less sterically demanding substituents were present (i.e. ^{t}Bu = $SiMe_3$ > allyl > Me). For high enantioselectivities, the bulky substituents at the *ortho* position need to be combined with small substituents at the *para* positions of the biaryl moiety (Table 1, entries 2-4). Therefore, activities and enantioselectivities were best with ligand **L6d**, which contain trimethylsilyl groups at the *ortho* positions of the biaryl phosphoroamidite moiety (Table 1, entry 4). This behavior contrasts with the effect of the biaryl-substituents on related monophosphite counterparts, for which enantioselectivities were higher when *tert*-butyl groups were present at both *ortho* and *para* positions.[5a]

We used ligands **L6h** and **L6i** to study the possibility of a cooperative effect between the stereocenters of the ligand backbone and the configuration of the biaryl phosphite moieties (Table 1, entries 6 and 7). The results indicated that the matched combination is achieved with ligand **L6h**, which has an *S*-configuration at carbon atom C-3 and also in the biaryl phosphoroamidite moiety. However, the enantioselectivities obtained with **L6h** are lower than those obtained using bulky-*ortho* substituted biphenyl ligand **L6d**. This contrasts with the higher

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enantioselectivites obtained when enantiopure unsubstituted binaphthyl phosphoroamidite moieties are present in related Feringa-type phosphoroamidites.[3e,4]

Table 1. Selected results for the Ni-catalyzed asymmetric addition of $AlMe_3$ to benzaldehyde using the phosphoroamidite library (**L6-L10a-e**,**h-i**).[a]

Entry	Ligand	L/Ni	% Conv[b]	% Yield[c]	% ee[d]
1	**L6a**	1	12	11	28 (R)
2	**L6b**	1	100	100	12 (S)
3	**L6c**	1	99	98	21 (S)
4	**L6d**	1	100	99	69 (R)
5	**L6e**	1	48	48	53 (R)
6	**L6h**	1	100	100	35 (R)
7	**L6i**	1	100	98	23 (S)
8	**L7b**	1	100	100	8 (R)
9	**L7c**	1	100	100	10 (R)
10	**L8d**	1	100	97	43 (R)
11	**L9c**	1	100	97	6 (R)
12	**L10c**	1	92	91	5 (R)
13	**L6d**	2	100	100	67 (R)
14	**L6d**	0.5	100	99	65 (R)

[a] T = -20 °C, $[Ni(acac)_2]$ (1 mol%), $AlMe_3$ (2 equiv.), substrate (0.25 mmol), THF (2 mL). [b] % Conversion determined by GC. [c] % Yield determined by GC using dodecane as internal standard. [d] Enantiomeric excess measured by GC.

With ligands **L7**, whose configuration at C-3 is opposite that of ligands **L6**, we studied the effect of this configuration on the product outcome. The results indicated that the configuration affects enantioselectivity (Table 1, entries 8 and 9). Therefore, ligands **L7** with

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Eva Raluy González
ISBN:978-84-692-9762-9/DL:T-202-2010

an *R*-configuration at C-3 provided lower enantioselectivities than when ligands **L6** were used.

Ligand **L8d** which has a pyranoside backbone provided slightly lower enantioselectivitities (up to 43%) than their related furanoside ligand **L6d** (Table 1, entry 10 vs 4).

Finally, the most flexible ligands **L9** and **L10**, the phosphoroamidite moiety of which is attached to a primary carbon, provided the lowest enantioselectivities (Table 1, entries 11 and 12).

Next, we used the ligand that provided the best results (ligand **L6d**) to study the effect of the ligand-to-nickel ratio on the product outcome. Our results show that no excess of ligand is needed for yields and enantioselectivities to be high (Table 1, entries 4, 13 and 14).

To further investigate the catalytic efficiency of these Ni/**L6-L10a-e**,**h-i** systems, we then tested them in the Ni-catalyzed addition of several trialkylaluminum sources (AlR'_3, R' = Me or Et; and DABAL-Me_3) to other benchmark aldehydes with different steric and electronic properties. The results are summarized in Table 2.

We found that enantioselectivity for $AlMe_3$ addition is hardly affected by the presence of electron-donating groups at the *para* position of the phenyl group (Table 2, entries 1, 3, 5 and 9). However, the presence of electron-withdrawing groups at the *para* position has a negative effect on enantioselectivity (Table 2, entry 7). The enantioselectivity of the reaction is also significantly influenced by steric factors (Table 2, entries 11 and 12).

The results of using triethylaluminum as alkylating reagent indicated that the catalytic performance follows the same trend as for the

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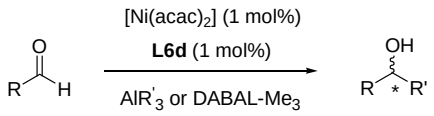
trimethylaluminum addition. However, enantioselectivities are slightly better (Table 2, entries 1, 3, 5, 7 and 9 vs 2, 4, 6, 8 and 10).

Table 2. Selected results for the Ni-catalyzed asymmetric addition of AlR'_3 (R' = Me or Et) and DABAL-Me_3 to aldehydes using ligand **L6d**.[a]



Entry	R	R'	% Conv.[b]	Yield[c]	% ee[d]
1	C_6H_5	Me	100	99	69 (R)
2	C_6H_5	Et	95	93	78 (R)
3	4-CH_3-C_6H_4	Me	100	95	62 (R)
4	4- CH_3-C_6H_4	Et	98	96	65 (R)
5	4-OMe-C_6H_4	Me	99	98	64 (R)
6	4-OMe-C_6H_4	Et	100	95	69 (R)
7	4-CF_3-C_6H_4	Me	28	26	41 (S)
8	4-CF_3-C_6H_4	Et	33	29	42 (S)
9	4-F-C_6H_4	Me	98	97	60 (S)
10	4-F-C_6H_4	Et	100	94	62 (S)
11	3-OMe-C_6H_4	Me	100	94	37 (R)
12	2-OMe-C_6H_4	Me	20	17	37 (R)
13[e]	C_6H_5	Me	85	82	67 (R)
14[e]	4-CH_3-C_6H_4	Me	84	80	60 (R)
15[e]	4-CF_3-C_6H_4	Me	16	15	43 (S)
16[e]	3-OMe-C_6H_4	Me	67	62	33 (R)

[a] T = -20 °C, $[Ni(acac)_2]$ (1 mol%), **L6d** (1 mol%), AlR'_3 (2 equiv.), substrate (0.25 mmol), THF (2 mL). [b] % Conversion determined by GC after 1 hour. [c] % Yield determined by GC using dodecane as internal standard. [d] Enantiomeric excess measured by GC. [e] DABAL-Me_3 (1.3 equiv), T = 5 °C.

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Recently, Woodward and co-workers reported for the first time the advantages of using DABAL-Me_3 as an air-stable methylating reagent in Ni-catalyzed additions to aldehydes.[3e] Our results using this reagent indicate that the catalytic performance follows the same trend as for the trimethylaluminum addition to aldehydes, which is not unexpected because the reactions have a similar mechanism. However, the yields were lower than in trimethylaluminum addition (Table 2, entries 13-16).

6.3.3. Conclusions

A library of readily available monophosphoroamidite ligands has been applied in the Ni-catalyzed trialkylaluminum addition to several aldehydes. By carefully designing this library we were able to systematically investigate the effect of varying the sugar backbone, the configuration at carbon C-3 of the ligand backbone and the type of substituents/configurations in the biaryl phosphoroamidite moiety. By judicious choice of the ligand components we obtained good enantioselectivities (ee values up to 78%) and high activities in several aryl aldehydes, with low catalyst loadings (1 mol%) and no excess of ligand.

6.3.4. Experimental Section

6.3.4.1. 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 **L6**-**L10a-e**,**h-i** has been

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previously described in Chapter 4. All other reagents were used as commercially available.

6.3.4.2. General procedure for the Ni-catalyzed enantioselective 1,2-addition of trialkylaluminum reagents to aldehydes

[$Ni(acac)_2$] (0.6 mg, 2.33 μmol, 1 mol %) and ligand (2.33 μmol, 1 mol %) were stirred in dry THF (2 mL) under argon atmosphere at -20 ^oC for 10 min. Neat aldehyde (0.25 mmol) was then added and trialkylaluminum (0.5 mmol) was added dropwise after a further 10 min. After the desired reaction time, the reaction was quenched with 2M HCl (2 mL). Then dodecane (20 μL) was added and the mixture was extracted with Et_2O (10 mL). The organic layer was dried over $MgSO_4$ and analyzed by GC using a Cyclodex-B column.[4a]

6.3.4.3. General procedure for the Ni-catalyzed enantioselective 1,2-addition of DABAL-Me_3 to aldehydes

[$Ni(acac)_2$] (0.6 mg, 2.33 μmol, 1 mol %) and ligand (2.33 μmol, 1 mol %) were stirred in dry THF (2 mL) under argon atmosphere at 5 ^oC for 10 min. Neat aldehyde (0.25 mmol) was then added and DABAL-Me_3 (84 mg, 0.325 mmol, 1.3 equiv) was added after a further 10 min. After the desired reaction time, the reaction was quenched with 2M HCl (2 mL). Then dodecane (20 μL) was added and the mixture was extracted with Et_2O (10 mL). The organic layer was dried over $MgSO_4$ and analyzed by GC using a Cyclodex-B column.[4a]

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6.3.5. Acknowledgements

We thank the Spanish Government (Consolider Ingenio CSD2006-0003, CTQ2007-62288/BQU, 2008PGIR/07 to O.P. and 2008PGIR/08 to M.D.) and the Catalan Government (2005SGR007777) for financial support.

6.3.6. References

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Chapter 7

Conclusions

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7. Conclusions

1. Chapter 3. *Asymmetric Pd-catalyzed allylic substitution*. The conclusions of this chapter can be summarized as follows:

- In the asymmetric Pd-catalyzed allylic substitution reactions using chiral phosphite-phosphoroamidite ligands we observed important effects of the position of the phosphoroamidite group, configuration at C-3 of the furanoside backbone and the substituents/configurations in the biaryl phosphite/phosphoroamidite moieties. However, the effects of these parameters depended on each substrate. High activities, regio- (up to 75%) and enantioselectivities (up to 98%) have been achieved in a wide range of substrates with different steric and electronic properties. This represent the first application of phosphite-phosphoroamidite ligands in this process.

The study of the Pd-1,3-diphenyl, 1,3-dimethyl and 1,3-cyclohexenyl allyl intermediates by NMR spectroscopy made it possible to understand the catalytic behaviour observed. Therefore, for enantioselectivities to be high, the position of the phosphoroamidite group, absolute configuration of C-3 and the substituents/configurations of the biaryl moieties need to be correctly combined in order to increase the electronic differentiation between the most electrophilic allylic terminus carbon atoms of the isomers formed and/or also form predominantly the isomer that reacts faster with the nucleophile. It also indicates that the nucleophilic attack takes place predominantly at the allylic terminal carbon atom located *trans* to the phosphoroamidite moiety.

Asymmetric substitution reactions with catalyst precursors containing the diphosphoroamidite ligands showed that catalytic

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performance is highly affected by the substituents and the axial chirality of the biaryl moieties of the ligand. However, these effects were different depending on the substrate in study. Good-to-excellent activities and enantioselectivities (ee's up to 95%) have been obtained for several substrates with different electronic and steric properties. This constitutes the first example of diphosphoroamidite ligands applied to this process. The study of the 1,3-diphenyl and cyclohexenyl Pd-π-allyl intermediates by NMR spectroscopy allows the understanding of the catalytic behaviour observed. This study indicates that the nucleophilic attack takes place predominantly at the allylic terminal carbon atom located *trans* to the phosphoroamidite moiety attached to C-5.

If we compare these results with those from the catalyst precursors containing the previous related phosphite-phosphoroamidite ligands, we found that the replacement of the phosphite moiety by a phosphoroamidite group provide comparable results.

2. Chapter 4. *Asymmetric Cu-catalyzed allylic alkylation*. The conclusions of this chapter can be summarized as follows:

- In the asymmetric Cu-catalyzed allylic alkylation reactions with catalysts precursors based on phosphite-phosphoroamidite and di- and monophosphoroamidite ligands, our preliminary results showed that selectivity depended strongly on the ligand parameters. We found that bidentate ligands provided higher enantioselectivities than monodentated ligands. Excellent regioselectivities (up to 99%) combined with moderate enantioselectivities (up to 54%) were obtained with the phosphite-phosphoroamidite ligand library.

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3. Chapter 5. *Asymmetric Cu-catalyzed 1,4-conjugate addition*. The conclusions of this chapter can be summarized as follows:

- In the asymmetric Cu-catalyzed 1,4-conjugate addition reactions of β-substituted and β,β'disubstituted enones using phosphite-phosphoroamidite and diphosphororoamidite ligand libraries, we observed that selectivity depended strongly on the ligand parameters and on the substrate structure. Moderate-to-good enantioselectivities (ee's up to 84%) were obtained in the 1,4-addition of several types of β-substituted cyclic and linear substrates. Of particular note is the high enantioselectivity (ee's up to 90%) obtained for the more challenging β,β'-disubstituted 3-methyl-cyclohexenone.

- In the asymmetric Cu-catalyzed asymmetric 1,4-conjugate addition of organometallic reagents to several enones with catalysts precursors based on sugar monophosphoroamidite and monophosphite ligands, we found good activities and enantioselectivities up to 60% for cyclic substrates and 72% for linear ones. Our results indicated that selectivity depended strongly on the configuration of carbon atom C-3, the size of the sugar backbone ring, the flexibility of the ligand backbone, the substituents and configurations in the biaryl phosphoroamidite moiety, the type of functional group attached to the ligand backbone and the substrate structure.

4. Chapter 6. *Asymmetric Ni-catalyzed 1,2-addition*. The conclusions of this chapter can be summarized as follows:

- In the asymmetric Ni-catalyzed 1,2-addition of trialkylaluminum to aldehydes with catalysts precursors based on phosphite-phosphoroamidite and diphosphoroamidite ligands, we found that the selectivity depends on the position of the phosphoroamidite group at

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either C-5 or C-3 of the furanoside backbone, the configuration of C-3, the introduction of a second phosphoroamidite moiety and the substituents in the biaryl phosphite/phosphoroamidite moieties. By carefully selecting the ligand components, we obtained high activities and enantioselectivities (ee's up to 84%). This represents the first successful application of bidentate ligands for this process.

- In the asymmetric Ni-catalyzed 1,2-addition of trialkylaluminum to aldehydes with catalysts precursors based on monophosphoroamidite ligands, selectivity depended strongly on the sugar backbone, the configuration at carbon C-3 of the ligand backbone and the type of substituents/configurations in the biaryl phosphoroamidite moiety. By judicious choice of the ligand components we obtained good enantioselectivities (ee values up to 78%) and high activities in several aryl aldehydes, with low catalyst loadings (1 mol%) and no excess of ligand.

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Chapter 8

Appendix

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8. List of papers and meeting contributions

List of papers by the author presented in this thesis (in chronological order):

1. Raluy, E.; Claver, C.; Pàmies, O.; Diéguez, M. "*First chiral phosphoroamidite-phosphite ligands for the highly enantioselective and versatile Pd-catalyzed asymmetric allylic substitution reactions*" *Org. Lett*. **2007**, *9*, 49. (Chapter 3).

2. Raluy, E.; Pàmies, O.; Diéguez, M. "*Sugar-based diphosphoroamidite as a promising new class of ligands in the Pd-catalyzed asymmetric allylic alkylation reactions*" *J. Org. Chem.* **2007**, *72*, 2842. (Chapter 3).

3. Raluy, E.; Pàmies, O.; Diéguez, M. "*Modular furanoside phosphite-phosphoroamidite, a readily available ligand library for asymmetric Pd-catalyzed allylic substitution reactions. Origin of enantioselectivity*" *Adv. Synth. Catal.* **2009**, *351*, 1648. (Chapter 3).

4. Raluy, E.; Pàmies, O.; Diéguez, M. "*Furanoside phosphite-phosphoroamidite: new ligand class for the asymmetric nickel-catalyzed trialkylaluminum addition to aldehydes*" *Tetrahedron Lett.* **2009**, *50*, 4495. (Chapter 6).

5. Raluy, E.; Pàmies, O.; Diéguez, M. "*Screening of a modular sugar-based phosphoroamidite ligand library in the asymmetric nickel-*

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catalyzed trialkylaluminum addition to aldehydes" *Tetrahedron: Asymmetry* **2009**, *20*, 1575. (Chapter 6).

6. Raluy, E.; Pàmies, O.; Diéguez, M., Rosset, S.; Alexakis, A. "*Furanoside phosphite-phosphoroamidite and diphosphoroamidite ligands for Cu-catalyzed asymmetric 1,4-addition reactions*" *Tetrahedron: Asymmetry* **2009**, *20*, 1930. (Chapter 5).

7. Raluy, E.; Pàmies, O.; Diéguez, M., Rosset, S.; Alexakis, A. "*Sugar-based phosphite and phosphoroamidite ligands for the Cu-catalyzed asymmetric 1,4-addition to enones*" *Tetrahedron: Asymmetry* **2009**, *20*, 2167 (Chapter 5).

8. Raluy, E.; Pàmies, O.; Diéguez, M., Rosset, S.; Alexakis, A. "*Furanoside phosphite-phosphoroamidite, di- and monophosphoroamidite ligands for asymmetric Cu-catalyzed allylic alkylations*" in preparation (Chapter 4).

Contributions to national and international meetings, directly related with the thesis.

1. Diéguez, M.; Pàmies, O.; Raluy, E.; Claver, C. "*Modular Phosphite-Oxazoline Ligands for Palladium-Catalyzed Enantioselective Substitution Reactions*". XXII International Conference on Organometallic Chemistry - ICOMC. Zaragoza. Spain. 2006. Poster communication.

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2. Diéguez, M.; Pàmies, O.; Raluy, E.; Claver, C. "*Modular Phosphite-Oxazoline Ligands for Palladium-Catalyzed Enantioselective Substitution Reactions*". STEREOCAT. Lisbon. Portugal. 2006. Poster communication.

3. Raluy, E.; Diéguez, M.; Pàmies, O. "*First Chiral Phosphoroamidite-Phosphite Ligands for Highly Enantioselective and Versatile Palladium-Catalyzed Asymmetric Allylic Substitution Reactions*". XVI International Symposium on Homogeneous Catalysis-ISHC. Florence. Italy. 2008. Poster communication.

4. Raluy, E. "*Screening of Carbohydrate Ligands in Asymmetric Catalysis*". Trobada de Joves Investigadors. Tarragona. Spain. 2008. Oral presentation.

5. Raluy, E.; Diéguez, M.; Pàmies, O. "*Chiral Diphosphoroamidite and Phosphoroamidite-Phosphite Ligands for Highly Enantioselective and Versatile Palladium-Catalyzed Asymmetric Allylic Substitution Reactions*". XV IUPAC Symposium on Organometallic Chemistry-OMCOS. Glasgow. United Kingdom. 2009. Poster communication.

6. Raluy, E. COSTD40 Innovation II Meeting. Tarragona. Spain. 2008. Attended to the meeting.

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