SCREENING OF MODULAR SUGAR DERIVED PHOSPHITE-BASED LIGAND LIBRARIES FOR M-CATALYZED REACTIONS. A GREEN APPROACH TO CATALYSTS DISCOVERY

Sabina Alegre Aragonés

Dipòsit Legal: T.194-2014

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Screening of modular sugar derived phosphite-based ligand libraries for M-catalyzed reactions. A green approach to catalysts discovery.

PhD-Thesis

Supervised by Prof. Montserrat Diéguez

and Dr. Oscar Pàmies

Departament de Química Física i Inorgànica

UNIVERSITAT ROVIRA I VIRGILI

TARRAGONA

December 2013

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

FEM CONSTAR:

Que la present memòria que porta per títol "Screening of modular sugar derived phosphite-based ligand libraries for M-catalyzed reactions. A green approach to catalysts discovery", que presenta SABINA ALEGRE ARAGONES per a obtenir el grau de Doctor en Química, ha estat realitzada sota la nostra direcció al Departament de Química Física i Inorgànica de la Universitat Rovira i Virgili i compleix amb els requeriments per a poder optar a Menció Europea.

Tarragona, Desembre de 2013

Prof. Montserrat Diéguez Fernández Dr. Oscar Pàmies Ollé

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Els agraïments semblen la part més fàcil d'escriure, el que es pot deixar per l'últim moment, però no es així perquè realment es una part complexa i difícil, ja que intentar expressar en paraules escrites el que un sent no és gaire fàcil…
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Moltes gràcies a tots. Muchas gracias a todos. Thank you very much everybody. Grazie a tutti.

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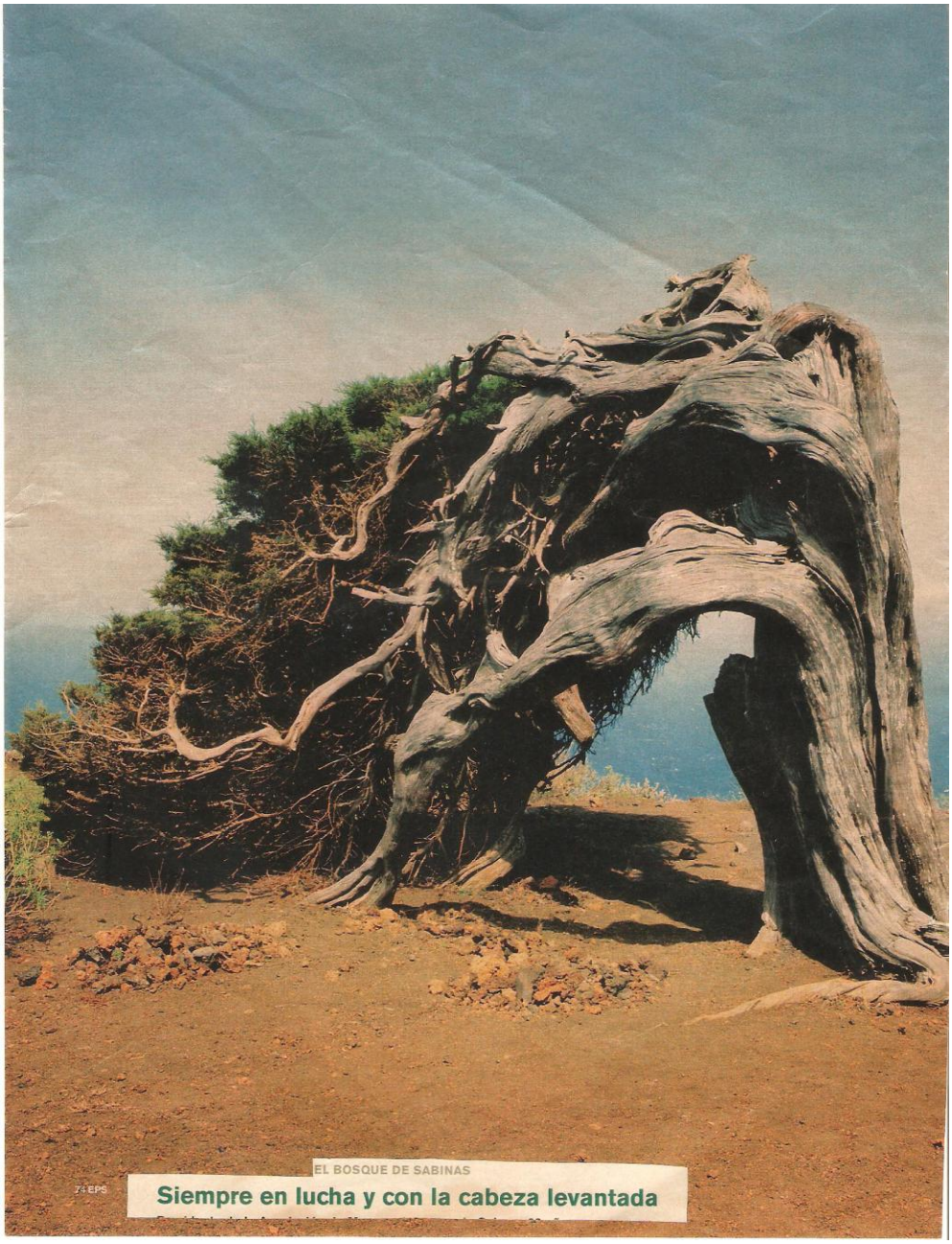

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Structure of the thesis

The thesis is divided into eight chapters.

- Chapter 1. *Introduction*. This chapter first presents the importance of metal-catalyzed asymmetric reactions 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 sugars are presented. These ligands are applied to three 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 sugar-derived 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 sugar-derived ligands in asymmetric catalysis.

- Chapter 3. *Asymmetric hydrogenation reactions*. This chapter contains three sections on the development and application of two ligand libraries in the asymmetric hydrogenation reactions. The first section, *Asymmetric Rh-catalyzed hydrogenation using a thioether-phosphite ligand library*, describes the design and application of a new thioether-phosphite ligand library in the asymmetric Rh-catalyzed hydrogenation of several olefins. The second section, *using a furanoside monophosphite second-generation ligand library. Scope and limitations*, describes the design and application of a furanoside monophosphite ligand library in the asymmetric Rh-catalyzed hydrogenation of several olefins. The third section, *Asymmetric Ir-catalyzed hydrogenation of minimally functionalized olefins using a thioether-phosphite ligand library derived from L-(+)-tartaric acid*, includes the application of a new thioether-phosphite ligand library in the asymmetric Ir-catalyzed hydrogenation of a broad range of minimally functionalized olefins.

- Chapter 4. *Asymmetric Pd-catalyzed allylic substitution*. This chapter contains two sections on the application of the thioether-phosphite and furanoside monophosphite ligand libraries in the asymmetric Pd-catalyzed allylic substitution reactions. The first section, *Asymmetric Pd-catalyzed allylic substitution using a thioether-phosphite ligand library*, discusses the application of the previously developed thioether-phosphite ligand library (see Chapter 3) in the Pd-catalyzed allylic substitution reactions of several linear substrates. The second section, *Asymmetric Pd-catalyzed allylic substitution using a furanoside*

monophosphite ligand library. Scope and limitations, describes the application of previously developed monophosphite ligand library (see Chapter 3) in the Pd-catalyzed allylic substitution reactions of several di- and monosubstituted substrates.

- Chapter 5. *Asymmetric Ni-catalyzed 1,2-addition.* This chapter contains two sections on the application of the thioether-phosphite (developed in Chapter 3), and furanoside monophosphite (developed in Chapter 3) ligand libraries in the asymmetric Ni-catalyzed 1,2-addition reactions. The first one, *Thioether-phosphite ligands derived from L-(+)-tartaric acid for the Ni-catalyzed trialkylaluminum addition to aldehydes*, reports the research on the Ni-catalyzed trialkylaluminum 1,2-addition to aldehydes using the thioether-phosphite ligand library. The second section, *Sugar-monophosphite ligands applied to the asymmetric Ni-catalyzed trialkylaluminum addition to aldehydes*, includes the application of the carbohydrate-based monophosphite ligand library in the Ni-catalyzed trialkylaluminum 1,2-addition to several aldehydes types.

- Chapter 6. *Conclusions*. This chapter presents the conclusions of the work presented in this thesis.

- Chapter 7. *Resum*. This chapter contains a summary of the thesis in Catalan.

- Chapter 8. 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

Nowadays the preparation of enantiomerically pure compounds is growing in several important areas such as pharmaceuticals, agrochemicals, fine chemicals and natural product chemistry,[1] this is because there are many applications in which only one of the enantiomers has the desired properties while the other enantiomer is either inactive or has undesirable side-effects. The discovery of synthetic routes for preparing enantioenriched compounds is therefore one of the most persistently pursued goals in chemistry. Of the various methods for producing enantiopure compounds, enantioselective homogeneous metal catalysis is an attractive one, as is reflected by the many publications in this field and the award of the Nobel Prize award in 2001 to W. S. Knowles, K.B. Sharpless and R. Noyori and in 2010 to E. Negishi, R. F. Heck and A. Suzuki.[1]

One of the main advantages of asymmetric catalysis over other methods used in asymmetric synthesis is that products can be selectively synthesized from cheap, commercially available prochiral starting materials without undesirable products being formed. 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.[2]

The most widely used chiral ligands in asymmetric catalysis are phosphorus donors.[3] Among them, phosphines and phosphinites have played a dominant role.[3] Despite the advantage of phosphite-based ligands, such as less sensitive to air and other oxidizing agents than phosphines and phosphinites and easy to synthesize from readily available alcohols, their use as efficient chiral

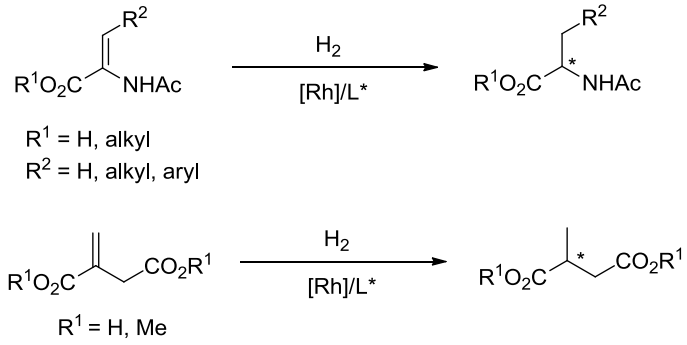
ligands has only been demonstrated more recently.[3d,4] In general, transition-metal complexes with chiral sulfur ligands have been less investigated than complexes with other donor atoms,[5] although in recent decades the number of studies on sulphur-containing catalytic systems has increased notably.[5] Compared to phosphorus, sulfur has a less donor and acceptor character. In addition to these electronic considerations, the sulfur atom in thioether ligands has only two substituents, which can create a less hindered environment than trivalent phosphorus. The formation of mixtures of diastereomeric thioether complexes (because the S atom becomes a stereogenic center when coordinated to the metal) and the difficulty to control their interconversion in solution have also been regarded as a problem for asymmetric induction in catalytic reactions. Nevertheless, in recent years, S-containing ligands have proven to be as useful as other classical chiral ligands, especially when combined with other donor atoms.[5] Thioethers have been combined with several donor atoms in heterodonor ligands. S,X-Donor ligands have several advantages over homodonors. They can provide different electronic environments because of the different *trans* influence of the sulfur and X atom.

In this context, this thesis focuses on the development of new chiral ligand libraries derived from sugars and their application in the enantioselective Rh- and Ir-catalyzed hydrogenation, asymmetric Pd-catalyzed allylic substitution and Ni-catalyzed asymmetric addition of trialkylaluminum to aldehydes. In the following sections, we describe the background of each of the catalytic reactions studied in this thesis.

1.1 Asymmetric Rh-catalyzed hydrogenation of functionalized olefins

The hydrogenation of functionalized carbon-carbon double bonds is widely used to prepare high value compounds that can be used as building blocks in asymmetric synthesis (Scheme 1.1.1). The hydrogenation of dehydroamino acid derivatives and esters provides access to unnatural amino acids and amines that are useful intermediates for the pharmatheutical and agrochemical industries.[1,6] Their hydrogenation is also a typical reaction for testing the efficiency of new chiral ligands. Rh- and Ru-complexes containing chiral ligands with phosphorus and nitrogen donor centers have proven to be the best catalyst for the asymmetric hydrogenation of this type of substrates. Excellent activities and enantioselectivities have been therefore achieved for the asymmetric hydrogenation of dehydroamino acids and other functionalized substrates.[1,6]

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



Scheme 1.1.1. Hydrogenation of dehydroamino acids.

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

1.1.1 Mechanism

Figure 1.1.1 shows the mechanism for the asymmetric hydrogenation of dehydroamino acids and their esters with cationic precursors with diphosphines.[7] In the last decade, this mechanism has proved to be valid for other phosphorus-based ligands (i.e. diphosphinites, diphosphites, etc.).[8] The catalytic cycle consists of two coupled diastereomeric manifolds. The species starting the catalytic cycle is a square planar Rh (I) complex containing the chelating diphosphine and two molecules of solvent **A**. This species reacts with the substrate e.g. methyl (*Z*)-α-acetamidoacrylate.

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

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

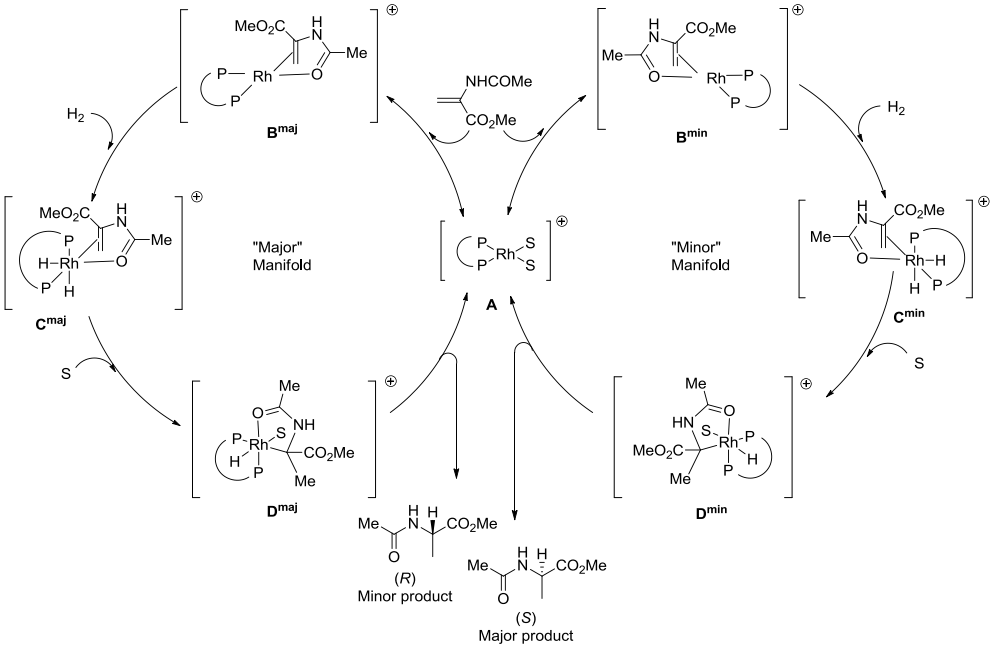


Figure 1.1.1 Mechanistic scheme for the Rh-catalyzed asymmetric hydrogenation of methyl (*Z*)-α-acetamidoacrylate.

1.1.2 Ligands

The development of homogeneous asymmetric hydrogenation was initiated by Knowles[9] and Homer[10] in the late 1960s after the discovery of Wilkinson's hydrogenation catalyst [$RhCl(PPh_3)_3$]. [11] By replacing the triphenylphosphine of Wilkinson's catalyst with resolved chiral monophosphines, Knowles and Horner reported the earliest examples of enantioselective hydrogenation, although with poor enantioselectivity. Later, two advances were made in asymmetric hydrogenation by Kagan and Knowles. Kagan reported the first diphosphine ligand successfully used in asymmetric hydrogenation (**DIOP**) (Figure 1.1.2).[12] Knowles made his significant discovery of the C_2-symmetric chelating diphosphine ligand, **DIPAMP** (Figure 1.1.2).[13] Because of its high catalytic efficiency, **DIPAMP** was used in the industrial production of L-Dopa, a drug used to treat Parkinson's disease.[14] For this work Knowles was awarded the Nobel Prize in 2001.[15]

Following the significant contributions by Kagan and Knowles came the development of hundreds of successful chiral diphosphorus ligands for asymmetric hydrogenation. These include Bonisch's **CHIRAPHOS** and **PROPHOS**, Kumada's ferrocene ligand **BPPFA** and **BPPFOH**, Achiwa's **BPPM**, Rhode Poulenc's **CBD** and Giongo's bis(aminophosphine) ligand **PNNP** (Figure 1.1.2). [16] However, development in the early 1980s focused mainly on the chiral Rh-catalyst, and the substrate scope was limited to α-dehydroamino acids. Noyori's research on the **BINAP**-Ru catalyst opened up opportunities for the efficient hydrogenation of various substrates (Figure 1.1.2). Several prochiral olefins and ketones were hydrogenated with excellent enantioselectivity.[17] For this work Noyori was awarded the Nobel Prize in 2001. In the 1990s, the introduction of some efficient chiral diphosphorus ligands, such as **DUPHOS** and **BPE** developed by Burk and coworkers (Figure 1.1.2) for the hydrogenation of various functionalized olefins, significantly expanded the scope of asymmetric hydrogenation.[18]

Nowadays, many chiral ligands, mainly phosphorus donor ligands with either C_2- or C_1-symmetry, have been successfully applied. Catalysts containing diphosphine and diphosphinite have played a dominant role among the P-ligands.[1,6,16] However, some catalysts containing a group of less electron-rich phosphorus compounds, phosphite and phosphoroamidite ligands, have also demonstrated their potential utility in asymmetric hydrogenation.[2e,3d,4,6,16] Other donor atoms, such as sulfur and heterodonor ligands, have also received attention. Several systems with dithioethers have led to low-to-moderate enantioselectivities

(from 6% to 68%).[5] Mixed P-S[5] and P-P'[4,19] (such as phosphine-phosphite and phosphoroamidite-phosphite) ligands have been developed and have proved to be very effective for this process. Although it has been generally accepted that bidentates are the most appropriate ligands for metal-catalyzed enantioselective hydrogenation, in recent years it has been shown that some monophosphorus ligands are very efficient for Rh-catalyzed asymmetric hydrogenation.[20]

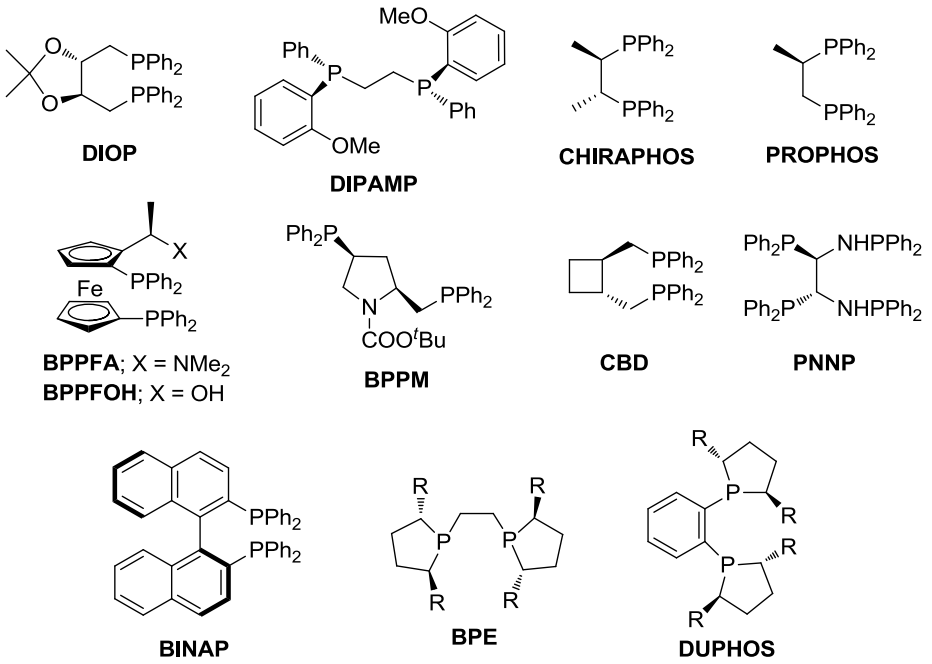


Figure 1.1.2. Successful diphosphine ligands in asymmetric hydrogenation.

As far as carbohydrate ligands are concerned, several types of ligands, mainly bidentate phosphorus donors (both homo- and heterodonors), have been used with excellent enantioselectivities.[2] Monodentate ligands have also exhibited good catalytic behaviour.[2]

In the next section, we summarize some of the most relevant catalytic data published for asymmetric hydrogenation with carbohydrate ligands.

1.1.2.1 P-donor ligands

Phosphine ligands

Inspired by Kagan's early work on **DIOP** chemistry, other research groups have improved enantioselectivities. They have increased the rigidity of the conformational flexibility of the seven-member chelate ring in the **DIOP** ligand by introducing first a methyl substituent in the α positions of the phosphine group, which led to ligands **1** and **2**,[21] and then a conformationally rigid 1,4-dioxane backbone, which led to ligands **3** and **4** (Figure 1.1.3).[22] These ligands have provided excellent enantioselectivities (ee's up to 99%) in the Rh-catalyzed hydrogenation of aryl enamides.[21,22]

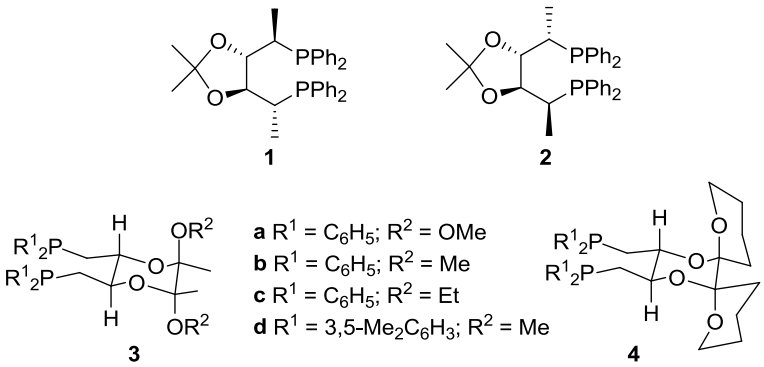


Figure 1.1.3. C_2-modified **DIOP** diphosphine ligands **1**-**4**.

Several diphospholanes, related to **DUPHOS**, have emerged as a powerful new class of ligands for asymmetric hydrogenation. These ligands are mainly derived from D-mannitol. In particular, Holz and coworkers and Zhang and coworkers developed novel diphospholanes **5**, **6a-c** and **7,** which have chiral information at both the α- and β-positions of the phosphorus atom (Figure 1.1.4). These ligands provided high enantioselectivities (from 93% to 99%). [23] Subsequently, Rieger and coworkers studied how the substituents in the α-position (R^2 groups) affect enantiodiscrimination with ligands **6b-f**. Their results indicated that the optimal substituents are generally Me and Et (Figure 1.1.4).[24]

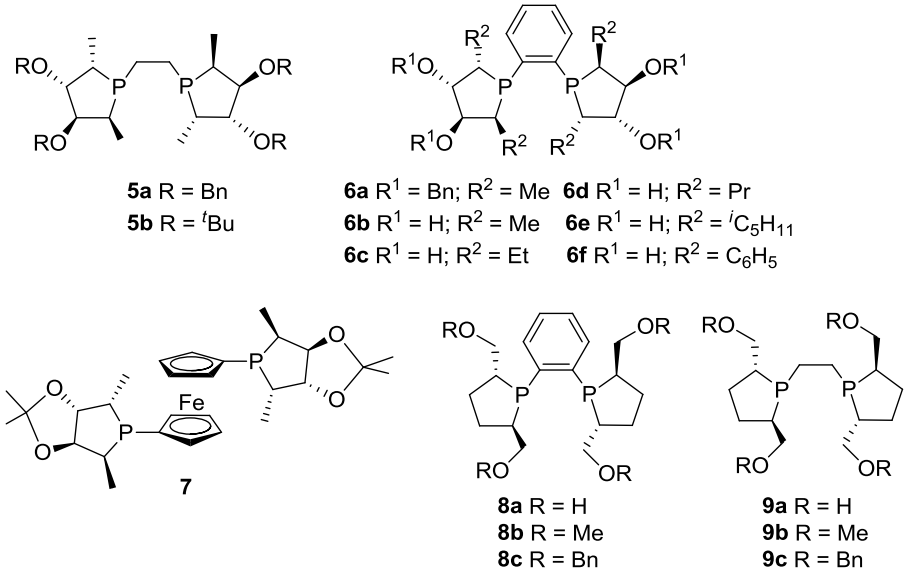


Figure 1.1.4. Diphospholane ligands **5**-**9**.

Another series of diphospholane ligands **8** and **9** (Figure 1.1.4) were efficiently used in the Rh-catalyzed asymmetric hydrogenation of α- and β-amino acid derivates, itaconates and an unsaturated phosphonate (ee's up to 99%).[25]

Another efficient structural variation combined a phospholane moiety, derived from D-mannitol, with a **DIPAMP** chiral phosphine through an ethylene bridge such as **BPE** (Figure 1.1.5). These ligands (**10** and **11**) were applied in the Rh-catalyzed hydrogenation of several itaconates with ee's ranging from 80 to 95%.[26]

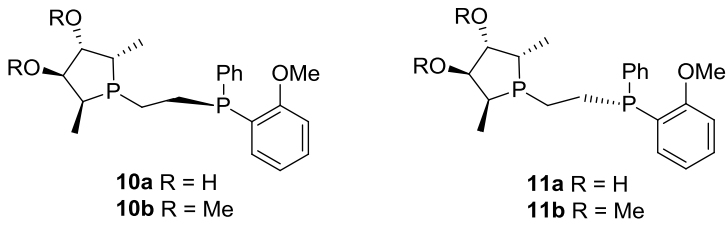


Figure 1.1.5. Phosphine-phospholane ligands developed by Brown and coworkers.

Another important series of compounds are the furanoside ligands **12**-**14** derived from D-(+)-xylose and D-(+)-glucose (Figure 1.1.6). These ligands were developed for the Rh asymmetric hydrogenation of dehydroamino acid and itaconic acid derivatives.[27] Ligands **13** and **14** differ from ligand **12** at C-5, where a

new stereogenic center was introduced. The result indicated that the methyl substituent at C-5 significantly increased activity (TOF were approximately double for ligands **13** and **14**). Moreover, the configuration of C-5 strongly influenced enantioselectivity. The best results (activity and enantioselectivity) were therefore obtained with ligand **13** with (*R*)-configuration at C-5.

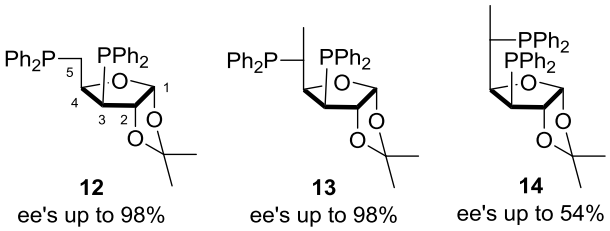


Figure 1.1.6. Diphosphines **12**-**14** derived from D-(+)-xylose and D-(+)-glucose. Enantioselectivities in the hydrogenation of α,β-unsaturated carboxylic derivatives are shown as examples.

Recently, phosphorus functionalities have been incorporated into cyclodextrins (ligand **15**, Figure 1.1.7) to take advantage of the properties of cyclodextrins as water-soluble chiral support. Ligand **15** contains phosphine at two of the positions six of a β-cyclodextrin. The Rh/**15** catalytic system has been tested in the hydrogenation of dehydroamino acids and itaconates with ee's up to 92%, but only organic solvents were used for these reactions.[28]

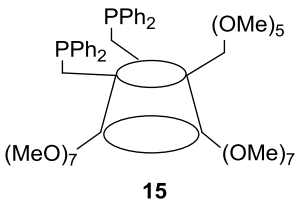


Figure 1.1.7. Cyclodextrin containing diphosphine **15**.

Phosphinite ligands

The first examples of diphosphinite ligands being used with a carbohydrate backbone in asymmetric catalysis were reported by Cullen,[29] Thompson,[30] Selke,[31] Descotes[32] and their respective groups. They studied a wide variety of 2,3-diphenylphosphinite pyranoside ligands in the asymmetric hydrogenation of dehydroamino acid derivatives. In particular, the best enantioselectivities (ee's up

to 96.6%) were obtained with a series of β-glucopyranoside 2,3-diphosphinite ligands **16**, mainly developed by Selke and coworkers (Figure 1.1.8, R^2 = Me, Ph, Bn and naphthyl; R^1 = Ph).[30,31,33] However, the scope was limited for the synthesis of substituted phenylalanines and the corresponding heteroatomic derivatives. In this context, RajanBabu and coworkers studied whether further modifications in the diphosphinite type ligand **16** (R^2 = Ph; R^1 = **a**-**h**) would overcome this limitation. They systematically studied the electronic and steric properties of the diphosphinite ligands by introducing different phosphinite groups (**a**-**h**) in the basic ligand framework **16** (Figure 1.1.8).[34]

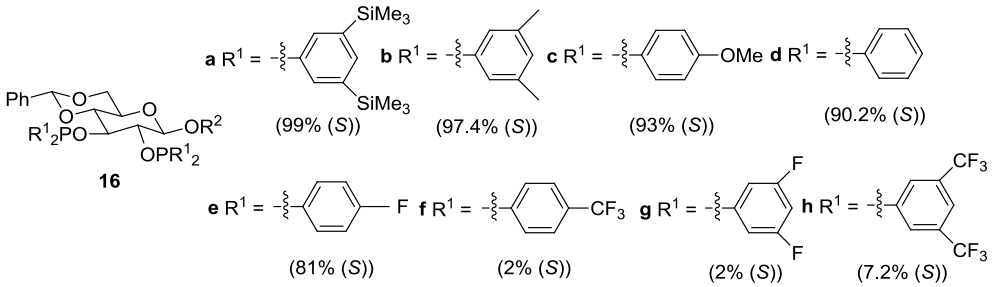
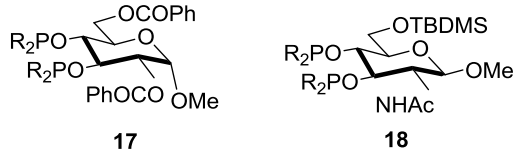


Figure 1.1.8. Diphosphinite ligand **16**. Enantioselectivities obtained in the hydrogenation of methyl α-acetamidocinnamate are shown as examples.

The Rh-hydrogenation results showed that electron-rich diphosphinite ligands considerably increased enantioselectivities, whereas electron-deficient ligands provided much lower selectivity. Enantioselectivities were therefore excellent over a wide range of dehydroamino acid derivatives with ligands **16a** and **16b** (ee's up to 99% (*S*)). In all cases the (*S*)-enantiomer of the hydrogenation product was obtained.

In the search for the (*R*)-enantiomer of the hydrogenation product (D-amino acids), rather than preparing the corresponding diphosphinite **16** from the expensive L-glucose, RajanBabu and coworkers developed pseudo-enantiomeric diphosphinite ligands to **16** with the corresponding 3,4-diphosphinite ligands **17** and **18** (Figure 1.1.9).[34] These ligands provided high enantioselectivities in favor of the (*R*)-enantiomer (ee's up to 98%) (Figure 1.1.9). As before, the enantioselectivities were best with electron-rich phosphinites. In summary, the sugar-diphosphinite ligands developed by RajanBabu appear to be among the most practical ligands for the synthesis of (*S*) and (*R*)-aromatic and heteroaromatic alanine derivatives.



17 **18**

Figure 1.1.9. 3,4-Diarylphosphinite ligands **17** and **18**.

Diphosphinite derivatives with a furanoside backbone **19** and **20** (Figure 1.1.10) were used in the Rh- and Ir-catalyzed asymmetric hydrogenation of prochiral substrates. The enantiomeric excess was dependent on both the absolute configuration of the C-3 stereocenter of the carbohydrate backbone and on the nature of the metal precursor. For instance, the enantiomeric excess in the hydrogenation of methyl α-acetamidoacrylate was 76% (*R*) with the Rh/**20** catalytic system and 78% (*R*) with the Ir/**19** catalytic system.[35] The phosphinite xylose derivatives **19** and **20** were also used as ligands in the Ir-catalyzed hydrogenation of imines although they provide only moderate enantioselectivities (ee's up to 57%).[36]

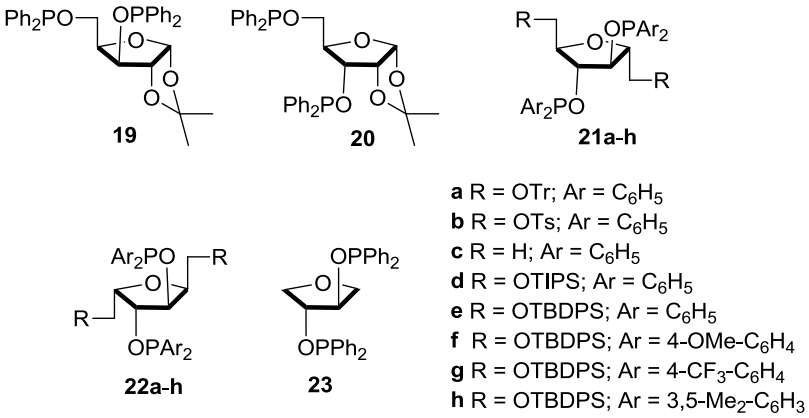


Figure 1.1.10. Diphosphinites ligands **19**-**23**.

Castillón and coworkers developed C_2-symmetric diphosphinites **21a-h** and **22a**-**d** derived from D-glucosamine and D-glucitol.[37] Ligands **21a**-**d** were used in the Rh-catalyzed hydrogenation of dehydroamino acids and itaconates. The best results were obtained with the catalytic system containing ligand **21c** (93% ee). Ligand **23**, which does not contain substituents at positions 2 and 5 of the tetrahydrofuran ring, gave an ee of only 18%. This indicates that stereogenic centers which are not directly bonded to the coordinating atoms also have a

strong influence on the selectivity. Substituents in **21** and **22** also affect the stereoselectivity. One of the advantages of diphosphinite ligands is their modular nature which allows different backbones as well as different substituents group.[38] Diphosphinites **22e**-**h** (Figure 1.1.10), modified with different electron-donating or electron-withdrawing groups on the aryl residue, have been used in the hydrogenation of *N*-(phenylethylidene)-benzylamine. The best enantioselectivity (ee's up to 76%) was obtained with ligand **22h**.

Phosphite ligands

A review of the research into carbohydrate phosphite ligands reveals two main trends: bidentate ligands and monodentate ligands.[4]

The first successful phosphite ligand for asymmetric hydrogenation came with the work of Reetz and coworkers. They developed a series of C_2-ligands from D-mannitol **24** with different phosphite substituents (**a**-**e**) (Figure 1.1.11).[39] These ligands were efficiently applied in the Rh-catalyzed hydrogenation of prochiral olefins (ee's up to 98%). Their results indicated that the sense of enantiodiscrimination is predominantly controlled by the configuration of the binaphthyl moiety. Moreover, they observed a cooperative effect between the stereogenic centers of the ligand backbone and the stereogenic binaphthyl phosphite moieties. This resulted in a matched combination for ligand **24e**.

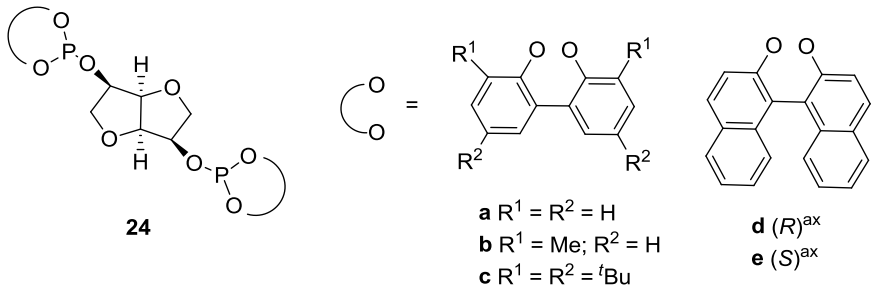


Figure 1.1.11. D-mannitol diphosphite ligand developed by Reetz et al.

Our group developed a series of highly efficient modular C_1-diphosphite ligands **25**-**30** (Figure 1.1.12) with a furanoside backbone for the Rh-catalyzed hydrogenation.[40] These ligands are derived from D-(+)-xylose and D-(+)-glucose and their most interesting feature is that they are modular, which allows sufficient flexibility to fine-tune: (a) the different configurations of the carbohydrate backbone (C-3 and C-5) and (b) the steric and electronic properties of the

diphosphite substituents (**a**-**h**). Excellent enantioselectivities (ee up to 99%) and activities were achieved in the Rh-catalyzed hydrogenation of several prochiral olefins. Systematic variation of stereocenters C-3 and C-5 at the ligand backbone showed that enantiomeric excesses depended strongly on the absolute configuration of C-3 and only slightly on the absolute configuration of the stereocenter C-5. Enantioselectivities were best with ligands **28** with (*R*)-configuration on both C-3 and C-5 stereocenters. Bulky substituents at the *ortho*-positions of the biaryl diphosphite moieties have a positive effect on enantioselectivity. Enantiomeric excess was highest for allofuranoside ligand **28d**, which has *o*-trimethylsilyl substituents in the biphenyl moieties. It was also found that a methyl substituent on the carbon C-5 significantly increased activity.

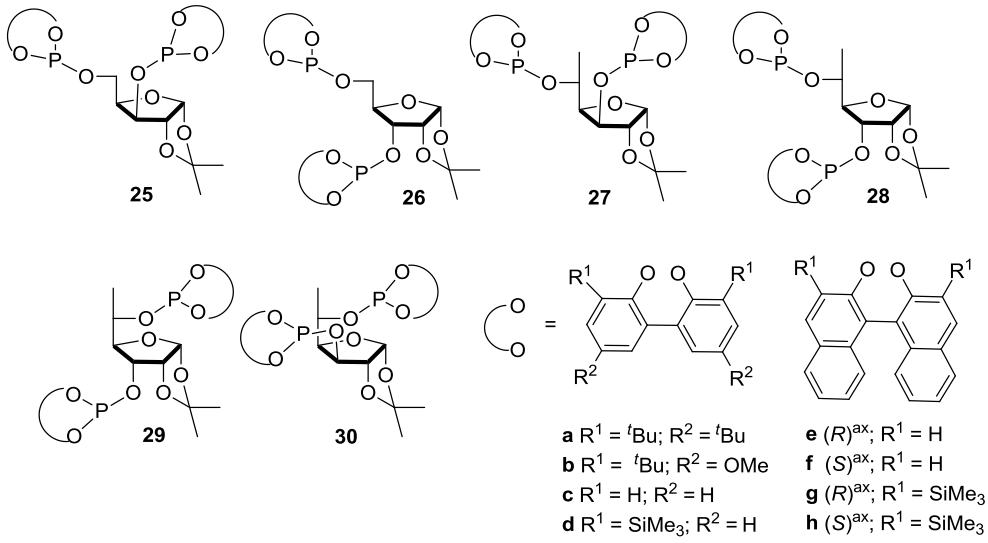


Figure 1.1.12. Diphosphite modular ligands **25**-**30**.

Diphosphite ligands **31**-**34** with C_2-symmetry and a tetrahydrofuran backbone have been synthesized starting from D-glucosamine and D-glucitol (Figure 1.1.13). These ligands have been used in the Rh-catalyzed asymmetric hydrogenation of methyl α-acetamidoacrylate with enantioselectivities up to 57%.[41]

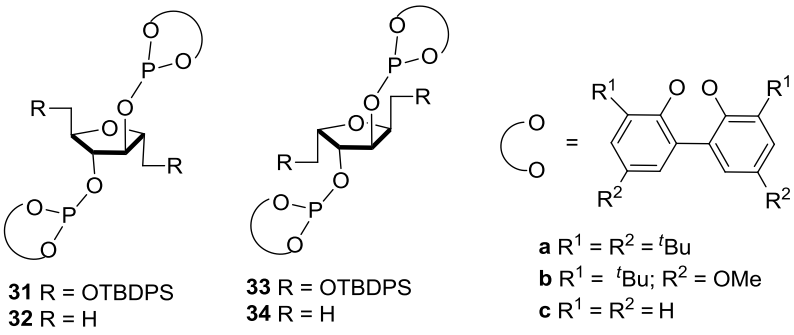
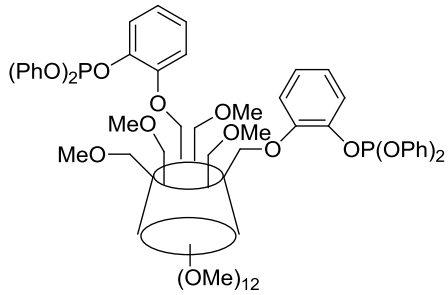


Figure 1.1.13. C_2-symmetric diphosphite ligands **31**-**34**.

Matt and coworkers successfully applied diphosphite ligand **35** (Figure 1.1.14), built on a cyclodextrin scaffold, in the Rh-catalyzed asymmetric hydrogenation of dimethyl itaconate with ee's up to 83%.[42]



35

Figure 1.1.14. Cyclodextrin-based diphosphite ligand **35** developed by Matt et al.

Although it has been generally accepted that bidentate ligands are the most appropriate for metal-catalyzed enantioselective hydrogenation, in the last decade it has been shown that some monophosphorus ligands are very efficient in Rh-catalyzed asymmetric hydrogenation.[20] Research in this area was initiated by Reetz and coworkers. They found that the monophosphite ligands **36a-b** related to the previously described diphosphite ligands derived from D-mannitol **24** provided similar enantioselectivities in both enantiomers of the product (ee's up to 97%) (Figure 1.1.15).[43]

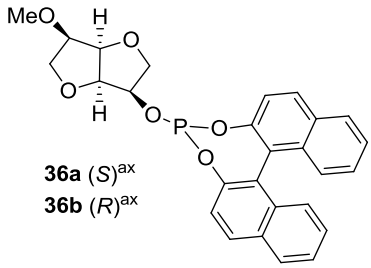


Figure 1.1.15. Monophosphite ligands **36**.

Other monophosphite ligands **37**-**44** (Figure 1.1.16), often containing a binaphthol moiety, were used for the Rh-catalyzed asymmetric hydrogenation of vinyl carboxylates, dehydroamino acids, and enamides.[44] The results of the vinyl carboxylate hydrogenation reported by Reetz and coworkers using ligands **37**-**39** show that there is a cooperative effect between the configuration of the binaphthyl moieties and the configuration of the sugar backbone. The results were best with the phosphite **37b**, prepared from (*R*)-Binol and a D-(+)-glucose derivative (ee's up to 94 %).[44a]

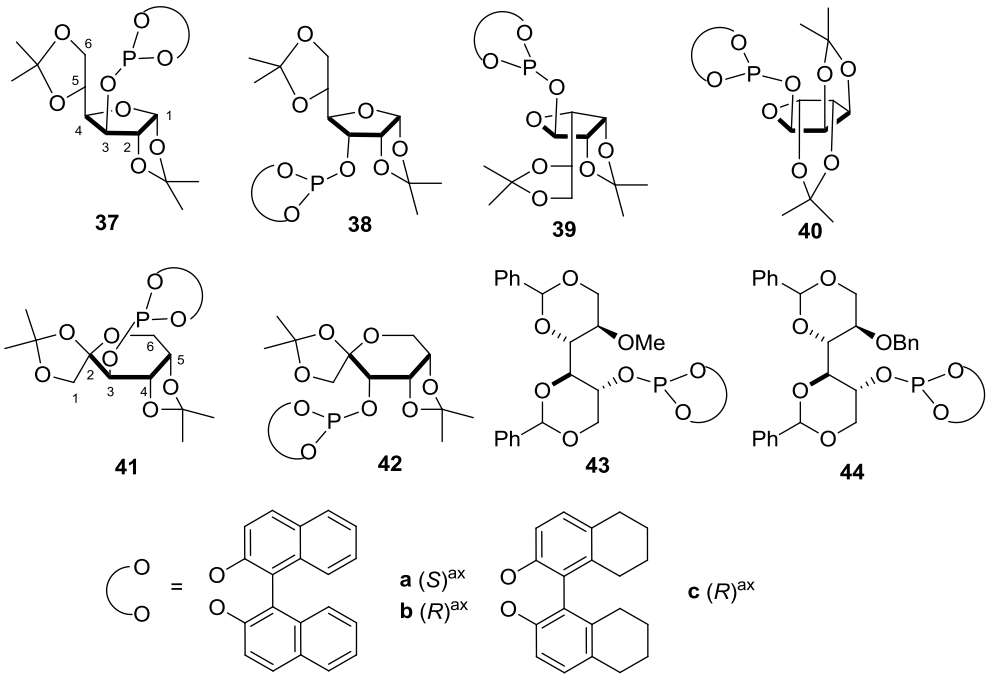


Figure 1.1.16. Monophosphite ligands **37**-**44**.

Chen and coworkers have also successfully used ligands **37**-**38** and **41**-**42** in the Rh-catalyzed hydrogenation of dehydroamino acids (ee's up to 98%) and enamides (ee's up to 99.9%).[44b-e] Their results indicate that the enantiomer excess depends strongly on the configuration of carbon atom C-3. In general, ligands **38** and **40** with an (*R*)-configuration produced a much higher enantioselectivity than ligands **37** and **39** with the opposite configuration. In this case, their results also suggest that there is a cooperative effect between the configuration of the binaphthyl moieties and the configuration of the carbohydrate backbone. The enantioselectivities (ee's up to 99.6%) were therefore best with ligands **42b**. Ligands **43** and **44** were also highly efficient in the hydrogenation of dehydroamino acids and enamides, providing high enantioselectivities (ee's up to 99.9%) and activities (TON's up to 5000).[44 d]

Phosphoroamidite ligands

In the last decade, several monophosphoroamidites derived from carbohydrates have been used for Rh-catalyzed asymmetric hydrogenation. However, only ligands **45** and **46** (Figure 1.1.17) derived from D-mannitol provided high enantioselectivities in the asymmetric hydrogenation of itaconic acid (ee's up to 94%) and α-acetamidocinnamic acid (ee's up to 89%). The best results were obtained with ligand **46e**.[24]

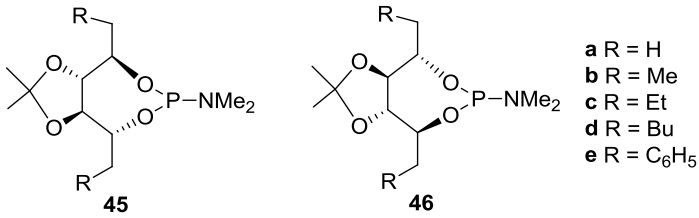


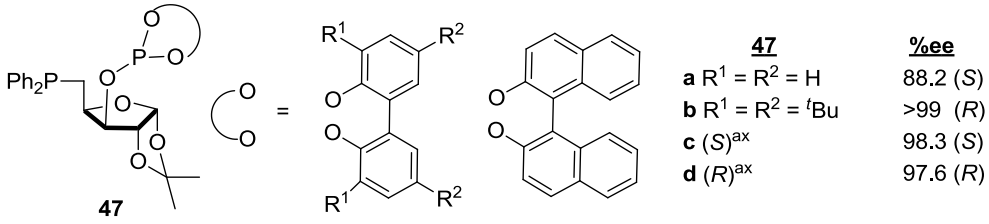
Figure 1.1.17. Phosphoroamidite ligands **45**-**46**.

1.1.2.2 Heterodonor ligands

P,P' ligands

Several types of mixed carbohydrate ligands have been developed for application in asymmetric hydrogenation catalysis. In particular, phosphine-phosphite and phosphite-phosphoroamidite have produced excellent results.[4,19]

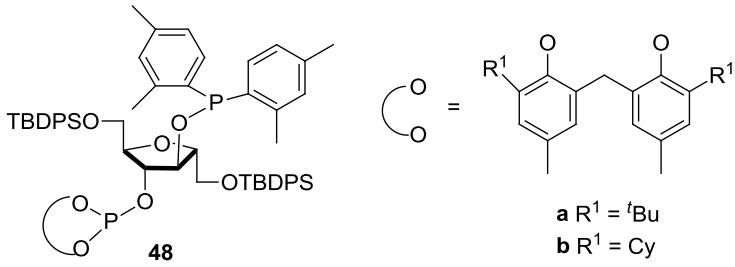
Furanoside phosphine-phosphite ligands **47** derived from D-(+)-xylose were used as ligands in the Rh-catalyzed asymmetric hydrogenation of several α,β-unsaturated carboxylic acid derivates (ee's up to >99%) under mild conditions (Figure 1.1.18).[8c,45] The best enantioselectivity was obtained using ligand **47b**, which contains bulky *tert*-butyl groups in the *ortho* and *para* positions of the biphenyl moiety. The results indicate that the sense of the enantioselectivity is mainly controlled by the configuration of the axial chiral phosphite moiety. Both enantiomers can therefore be obtained with high enantioselectivities.



47	%ee
a $R^1 = R^2 = H$	88.2 (*S*)
b $R^1 = R^2 = {}^t$Bu	>99 (*R*)
c $(S)^{ax}$	98.3 (*S*)
d $(R)^{ax}$	97.6 (*R*)

Figure 1.1.18. Phosphine-phosphite ligands **47**. This figure also shows the enantioselectivities obtained in the hydrogenation of α,β-unsaturated carboxylic acid derivates.

Phosphinite-phosphite ligands **48** modified with different substituents (Figure 1.1.19) have shown not only considerable activity and selectivity but also higher enantioselectivities than the related diphosphite ligands **31**. These ligands have provided moderate enantioselectivities (ee's up to 76%) in the Ir-catalyzed hydrogenation of amines.[38] The best enantioselectivity was obtained with ligand **48a**.



a $R^1 = {}^t$Bu
b R^1 = Cy

Figure 1.1.19. Phosphinite-phosphite ligands **48**.

To investigate the potential of phosphite-phosphoroamidite as a new class of ligands for Rh-catalyzed asymmetric hydrogenation, our group developed a furanoside ligand library **49**-**52a**-**f** (Figure 1.1.20).[46,47] With this library the authors

investigated the position of the phosphoroamidite group (at C-3 or C-5), the configuration of C-3 and the substituents/configurations at the biaryl moieties Enantioselectivities were best (up to >99% ee for dimethyl itaconate and α-dehydroamino acid esters and up to 92% ee for arylenamides) with ligands **49a** and **49f**, which contain the optimal combination of ligand parameters.

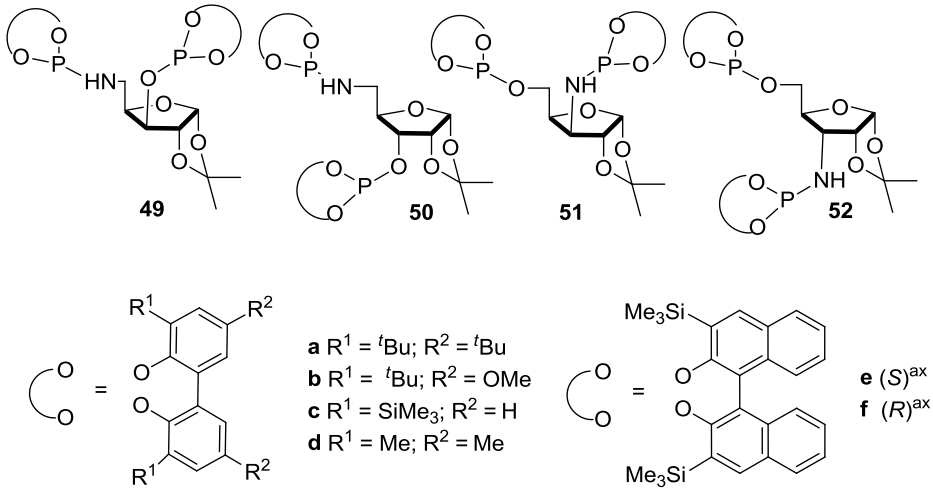


Figure 1.1.20. Library of phosphite-phosphoroamidite ligands **49**-**52a**-**f**.

P,S ligands

The furanoside phosphinite-thioether ligands **53** (Figure 1.1.21) were successfully applied in the Rh- and Ir-catalyzed asymmetric hydrogenation of α-acylaminoacrylates and itaconic acid derivatives (ee's up to 96%) [48] The enantiomeric excesses depend strongly on the steric properties of the substituent in the thioether moiety, the metal source and the substrate structure. A bulky group in the thioether moiety in conjunction with the metal Rh has a positive effect on enantioselectivity.

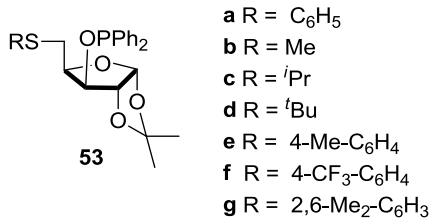
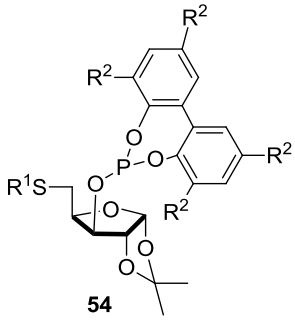


Figure 1.1.21. Furanoside phosphinite-thioether ligands **53**.

In contrast to phosphinite-thioether, phosphite-thioether ligands have been studied very little in hydrogenation. To the best of our knowledge, only one type of carbohydrate-based phosphite-thioether ligand has been applied to asymmetric hydrogenation: the phosphite-thioether ligands **54** (Figure 1.1.22).[49] These ligands have been applied in the Rh- and Ir-catalyzed asymmetric hydrogenation of itaconic acid with enantioselectivities up to 51%.



a $R^1 = C_6H_5$; $R^2 = {}^t$Bu
b $R^1 = {}^i$Pr; $R^2 = {}^t$Bu
c R^1 = Me; $R^2 = {}^t$Bu
d $R^1 = C_6H_5$; R^2 = H
e $R^1 = {}^i$Pr; R^2 = H

Figure 1.1.22. Furanoside phosphite-thioether ligands **54**.

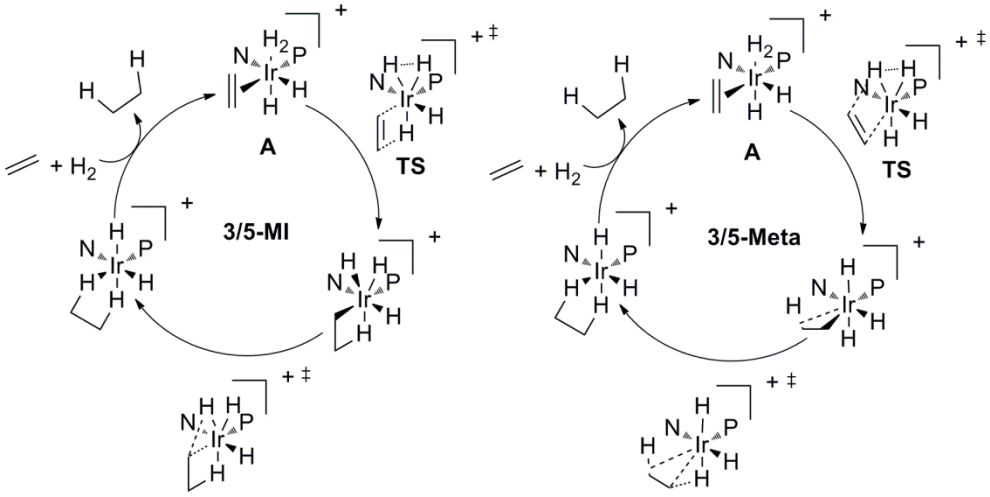
1.2 Asymmetric Ir-catalyzed hydrogenation of unfunctionalized olefins

Whereas the reduction of olefins containing an adjacent polar group (i.e. dehydroamino acids) by Rh- and Ru- catalyst precursors modified with phosphorus ligands has a long history,[1,6] the asymmetric hydrogenation of minimally functionalized olefins is less developed because they have no adjacent polar group to direct the reaction. Iridium complexes with chiral P,N ligands have become established as efficient catalysts for the hydrogenation of unfunctionalized olefins, and their scope is complementary to those of Rh– and Ru–diphosphine complexes.[50]

1.2.1 Mechanism

Although the mechanism of olefin hydrogenation (and consequently of stereocontrol) by Rh catalysts is well understood,[7,8a] the mechanism that uses chiral iridium catalysts is not, despite having been investigated both experimentally and computationally. In the first case, there is enough evidence to support a Rh^{I}/Rh^{III} mechanism in which substrate chelation to metal plays a pivotal role in stereodiscrimination (Figure 1.1.1), but in the second four different

mechanisms have been proposed (two of them involving Ir^{I}/Ir^{III} intermediates[51] and the other two Ir^{III}/Ir^{V} species[52]). Andersson and coworkers have recently used DFT calculations and a full, experimentally tested combination of ligands (mainly phosphine/phosphinite,N) and substrates to study all of the possible diastereomeric routes of the four different mechanisms.[53] Their studies agree with the two already proposed catalytic cycles involving Ir^{III}/Ir^{V} intermediates;[52] however, they fail to distinguish the two Ir^{III}/Ir^{V} mechanisms. One of the mechanisms involves an Ir^{III}/Ir^{V} migratory-insertion/reductive-elimination pathway (labeled 3/5-MI in Scheme 1.2.1)[52c] whereas the second mechanism uses an Ir^{III}/Ir^{V} σ-metathesis/reductive-elimination pathway (labeled 3/5-Meta in Scheme 1.2.1).52[a,b] From these cycles, it has been demonstrated that the π-olefin complex **A** and the transition states for the migratory-insertion in 3/5-MI (**TS**) and the σ-metathesis in 3/5-Meta (**TS'**) are responsible for the enantiocontrol in iridium hydrogenation.[53] It has been demonstrated that the enantioselectivity can be reliably obtained from the calculated relative energies of migratory insertion transition states.[53] Very recently Hopmann and coworkers performed a computational study using a phosphine-oxazoline (**PHOX**)-based iridium catalyst.[54] At the same time our group, in conjunction with Norrby's and Andersson's groups have also performed DFT calculation using Ir-phosphite-oxazoline ligands.[55] Both studies indicate that the hydrogenation of unfunctionalized olefins follows the 3/5-Meta pathway.



Scheme 1.2.1. 3/5-MI and 3/5-Meta catalytic cycles for the Ir-hydrogenation of unfunctionalized olefins.

1.2.2 Ligands

A breakthrough in the hydrogenation of unfunctionalized olefins came in 1997 when Pfaltz and coworkers used phosphine-oxazoline ligands **PHOX**[56] (Figure 1.2.1) to design [Ir(**PHOX**)(cod)]PF_6 (cod = 1,5-cyclooctadiene), a chiral analogue of Crabtree's catalyst ([Ir(py)(PCy_3)(cod)]PF_6)[57] that enantioselectively hydrogenated prochiral imines.[58] Although this catalyst also hydrogenated prochiral olefins highly enantioselectively, it was unstable to the reaction conditions. Pfaltz and coworkers overcame this problem by changing the catalyst anion to [(3,5-$(F_3C)_2$-$C_6H_3)_4B]^-$ ([$BAr_F]^-$). The result was [Ir(**PHOX**)(cod)]BAr_F (Figure 1.2.1), an active, enantioselective, and stable catalyst library for olefin hydrogenation. These catalysts have been successfully used for the asymmetric hydrogenation of a limited range of alkenes (mainly trisubstituted *E*-olefins, Figure 1.2.1).[59] Bolm's group have recently successfully applied Ir-**PHOX** catalytic systems in the hydrogenation of α,β-unsaturated ketones (ee's up to 99%, Figure 1.2.1).[60] Hydrogenation of α,β-unsaturated ketones leads to the formation of ketones with α-chiral carbon centers; which are an important group of compounds in organic synthesis.[61]

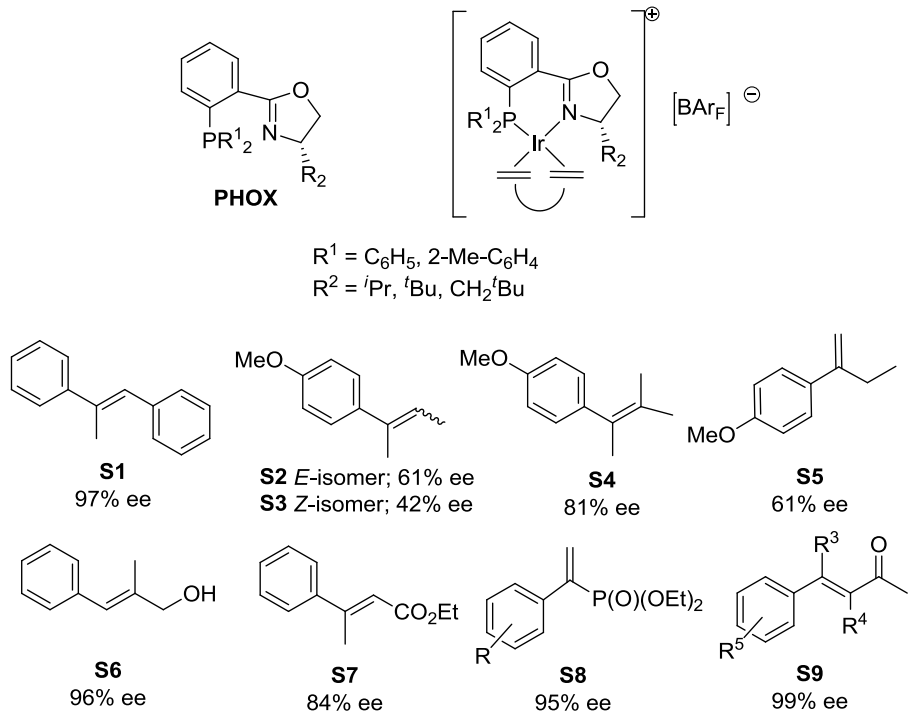


Figure 1.2.1. Selected Ir-hydrogenation results using PHOX ligands.

Since then, the composition of the ligands has been extended by initially replacing the phosphine moiety with a phosphinite or a carbene group, and the oxazoline moiety with other N-donor groups (such as pyridine, thiazole and oxazole).[50] The structure of the chiral ligand's backbone has also been modified. More recently, the use of iridium catalyst containing P,S[62] and P,O[63] heterodonor ligands have been also developed. All, these modifications have led to the discovery of new ligands[64] that have considerably broadened the scope of Ir-catalyzed hydrogenation.[59g,65] Figure 1.2.2 shows the most representative ligands applied to the asymmetric Ir-catalyzed hydrogenation of unfunctionalized olefins. Of them all, chiral Ir-P,N compounds have been the most studied and they have therefore become extremely useful catalytic precursors for the hydrogenation of unfunctionalized tri- and tetra-substituted olefins.[50] The most successful P,N-ligands contain a phosphine or phosphinite moiety as P-donor group and either an oxazoline,[65b,g] oxazole,[65d] thiazole[65h] or pyridine[65c] as N-donor group (Figure 1.2.2). The latest innovation in the design of ligands for this process was the replacement of the phosphine/phosphinite moiety by a biaryl phosphite group.[50e, 66] The presence of biaryl-phosphite moieties in these P,N-ligands provides greater substrate versatility than previous Ir-phosphine/phosphinite, N catalyst systems. Nowadays, several unfunctionalized olefins, vinyl phosphonates, vinyl fluorides, CF_3-substituted olefins, vinyl silanes, enol phosphinate esters, enol ethers, enamines, and even heteroaromatic rings, can be hydrogenated.[50]

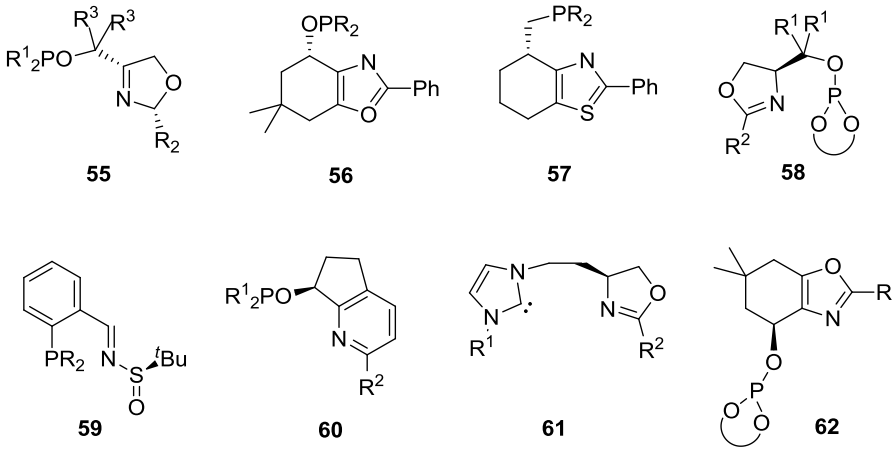
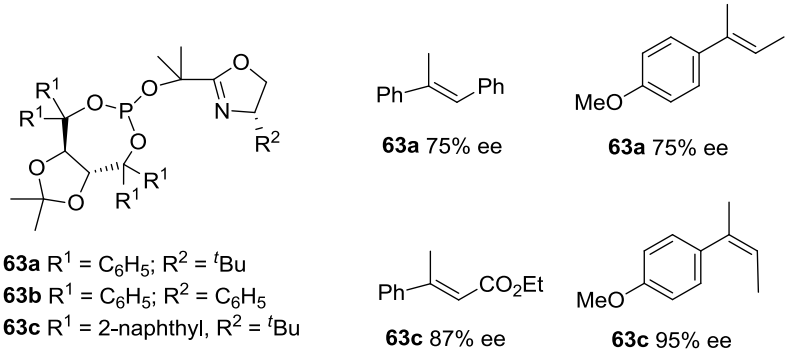


Figure 1.2.2. Representative chiral ligands applied to the Ir-catalyzed asymmetric hydrogenation of minimally functionalized olefins.

1.2.2.1 Phosphorus-nitrogen donor ligands

Although carbohydrate-based ligands have been successfully used in other enantioselective reactions, only two reports have been published on the highly enantioselective Ir-catalyzed asymmetric hydrogenation of unfunctionalized olefins using this type of ligand.

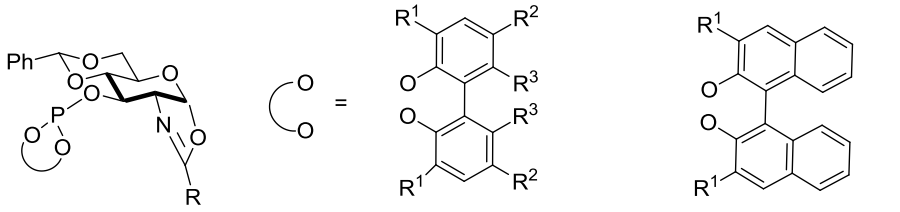
The first application of carbohydrate ligands in this process used the **TADDOL-**based phosphite-oxazoline ligands **63** developed by Pfaltz and coworkers (Figure 1.2.3). These ligands provided enantioselectivities up to 95% in the hydrogenation of a limited range of *E*- and *Z*-trisubstituted alkenes (Figure 1.2.3).[67] However, they required high catalyst loadings (4 mol %) and high pressures (100 bars) to achieve full conversion.



63a $R^1 = C_6H_5$; $R^2 = {}^t$Bu
63b $R^1 = C_6H_5$; $R^2 = C_6H_5$
63c R^1 = 2-naphthyl, $R^2 = {}^t$Bu

Figure 1.2.3. TADDOL-based phosphite-oxazoline **63**. Summary of the best results obtained.

Diéguez and Andersson applied pyranoside biaryl phosphite-oxazoline ligands derived from D-(+)-glucosamine (Figure 1.2.4).[55,66a] The modular ligand design has been shown to be highly successful not only at finding highly selective ligands for each substrate, but also at identifying two general ligands (**68c** and **68e**) that perform well over the entire range of *E*- and *Z*-trisubstituted substrates (Figure 1.2.5). Even the performance of the very challenging class of terminally disubstituted olefins is good. The enantioselectivity was below 90% for olefins with two similarly sized substituents, such as aryl *vs* aryl or *n*-alkyl, but even a moderate size difference like aryl *vs n*-alkyl allowed good enantioselectivities in the range 90-99%. It should be pointed out that these catalysts are also very tolerant to the presence of a neighboring polar group. Thus, a range of allylic alcohols, acetates, α,β-unsaturated ketones, α,β-unsaturated esters and vinylboronates were hydrogenated in high enantioselectivities (ee's up to >99%).

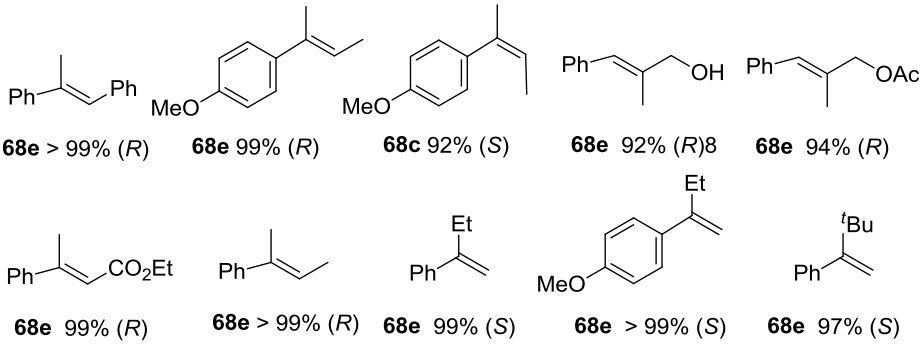


64 R = Me
65 R = ^{i}Pr
66 R = ^{t}Bu
67 R = Bn
68 R = C_6H_5

a $R^1 = R^2 = R^3 = H$
b $R^1 = R^2 = Me$; $R^3 = H$
c $R^1 = R^2 = {}^{t}Bu$; $R^3 = H$
d $R^1 = {}^{t}Bu$; $R^2 = OMe$; $R^3 = H$
e $R^1 = SiMe_3$; $R^2 = R^3 = H$
f $(S)^{ax}$; $R^1 = {}^{t}Bu$; $R^2 = R^3 = Me$
g $(R)^{ax}$; $R^1 = {}^{t}Bu$; $R^2 = R^3 = Me$

h $(S)^{ax}$; $R^1 = H$
i $(R)^{ax}$; $R^1 = H$
j $(S)^{ax}$; $R^1 = SiMe_3$
k $(R)^{ax}$; $R^1 = SiMe_3$

Figure1.2.4. Pyranoside phosphite-oxazoline ligands **64**-**68a-k**.

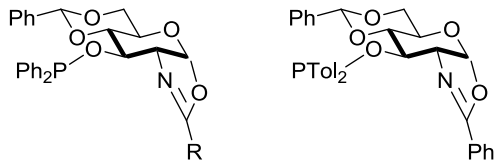


68e > 99% (*R*) **68e** 99% (*R*) **68c** 92% (*S*) **68e** 92% (*R*)8 **68e** 94% (*R*)

68e 99% (*R*) **68e** > 99% (*R*) **68e** 99% (*S*) **68e** > 99% (*S*) **68e** 97% (*S*)

Figure 1.2.5. Summary of the best results obtained in the asymmetric hydrogenation of unfunctionalized olefins using ligands **68c**,**e**. In all cases full conversions were obtained.

Recently our group applied pyranoside phosphinite-oxazoline ligands **69**-**72** (Figure 1.2.6), related to privileged phosphite-oxazoline ligands **64**-**68**, to the Ir-catalyzed hydrogenation of minimally functionalized olefins.[68] The best results were obtained with ligands **71** and **72** (ee's up to 93%). The reactivity and selectivity of these pyranoside Ir-phosphinite-oxazoline catalysts are high but somewhat lower compared to privileged phosphite-oxazoline analogues (Figure 1.2.4).[55,66a] Nevertheless, these Ir/phosphinite-oxazoline systems represent one of the very few phosphinite-containing P,N catalysts[69] able to hydrogenate a broad range of terminal disubstituted olefins with high enantioselectivities.



69: R = Me
70: R = ^{t}Bu
71: R = Ph

72

Figure 1.2.6. Pyranoside phosphinite-oxazoline ligands **69-72**.

1.2.2.2 Phosphorus non-N-donor heterodonor ligands

As previously mentioned, Ir complexes containing chiral P,N- ligands emerged as powerful tools in the asymmetric hydrogenation of minimally functionalized olefins.[50] However, the possibility of changing the nature of the N-donor atom in these heterodonor ligands has never been contemplated. Our group has recently reported new classes of non N-donor heterodonor ligands thioether-phosphite and thioether-phosphinite (Figure 1.2.7) for the asymmetric Ir-catalyzed hydrogenation of minimally functionalized olefins.[62,70,71]

These ligands are derived from natural D-(+)-xylose and they combine the advantages of phosphite/phosphinite and sugar cores. Moreover, the introduction of a thioether moiety in the ligand design is beneficial because the S atoms become a stereogenic center when coordinated to metal, which moves the chirality closer to the metal, and the thioether group is more stable than the oxazoline moiety.[5c,e] The results indicated that enantioselectivities were highly affected by the position of the thioether group at either C-5 or C-3 of the furanoside backbone, the configuration of C-3, the thioether substituent, the substituents/configuration in the biaryl phosphite moiety (**a**–**h**) and the replacement of the phosphite moiety by a phosphinite group. Enantioselectivities were excellent (ee's up to >99%) in a wide range of *E*- and *Z*-trisubstituted alkenes with ligands **83a** and **83e**, which contain the optimal combination of ligand parameters. It should be pointed out that these catalysts are also very tolerant to the presence of a neighboring polar group. Thus, a range of allylic alcohols, acetates, α,β-unsaturated esters and vinylboronates were hydrogenated in high enantioselectivities, and again ligands **83a** and **83e** provided the best results (ee's from 90% to 99%). Also these ligands were applied in the asymmetric hydrogenation of terminal disubstituted aryl/alkyl olefins. For this substrate class, the results indicated that enantioselectivity is dependent on the nature of the alkyl

substrate substituent, which has been attributed to the presence of an isomerization process under hydrogenation conditions. Enantioselectivities were therefore best in the asymmetric reduction of aryl and heteroaryl/*tert*-butyl substrates with ligands **83a** and **83e-f** (ee's up to 99%).[62]

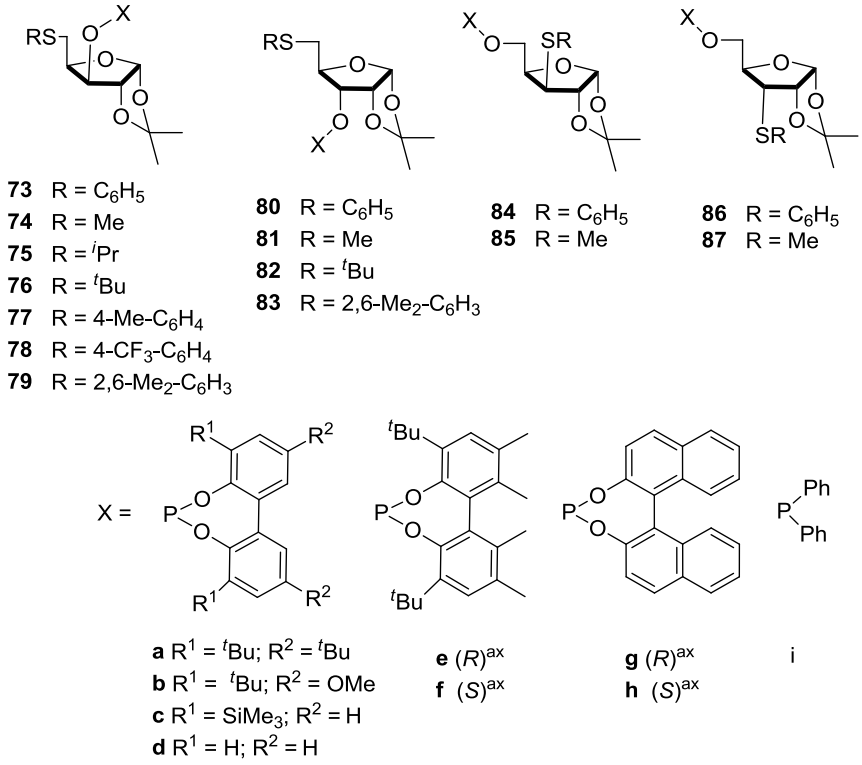


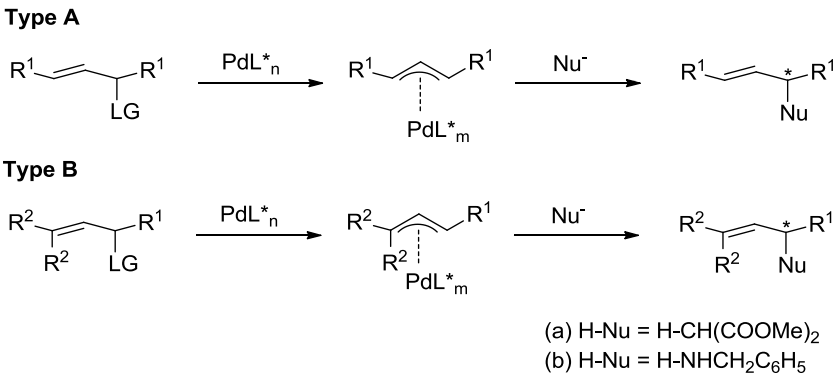
Figure 1.2.7. Thioether-phosphite/phosphinite ligands **73**-**87a**-**i**.

1.3 Asymmetric Pd-catalyzed allylic substitution

Enantioselective Pd-catalyzed allylic substitution is an important synthetic strategy for the construction of asymmetric carbon-carbon and carbon-heteroatom bonds. Besides having a high level of asymmetric induction, the fact that it is tolerant to a wide range of functional groups means that it is an attractive option for application in the synthesis of optically active compounds.[1b,56b,72]

In this process, an allylic racemic substrate which contains a leaving group (LG), normally an acetate or carbonate, is attacked by a nucleophile (typically a carbon or nitrogen nucleophile). Scheme 1.3.1 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 the 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 with two identical geminal substituents at one of the allylic termini react via the 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 1.3.1. Two classes of asymmetric allylic substitution reactions.

In this reaction, the range of substrates tested (linear and cyclic) is quite wide (Figure 1.3.1). However, 1,3-diphenylprop-2-enyl acetate is widely used as 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.[1b,56b,72] However, the most widely used catalysts are palladium complexes. A wide range of carbon- and heteroatom-stabilized nucleophiles such a carbonyl, sulfone, nitrile or nitro groups have been used in this process. Nevertheless, dimethyl malonate has become the standard nucleophile for testing new catalysts. There are only few examples of enantioselective reactions with non-stabilized nucleophiles such as diorganozinc or Grignard reagents.[1b,56b,72]

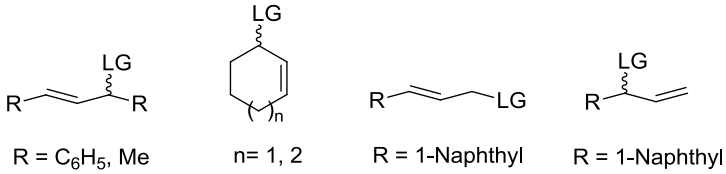


Figure 1.3.1. The most common substrates for the enantioselective allylic substitution.

1.3.1 Mechanism

The catalytic cycle for Pd-catalyzed asymmetric allylic substitution with stabilized nucleophiles is well established and involves four steps (Figure 1.3.2).[1b,56b,72] The first step is the coordination of an allylic substrate **89** to the catalyst precursor **88**, which enters the cycle at the Pd(0) oxidation level. Both Pd(0) and Pd(II) complexes can be used as precatalysts because Pd(II) is easily reduced *in situ* by the nucleophile to the Pd(0) form. The most widely used precursors are $Pd_2(dba)_3$·dba, (dba = dibenzylideneacetone), $Pd(OAc)_2$ and $[Pd(\eta^3\text{-}C_3H_5)(\mu\text{-}Cl)]_2$. The next step is the oxidative addition of complex **90** to form the π-allyl intermediate **91**, which is usually the rate-determining step of the reaction. The product of this oxidative addition has two positions that are susceptible to nucleophilic attack (C-1 and C-3). After nucleophilic addition, an unstable Pd(0)-olefin complex **92** is produced, which readily releases the final product **93**.

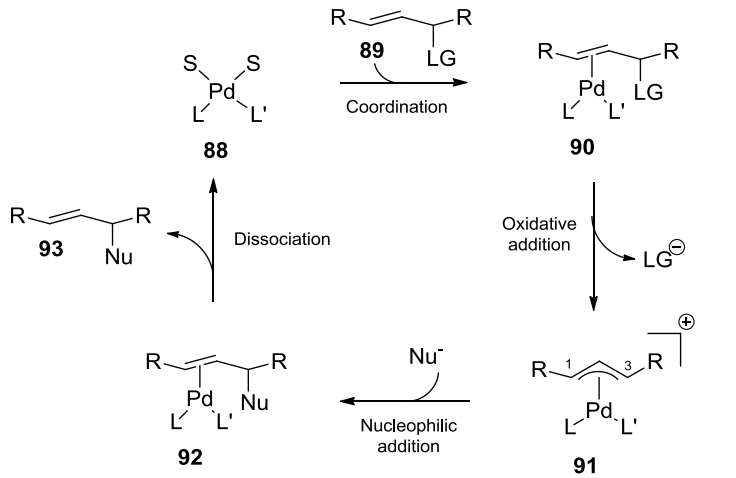


Figure 1.3.2. Accepted mechanism for Pd-catalyzed allylic substitutions.

It is accepted, that the enantioselectivity of the process is controlled by the external nucleophilic attack on the most electrophilic allylic carbon terminus of the π-allyl intermediate **91**.[1b,56b,72] Hence, the π-allyl intermediate **91** plays an important role in the catalytic cycle and is the intermediate that controls regio- and enantioselectivity. This intermediate can be isolated in the absence of nucleophiles and it is known, that allyl complex type-**91** can show a dynamic behavior in solution, which leading in a mixture of isomers (Figure 1.3.3).

If we assume that the reaction rates are similar for all possible isomers, a single isomer needs to be formed if enantioselectivities are to be high. Both the oxidative addition and the nucleophilic attack generally occurs stereoselectively with inversion of configuration. Therefore, if the configuration of the intermediate allyl complex is not changed by isomerization, the overall process **88** to **93** proceeds with the retention of configuration; for instance, the nucleophile is introduced on the same side of the allyl plane that was occupied by the leaving group LG.

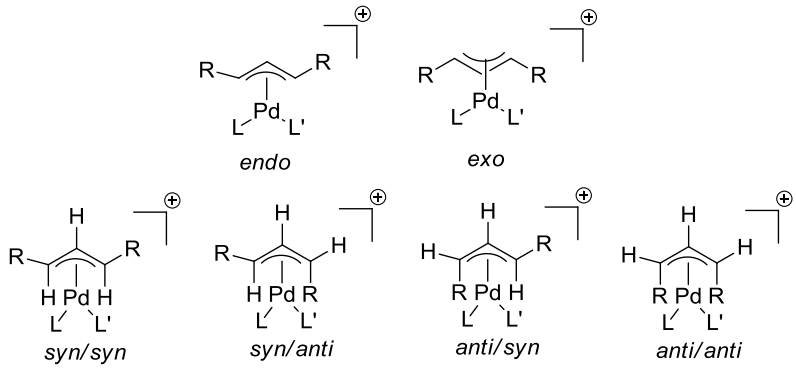


Figure 1.3.3. Possible isomers adopted by the Pd-allyl complex **91**.

1.3.2 Ligands

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**, the scope of standard diphosphines in this process seems limited (Figure 1.1.2).[1,72]

Most of the successful ligands reported to date for this process have been designed using three main strategies. The first one, developed by Hayashi and coworkers, was the use of a secondary interaction of the nucleophile with a side chain of the ligand to direct the approach of the nucleophile to one of the allylic

terminal carbon atoms (Figure 1.3.4).[73] The second one, developed by Trost and co-workers, was to increase the ligand's bite angle in order to create a chiral cavity in which the allyl system is perfectly embedded (Figure 1.3.4). This idea paved the way for the successful application of ligands with large bite angles for the allylic substitution of sterically undemanding substrates.[74] The third strategy, developed by groups led by Helmchen, Pfaltz and Williams, was the use of heterodonor ligands that result in an electronic discrimination of the two allylic terminal carbon atoms due to the different *trans* influences of the donor groups (Figure 1.3.4).[75] This made it possible to successfully use a wide range of heterodonor ligands (mainly P,N-ligands) in allylic substitution reactions.[1,72] More recently, we found that the use of biaryl phosphite-containing heterodonor ligands is highly advantageous by overcoming the most common limitations of this process, such as low reaction rates and high substrate specificity.[76] Introducing a biaryl phosphite in the ligand design was beneficial because of its larger π-acceptor ability, which increases reaction rates, and because of its flexibility that allows the catalyst chiral pocket to adapt to both hindered and unhindered substrates. In addition, the presence of a biaryl phosphite moiety was also beneficial in the allylic substitution of more challenging monosubstituted substrates. Regioselectivity towards the desired branched isomer in this substrate class increases thanks to the π-acceptor ability of the phosphite moiety, which decreases the electron density of the most substituted allylic terminal carbon atom via the *trans* influence, favoring the nucleophilic attack to this carbon atom.[76]

Other ligands, such as bidentate nitrogen and sulfur, have also exhibited very good catalytic behavior.[5c,72b,e]

Carbohydrate ligands have only recently shown their huge potential as a source of highly effective chiral ligands in the Pd-catalyzed asymmetric allylic substitution reaction. Several types of ligands, mainly heterodonors, have been developed for this process and some of the results are among the best ever reported.[2]

In the next section, we summarize the most relevant catalytic data published for the Pd-catalyzed allylic substitution reactions with carbohydrate ligands.

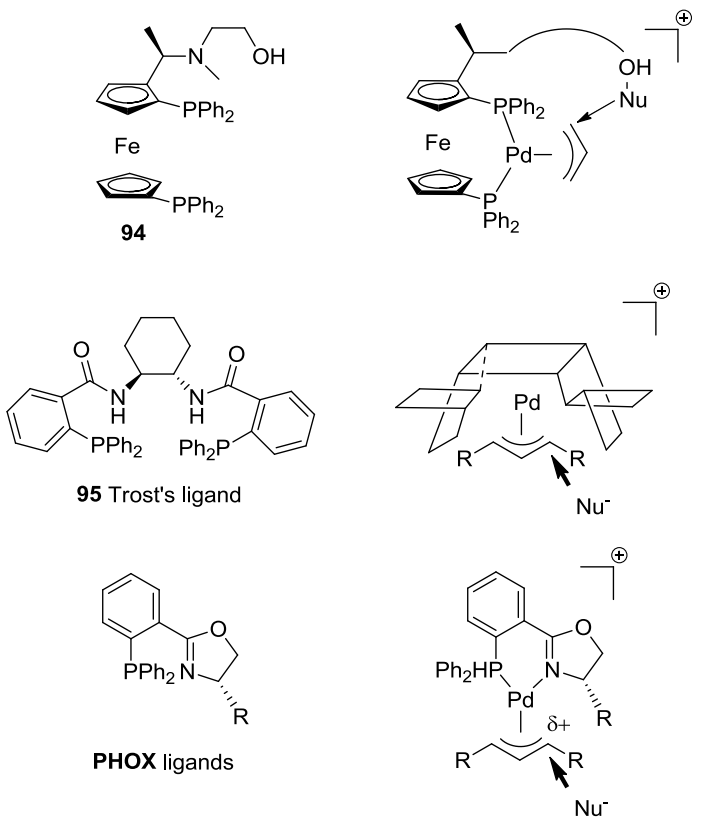


Figure 1.3.4. Representative ligands developed for the Pd-catalyzed allylic substitution reaction.

1.3.2.1 P-donor ligands

Phosphine ligands

In 2000, the above mentioned C_1-symmetric diphosphine ligands **12-14** with a furanoside backbone (Figure 1.1.6) were applied in Pd-catalyzed asymmetric allylic substitution reactions with moderate success.[77] The results for the allylic alkylation of dimethyl malonate to 1,3-diphenylprop-2-enyl acetate showed that the configuration of C-5 has no relevant influence on enantiodiscrimination (ee's up to 61%).

At the same time, one of the best results obtained in the allylic substitution that used phosphine ligands was achieved with the family independently developed by RajanBabu and Zhang. These authors reported the use of the above mentioned diphospholane ligands **6** (Figure 1.1.4) and

phospholanes **96-98**, derived from D-mannitol, in the Pd-catalyzed allylic alkylation of substrate 1,3-diphenylprop-2-enyl acetate (Figure 1.3.5), with high enantioselectivities (ee's up to 99%).[78,23c] It was also observed that the sense of the asymmetric induction is controlled by the absolute stereochemistry of the P-carrying carbons. Both enantiomers of the product can therefore be obtained.

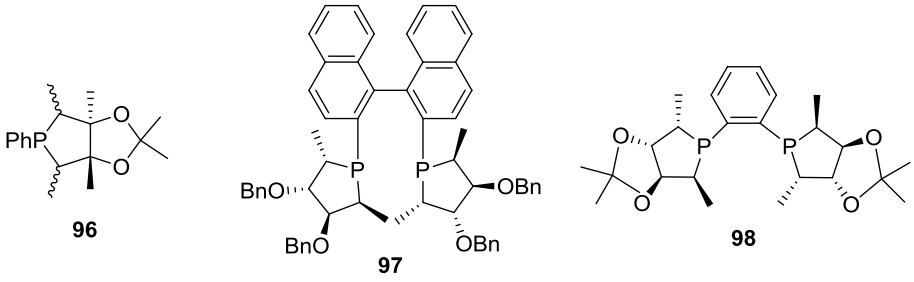


Figure 1.3.5. Phospholane ligands derived from D-mannitol.

In 2006, Ruffo and coworkers developed a modification of the Trost-bis(phosphinoamides) ligands using diamines based on D-glucose and D-mannose as chiral auxiliaries (Figure 1.3.6, ligands **99** and **100**).[79] These ligands provided high enantioselectivities in the 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 D-glucose (**99**) to D-mannose (**100**) derivative ligands.

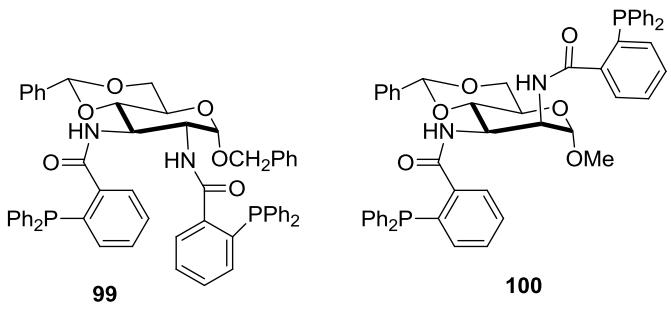
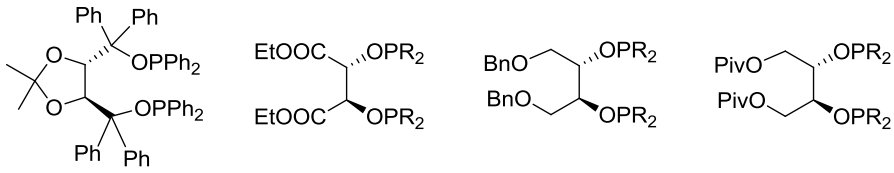


Figure 1.3.6. Bis(phosphinylamides) ligands **99** and **100** developed by Ruffo et al.

Phosphinite ligands

In 1995, Seebach and coworkers first prepared C_2-symmetric diphosphinite **101** from TADDOL, tested it in the asymmetric allylic substitution and obtained ee's of up to 76% ee (Figure 1.3.7).[80] Subsequently, RajanBabu and coworkers tested the above mentioned ligands **16** (R^2 = Ph) (Figure 1.1.8) and ligands **102-104** (Figure 1.3.7), derived from tartaric acid, in the Pd-catalyzed asymmetric allylic alkylation of diethyl malonate to 1,3-diphenylprop-2-enyl acetate with low-to-moderate enantioselectivities. For ligands **16**, the best enantioselectivity (59% ee) was achieved with the ligand containing cyclohexyl as substituent R.[1, 81] Interestingly, electron-withdrawing and electronic-rich diphosphinite ligands lead to products with opposite stereochemistries. Moreover, sterically bulky substituents have the same effect as electron-rich ones. For diphosphinite ligands **102-104**, the electronic effects were similar to those with ligands **16**, but enantioselectivities were up to 77% (Figure 1.3.7).[82]



101 (76%(*R*)) **102** (73%(*R*)) **103** (31%(*S*)) **104** (77%(*R*))

Figure 1.3.7. Diphosphinite ligands **101-104**. Enantioselectivities are shown in parentheses.

Phosphite ligands

The series of previously reported furanoside diphosphite ligands **25-30** (Figure 1.1.12) were also successfully applied in the Pd-catalyzed allylic substitution of diethyl malonate and benzylamine to several acyclic and cyclic allylic esters (Figure 1.3.8).[83,77a,84]

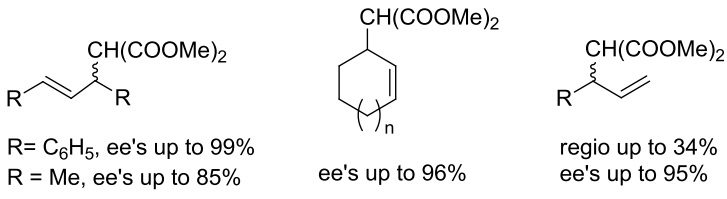


Figure 1.3.8. Acyclic and cyclic allylic esters tested with ligands **25**-**30**.

Results indicated that activities were best when the substituent at C-5 was methyl and when the ligand contained bulky substituents at the *ortho* positions on the phosphites and electrodonating substituents at the *para* positions of the biphenyl moieties (i.e., b ~ c > d > a). Enantioselectivities were affected by the substituent at C-5, the phosphite moieties, the configuration of the carbon atoms C-3 and C-5, and the configurations of the biaryl moieties. Enantioselectivities were best with ligand **27c**, which has a glucofuranoside backbone and bulky *tert*-butyl substituents 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 **25c** was also used to stabilize Pd-nanoparticles. These particles catalyzed the allylic alkylation of 1,3-diphenylprop-2-enyl acetate 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.[85]

Next, the above mentioned furanoside ligands of C_2-symmetry **31** and **33** (Figure 1.1.13), systematically modified at positions 2 and 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 1,3-diphenylprop-2-enyl acetate. Ligand **31** provided excellent activities and enantioselectivities (ee's up to 99% (*S*)).[86]

More recently, Claver and coworkers have reported further modifications to the privileged ligand **27c** by: (a) replacing the methyl substituent at C-5 with increasingly sterically demanding ether substituents (ligands **105**-**107**, Figure 1.3.9) and (b) replacing the 1,2-acetal protection with an alkyl chain in C-2 (ligands **108** and **109**, Figure 1.3.9).[87] These ligands were applied to the Pd-catalyzed allylic alkylation of di- and monosubstituted linear substrates. The best enantioselectivities (up to 98%) were obtained in the Pd-allylic alkylation of 1,3-diphenylprop-2-enyl acetate using ligand **108a**.

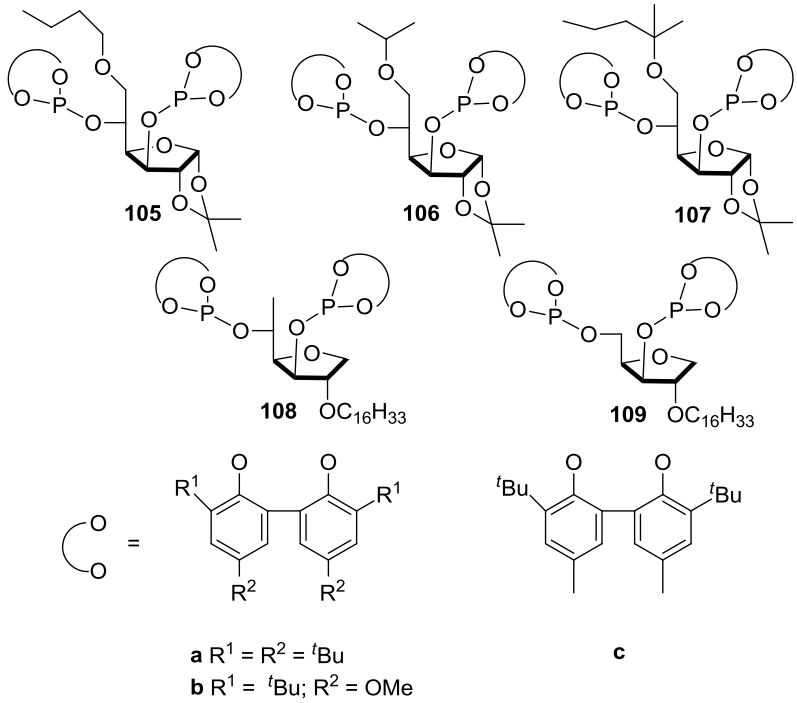


Figure 1.3.9. Furanoside diphosphite ligands **105**-**109a**-**c**.

Phosphoroamidite ligands

In recent decades, there has been a huge advance in the use of phosphoroamidite ligands for several asymmetric processes.[88] However, to the best of our knowledge, only one family of diphosphoroamidite ligands (**110**) based on carbohydrates has been successfully applied in asymmetric catalysis (Figure 1.3.10). Good-to-excellent activities and enantioselectivities (ee's up to 95%) have been obtained in Pd-catalyzed allylic alkylation for several di- and monosubstituted linear and cyclic substrates (Figure 1.3.10).[89] The results indicate that catalytic performance is highly affected by the substituents and the axial chirality of the biaryl moieties of the ligand. The study of the 1,3-diphenyl and cyclohexenyl Pd-π-allyl intermediates indicates that the nucleophilic attack takes place predominantly at the allylic terminal carbon atom located *trans* to the phosphoroamidite moiety attached to C-5.

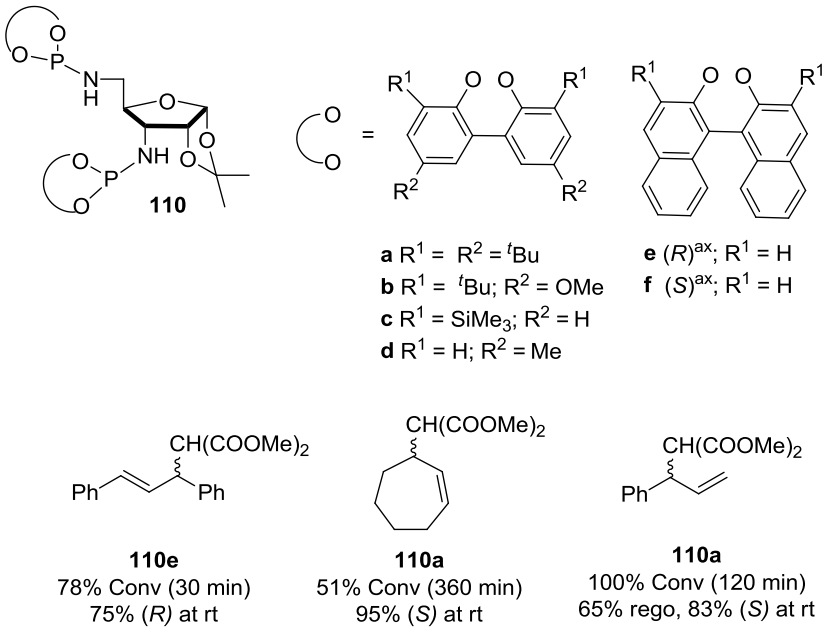


Figure 1.3.10. Furanoside diphosphoroamidite ligands **110**. Summary of the best results obtained with acyclic and cyclic substrates.

1.3.2.2 S-donor ligands

Sulfur donor ligands have been used much less than phosphorus ligands in Pd-catalyzed allylic substitution reactions because a complex mixture of diastereomers may be formed when the thioether ligand coordinates to the metal, which can lead to a decrease in stereoselectivity if the relative rates of the catalytically active intermediates, are similar. Despite this problem, high enantiomeric excesses have been achieved.[5c,72f] In this context, Khiar and coworkers used a combinatorial approach to find the best dithioether ligand **111** (Figure 1.3.11) from a library of 64 potential ligands made by combining four linkers, four carbohydrate residues and four protective groups (Figure 1.3.12) for the Pd-catalyzed allylic alkylation of dimethyl malonate to 1,3- diphenylprop-2-enyl acetate (ee's up to 90%).[90a] To have access at both enantiomers of the alkylation product, the authors successfully prepared ligands **112** and **113** derived from D-galactose and D-arabinose, respectively (Figure 1.3.11).[90b] These ligands act as *pseudo*-enantiomers.

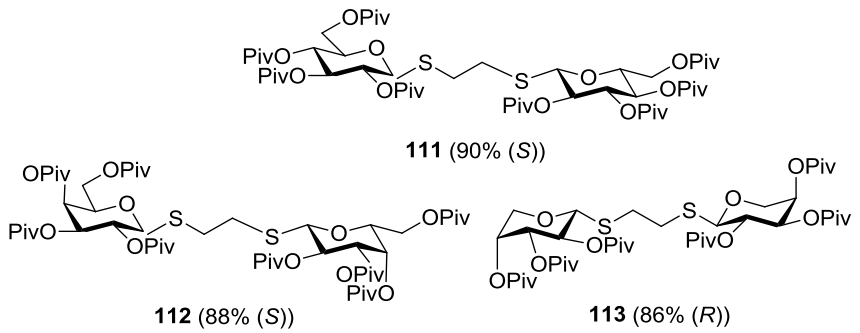


Figure 1.3.11. Summary of the best results obtained in the Pd-catalyzed allylic alkylation of 1,3-diphenylprop-2-enyl acetate using dithioether ligands **111**-**113**.

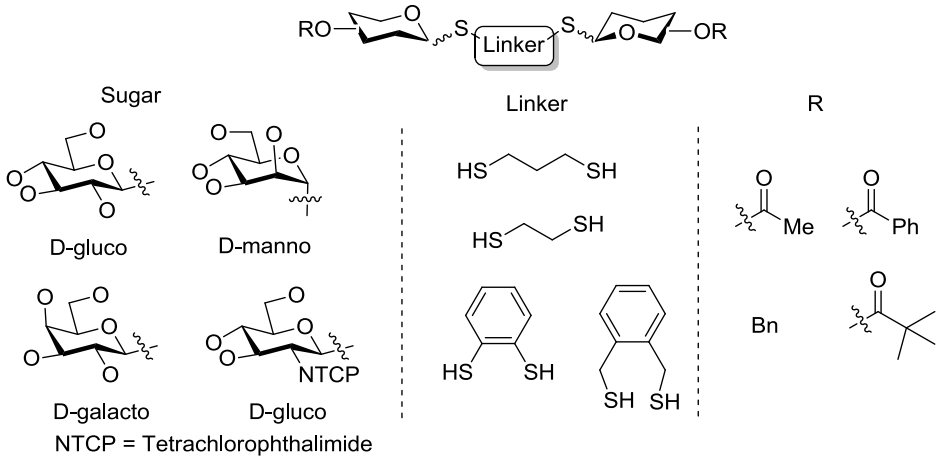


Figure 1.3.12. Dithioether ligand library studied by Khiar and coworkers.

1.3.2.3 Heterodonor ligands

P-S ligands

Several combinations of P-S ligands have been studied: for example, phosphine-thioethers, phosphinite-thioethers, phosphine-oxathianes and phosphitethioethers. In particular, the phosphine-thioethers, phosphinite-thioethers and phosphine-oxathianes have proven to be effective in enantioselective Pd-catalyzed allylic substitutions.

Ferrocenylphosphine-thioglucoside ligand **114** (Figure 1.3.13) with multiple stereogenic units afforded an ee of 88% in the palladium allylic substitution of diethyl malonate with 1,3-diphenylprop-2-enyl acetate.[91] However, when the

thiosugar moiety was the sole stereogenic unit on ligands **115** (Figure 1.3.13), enantioselectivities were only moderate (ee's up to 64%).[92]

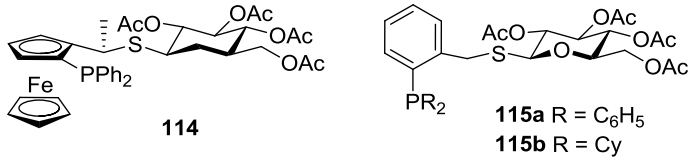


Figure 1.3.13. Ferrocenyl-based phosphine-thioether ligands

Khiar and coworkers reported the successful use of phosphine-thioether ligand **116** (Figure 1.3.14) in the Pd-catalyzed asymmetric allylic alkylation of 1,3-diphenylprop-2-enyl acetate (ee's up to 90% (*S*)).[93] The same group also reported the application of ligand **117** (Figure 1.3.14), but with little success (ee's up to 30% (*R*)).[94]

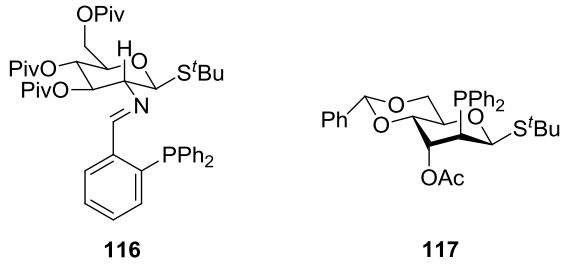


Figure 1.3.14. Phosphine-imine thioglycoside ligand **116** and phosphine-thioether ligand **117**.

In 2003, the phosphine-oxathiane ligand **118** (Figure 1.3.15), derived from D-(+)-xylose, was developed for Pd-catalyzed allylic substitution reactions. Good enantioselectivities were obtained in the addition of dimethyl malonate and benzylamine to 1,3-diphenylprop-2-enyl acetate (ee's up to 91% (*S*) and 94% (*R*), respectively).[95]

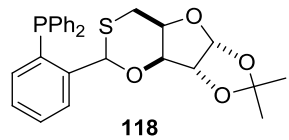
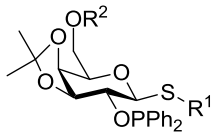


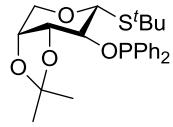
Figure 1.3.15. Phosphine-oxathiane ligand **118**.

The series of above mentioned phosphinite-thioether ligands with a furanoside backbone **53** (Figure 1.1.21), derived from D-(+)-xylose, were applied in the Pd-catalyzed allylic substitution of mono- and disubstituted linear and cyclic substrates (ee's up to 95%).[96] 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. Enantioselectivities were best when the bulkiest ligands **53c-d** were used.

At the same time, the phosphinite-thioether ligands **119** and **120** with a pyranoside backbone (Figure 1.3.16) were successfully applied in the Pd-catalyzed allylic substitution of 1,3-diphenylprop-2-enyl acetate (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 ligands **119a** and **120**.[97]



119



120

a R^1 = 2-OMe-C_6H_4; R^2 = Ac
b R^1 = 4-Me-C_6H_4; R^2 = Ac
c R^1 = ^{t}Bu; R^2 = Ac
d R^1 = ^{t}Bu; R^2 = H
e R^1 = ^{t}Bu; R^2 = TBDMS

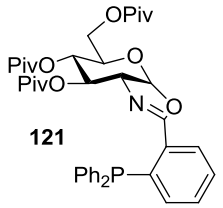
Figure 1.3.16. Phosphinite-thioglycoside ligands **119** and **120**.

Several combinations of P-S ligands mainly phosphine-thioether and phosphinite-thioether have been studied and have prove to be effective but less attention has been paid to catalysts containing phosphite-thioether ligands. Until now, there were only three phosphite-thioether ligands applied in the Pd-catalyzed allylic substitution but with moderate success (ligands **54a**-**b**,**d**; Figure 1.1.22).[83]

P-N ligands

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

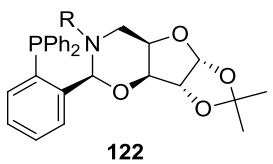
Kunz and coworkers developed a phosphine-oxazoline ligand **121** derived from D-glucosamine for the Pd-catalyzed allylic alkylation of dimethyl malonate to symmetrically and non-symmetrically substituted allyl acetates with high enantioselectivities (ee's up to 98%) (Figure 1.3.17).[98] These results are in line with a nucleophilic attack *trans* to the phosphorus atom.



121

Figure 1.3.17. Phosphine-oxazoline ligand **121** developed by Kunz and coworkers.

In 2003, phosphine-oxazine ligands **122**, related to ligand **118** (Figure 1.3.15), were developed for the Pd-catalyzed allylic substitution of 1,3-diphenylprop-2-enyl acetate (Figure 1.3.18). Enantioselectivities up to 75% were obtained.[95c]



122

	R	%ee
a	^{i}Pr	46 (*S*)
b	Bn	75 (*S*)
c	$CH_2C_{10}H_7$	49 (*S*)
d	(*R*)-$CHMeC_6H_5$	73 (*S*)

Figure 1.3.18. Phosphine-oxazine ligands **122**. This figure also shows the enantioselectivities obtained.

Several phosphine-imine ligands with a pyranoside backbone **123-128** have been developed for Pd-catalyzed allylic substitution reactions (Figure 1.3.19).[99] The results indicated that having the imine-phosphine residue at C-2 (ligands **127**) provided better enantioselectivities than having it at the C-1 position of the pyranoside backbone (ligands **123-126**). It should be noted that ligands with the general structure **126** have provided enantioselectivities up to 99% in the amination of 1,3-diphenylprop-2-enyl acetate using morpholine as the nucleophile.[99c] Recently, the imine group in ligands with the general structure **126** has been replaced by an amine group (ligand **128**, Figure 1.3.19). The results were also good.[99d]

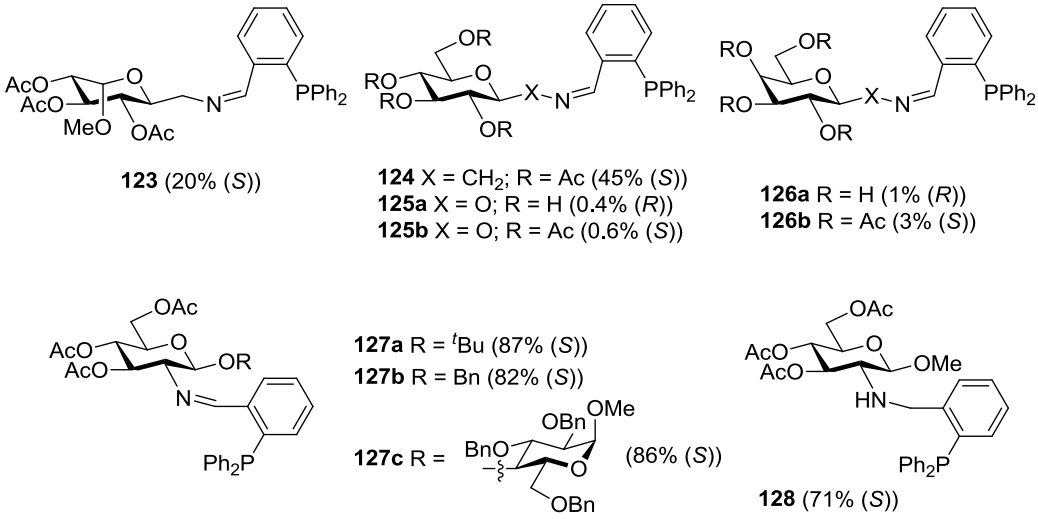
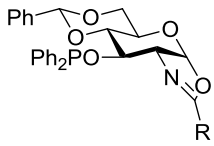


Figure 1.3.19. Phosphine-imine **123-127** and phosphine-amine **128** ligands. This figure also shows the enantioselectivities obtained in the Pd-allylic alkylation of 1,3-diphenylprop-2-enyl acetate.

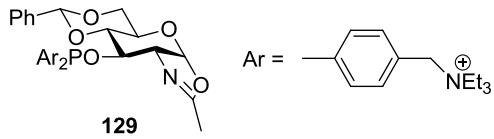
Uemura and coworkers successfully applied the previously mentioned phosphinite-oxazoline ligands **69**-**71** (Figure 1.2.6) in the Pd-catalyzed allylic substitution reactions (Figure 1.3.20). [100] These ligands showed high enantioselectivities with 1,3-diphenylprop-2-enyl acetate as a substrate, but low-to-moderate enantioselectivities for unhindered linear and cyclic substrates. The results of the allylic alkylation of dimethyl malonate with 1,3- diphenylprop-2-enyl acetate indicated that the best enantioselectivity was obtained with the smallest substituent on the oxazoline (R = Me, ligand **69**). Their results also indicate that the nucleophilic attack took place *trans* to the phosphorus atom thought an *endo* π-allyl Pd-intermediate.



	R	%ee
69	Me	96 (*S*)
70	^{t}Bu	83 (*S*)
71	C_6H_5	94 (*S*)

Figure 1.3.20. Phosphinite-oxazoline ligands **69**-**71**. This figure also shows the enantioselectivities obtained in the allylic alkylation of substrate 1,3-diphenylprop-2-enyl acetate.

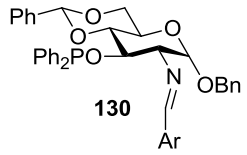
Water-soluble ligand **129** (Figure 1.3.21), related to **69**, was effective for the Pd-catalyzed allylic alkylation of several nucleophiles with 1,3-diphenylprop-2-enyl acetate in aqueous or biphasic media (ee's up to 85%).[101]



129

Figure 1.3.21. Water-soluble ligand **129**.

In 2010, Chen and coworkers developed the new carbohydrate-based phosphinite-imine ligands **130a-g** (Figure 1.3.22). These ligands, derived from *N*-acetylglucosamine, provided high enantioselectivities in the Pd-catalyzed asymmetric allylic alkylation of 1,3-diphenylprop-2-enyl acetate with dimethyl malonate (ee's up to 95%).[102]



130

	R	%ee
a	C_6H_5	82 (*S*)
b	4-Cl-C_6H_4	83 (*S*)
c	4-OMe-C_6H_4	75 (*S*)
d	4-NO_2-C_6H_4	95 (*S*)
e	2-CF_3- C_6H_4	57 (*S*)
f	3-Cl-C_6H_4	86 (*S*)
g	3-NO_2-C_6H_4	89 (*S*)

Figure 1.3.22. Carbohydrate-based phosphinite-imine ligands **130a**-**g**. This figure also shows the enantioselectivities obtained in the allylic alkylation of 1,3-diphenylprop-2-enyl acetate.

The above mentioned phosphite-oxazoline ligands **64**-**68a**-**k** (Figure 1.2.4), related to ligands **69-71** (Figure 1.3.20) were applied to the Pd-catalyzed allylic substitution of several substrate types (Figure 1.3.23).[103] The introduction of a biaryl phosphite moiety in the ligand design proved to be highly advantageous.[104] Ligands **64**-**68a**-**k**, then, 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 opens up the possibility of using the Pd-phosphite-oxazoline catalytic systems to a wide range of different substrate types in this

catalytic process (Figure 1.3.23). These ligands were also used to stabilize Pd-nanoparticles.[105]

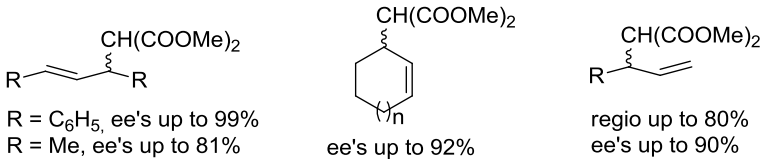


Figure 1.3.23. Acyclic and cyclic allylic esters tested with ligands **64**-**68a**-**k**.

Pfaltz and coworkers have also applied the previously reported phosphite-oxazoline ligand **63** (Figure 1.2.3) 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 acetate (ee's up to 94%), whereas enantioselectivities were low in the reaction of substrate 1,3-diphenylprop-2-enyl acetate (ee's up to 20%).[106]

P-O ligands

Phosphine-amide ligands **131-136** (Figure 1.3.24) with a pyranoside backbone have been extensively studied for the Pd-catalyzed allylic alkylation of 1,3-diphenylprop-2-enyl acetate with dimethyl malonate.[99c,107] The results clearly show 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. Ligands **131**, **135** and **136** that forms a six-membered chelate ring and with a β anomeric carbon afforded higher enantioselectivities than ligands **132** with an α anomeric carbon and **134** that form a seven membered chelate ring. Moreover, the results achieved with ligands **135** and **136** indicated a cooperative effect between the additional stereocenters in **135** and the carbohydrate backbone that resulted in a matched combination for ligand (*S*)-**135**.

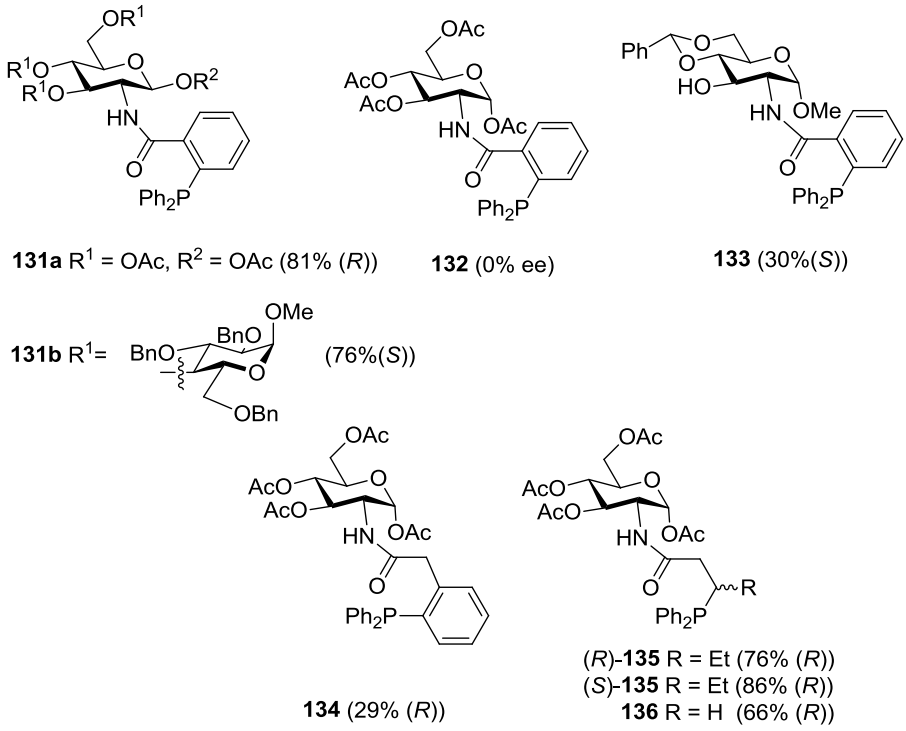
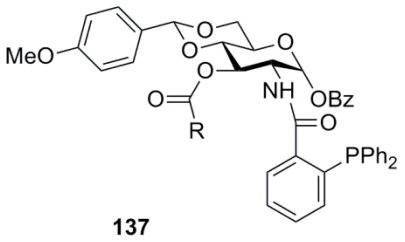
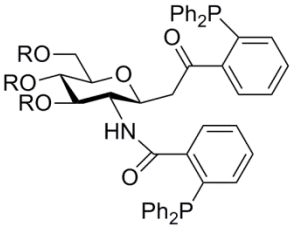


Figure 1.3.24. Phosphine-amide ligands **131**-**136**. The enantioselectivities are also shown in brackets.

Recently, Ruffo and coworkers reported the modular ligand library naplephos (**137**, Figure 1.3.25), derived from *N*-acetylglucosamine, for the Pd-catalyzed allylic alkylation of 1,3-diphenylprop-2-enyl acetate with dimethyl malonate. Enantioselectivities were good (ee's up to 97%).[108] These ligands were also effective in the desymmetrization of *meso*-cyclopent-2-ene-1,4-diol (ee's up to 98%).[79b] In the search for the opposite enantiomer of the alkylation product, the same authors developed the *pseudo*-enantiomeric ligands Elpanphos (**138**, Figure 1.3.25).[109]



137



138
a R = Ac
b R = H

a R = 2-C_6H_4-PPh_2; **b** R = Me; **c** R = Bn; **d** R = CH_2Cy;
e R = ^{t}Bu; **f** R = (*R*)-$CHMeC_6H_5$; **g** R = (*S*)-$CHMeC_6H_5$;
h R = $CH(C_6H_5)_2$; **i** R = $CMe(C_6H_5)_2$; **j** R = $CHCy_2$; **k** R = C_6H_5;
l R = $CH_2C_6F_5$

Figure 1.3.25. Naplephos (**137a**-**l**) and Elpanphos (**138a**-**b**) ligands.

P-P' ligands

The first successful family of P-P' carbohydrate ligands contains the above mentioned phosphite-phosphoroamidite ligands **49**-**52** (Figure 1.1.20). These ligands were successfully applied in the Pd-asymmetric allylic substitution (ee's up to 98%; Figure 1.3.26).[110] Interestingly, this ligand family also provides high activity (because of the high π-acceptor capacity of the phosphoroamidite moiety) and high enantioselectivities for different substrate types mono- and disubstituted linear and cyclic substrates (Figure 1.3.26). The related phosphine-phosphite ligands **47** (Figure 1.1.18) have also been used in the model enantioselective Pd-catalyzed allylic alkylation and amination substitutions of 1,3-diphenylprop-2-enyl acetate reactions providing ee's up to 42% (*S*) and 66% (*R*), respectively.[83]

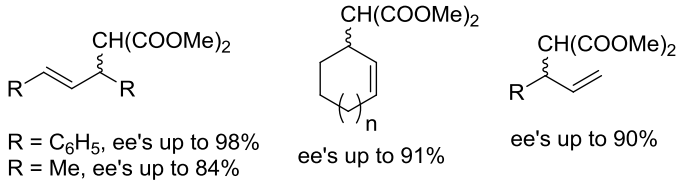


Figure 1.3.26. Acyclic and cyclic allylic esters tested with ligands **49**-**52**.

Pyranoside phosphite-phosphoroamidite ligands **139** (Figure 1.3.27) 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.[111]

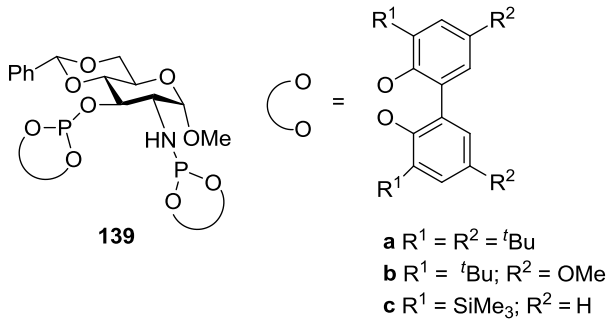
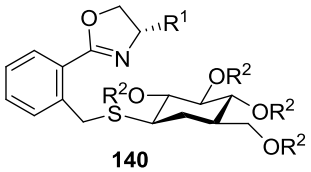


Figure 1.3.27. Phosphite-phosphoroamidite ligands **139**.

N-S ligands

Thioglucoside-derived ligands **140**, containing a chiral oxazoline moiety (Figure 1.3.28), used as ligands in the palladium-catalyzed allylic alkylation of 1,3-diphenylprop-2-enyl acetate have provided some of the best results achieved in this reaction with mixed N,S-donor ligands.[112] 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.



	R^1	R^2	%ee
a	^{i}Pr	C(O)Me	93(*S*)
b	^{i}Pr	C(O)^{t}Bu	97(*S*)
c	C_6H_5	C(O)Me	90(*S*)
d	C_6H_5	C(O)^{t}Bu	96(*S*)

Figure 1.3.28. Thioether-oxazoline ligands **140**. This figure also shows the enantioselectivities obtained in the allylic alkylation of 1,3-diphenylprop-2-enyl acetate.

More recently, the pyranoside thioether-imine ligand **141** (Figure 1.3.29), related to P-S ligand **116** (Figure 1.3.14), was applied in the allylic alkylation of 1,3-diphenylprop-2-enyl acetate with low enantioselectivity (ee's up to 34%).[93]

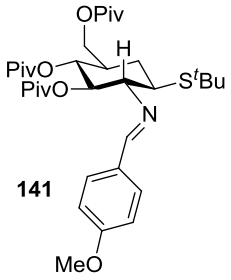
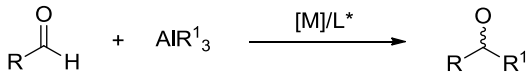


Figure 1.3.29. Thioether-imine ligand **141**.

1.4 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.[113] 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 organometallic reagents because they are economically available in industrial scale from aluminum hydride and olefins.[114] Despite this advantage, trialkylaluminum are less documented.[88g,115,116] In this respect, the few successful catalysts developed for the enantioselective addition of trialkylaluminum to aldehydes (Scheme 1.4.1) can be grouped in two types. The first group is 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.[115a-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%).[115e,f,116a]



Scheme 1.4.1. 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 contaminated with oxo-containing by-products formed through accidental exposure to traces of air and moisture, such impurities modify the reactivity of the reagent.[117] Recently, the group of Woodward reported the preparation of DABAL-Me_3 (Figure 1.4.1) 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).[88g]

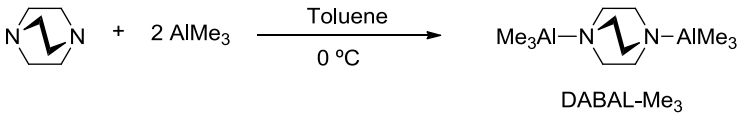


Figure 1.4.1. Formation of DABAL-Me_3**.**

1.4.1 Mechanism

The tentative mechanism proposed for the Ni-catalyzed 1,2-addition of trimethylaluminum reagents to aryl aldehydes is shown in Figure 1.4.2.[115e] The reductive generation of the active Ni(0)-catalyst **142** is followed by the formation of a π-aldehyde complex **143**, as showed possible by the seminal work of Walther who crystallized $Ni(\eta^2\text{-}O{=}CHAr)(PCy_3)_2$ (Ar = Ph, 2,4-$(MeO)_2C_6H_3$). [118] Then aluminum Lewis acid promoted the oxidative addition of the ketone complex **143** and produces Ni(II)-complex **144**. Finally, by reductive elimination, they generated the final product **145** and regenerate the catalytically active species **142**.

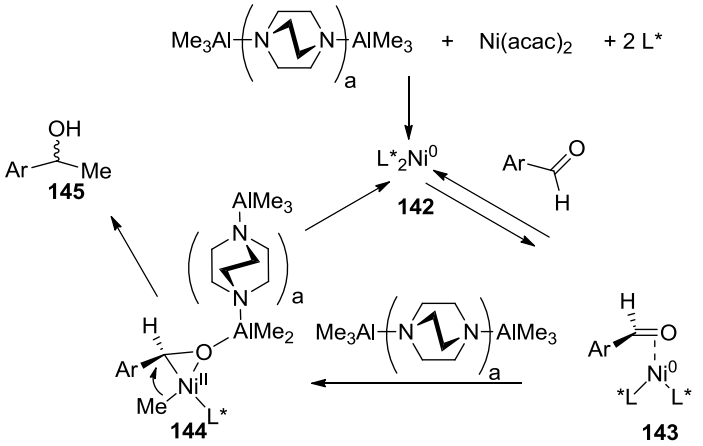
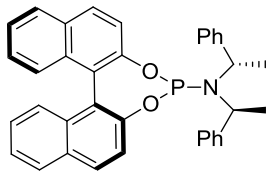


Figure 1.4.2. Proposed catalytic cycle for the Ni-catalyzed 1,2-addition of DABAL-Me_3 (a = 1) or $AlMe_3$ (a = 0) to aromatic aldehydes**.**

1.4.2 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 **146** (Figure 1.4.3).[88g]



146
(ee's up to 96%)

Figure 1.4.3. Monophosphoroamidite ligand **146**.

1.4.2.1 P-donor ligands

Phosphite ligands

The previously mentioned carbohydrate-based monophosphite ligands **37**-**41** (Figure 1.1.16), derived from D-glucose, D-galactose and D-fructose, have been successfully applied in the asymmetric Ni-catalyzed 1,2-addition of several aryl aldehydes (ee's up to 94%).[116a] The best enantioselectivity were achieved using glucofuranoside ligands **37**.

Phosphoroamidite ligands

Our group screened the modular sugar-based monophosphoroamidite ligand library **147**-**151a**-**g** (Figure 1.4.4), related to phosphite ligands **37**-**42** (Figure 1.1.16), for the Ni-catalyzed trialkylaluminum addition to several aldehydes.[119] The results showed that enantioselectivities depends of 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 were 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.

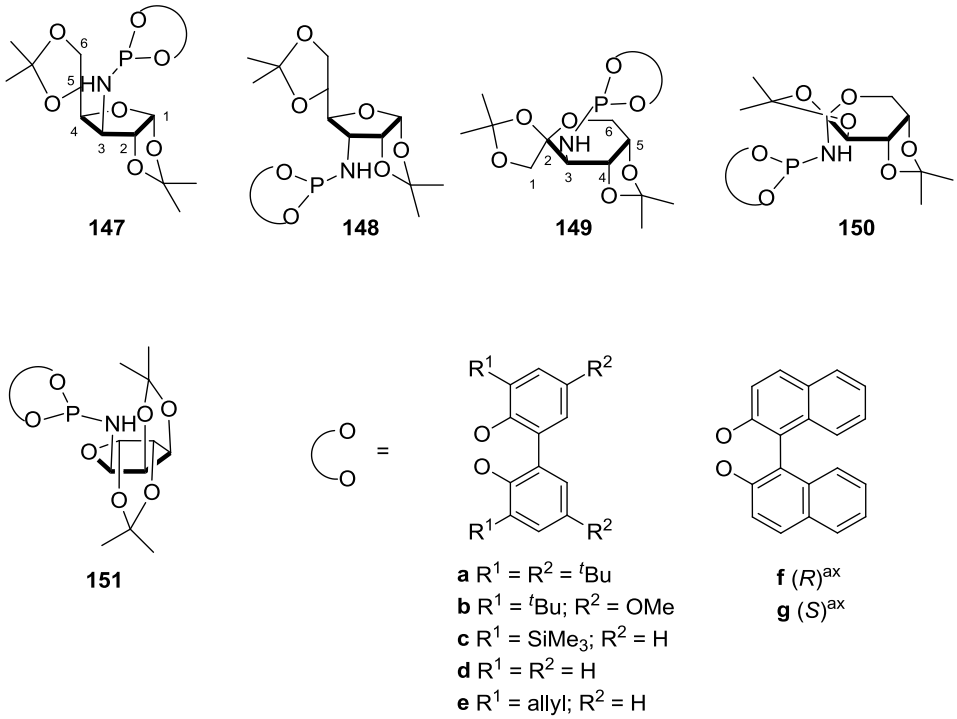


Figure 1.4.4. Modular sugar monophosphoroamidite ligand library **147**-**151a**-**g**.

1.4.2.2 Heterodonor ligands

P-P' and P-N ligands

The previously mentioned carbohydrate-based phosphite-oxazoline (**64**-**68c**-**e**, Figure 1.2.4) and phosphite-phosphoroamidite (**139**; Figure 1.3.27) ligands were applied in the asymmetric Ni-catalyzed 1,2-addition of trialkylaluminum reagents to aldehydes giving poor-to-moderate enantioselectivities (ee's up to 59%).[116b]

Recently, our group tested the phosphite-phosphoroamidite **49**-**52a**-**f** ligand library (Figure 1.1.20) in the asymmetric Ni-catalyzed trialkylaluminum addition to aldehydes.[120] High activities and enantioselectivities (ee's up to 84%) were obtained. These ligands constitute the first successful application of bidentate ligands in the asymmetric Ni-catalyzed trialkylaluminum addition to several aldehydes.

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Chapter 2

Objectives

UNIVERSITAT ROVIRA I VIRGILI
SCREENING OF MODULAR SUGAR DERIVED PHOSPHITE-BASED LIGAND LIBRARIES FOR M-CATALYZED REACTIONS. A GREEN APPROACH TO CATALYSTS DISCOVERY
Sabina Alegre Aragonés
Dipòsit Legal: T.194-2014

2. Objectives

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

The more specific aims are:

1. To synthesize and apply a thioether-phosphite ligand library (**L1**-**L8a**-**e**; Figure 2.1), derived from L-(+)-tartaric acid, in the following asymmetric metal-catalyzed reactions: a) Rh- and Ir-catalyzed hydrogenation of functionalized and unfunctionalized olefins, respectively; b) Pd-catalyzed allylic substitution; and c) Ni-catalyzed 1,2-addition of trialkylaluminum reagents to aldehydes.

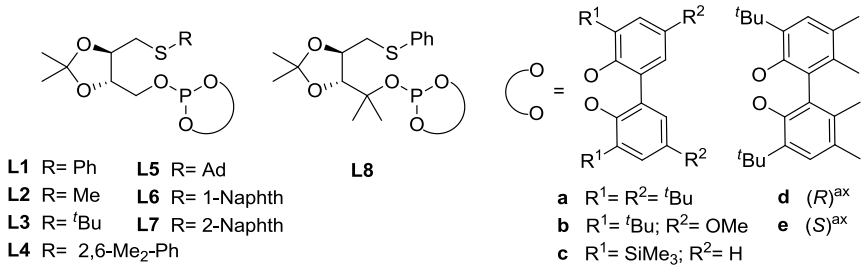


Figure 2.1. Thioether-phosphite ligand library **L1-L8a-e**.

2. To synthesize and apply a monophosphite ligand library (**L9**-**L14a**,**f**,**g**; Figure 2.2), derived from D-(+)-glucose, in the following asymmetric metal-catalyzed reactions: a) Rh-catalyzed hydrogenation of functionalized olefins, b) Pd-catalyzed allylic substitution, and c) Ni-catalyzed 1,2-addition of trialkylaluminum reagents to aldehydes. For purpose of comparison, in the Pd-catalyzed allylic substitution we have also prepared and screened monophosphite ligands **L15-L19a**-**c**,**f**,**g** (Figure 2.3), derived from D-(+)-glucose, D-(+)-galactose and D-(+)-fructose.

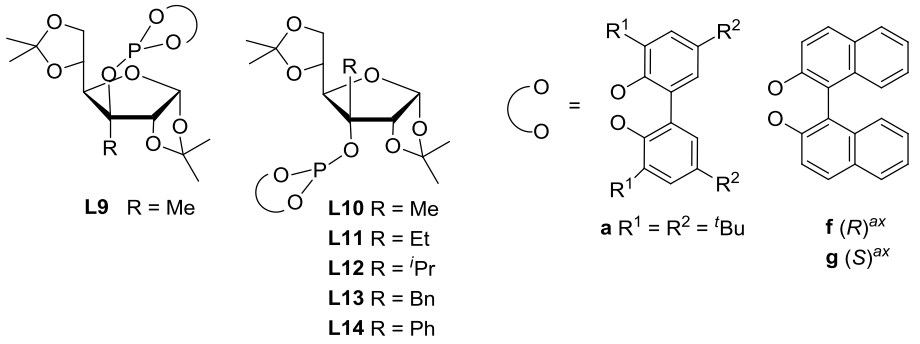


Figure 2.2. Furanoside monophosphite ligand library **L9-L14a**,**f**,**g**.

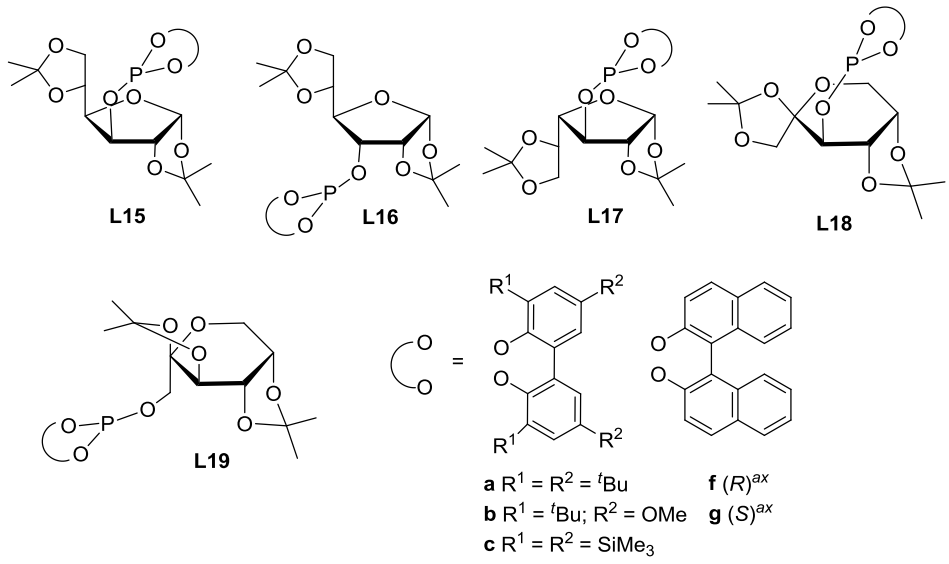


Figure 2.3. Monophosphite ligand library **L15-L19a-c**,**f**,**g** applied in the Pd-catalyzed allylic substitution reaction.

Chapter 3

Asymmetric hydrogenation reactions

UNIVERSITAT ROVIRA I VIRGILI
SCREENING OF MODULAR SUGAR DERIVED PHOSPHITE-BASED LIGAND LIBRARIES FOR M-CATALYZED REACTIONS. A GREEN APPROACH TO CATALYSTS DISCOVERY
Sabina Alegre Aragonés
Dipòsit Legal: T.194-2014

3. Asymmetric hydrogenation reactions

3.1 Background

The enantioselective hydrogenation of olefins is one of the most powerful and sustainable transformations in asymmetric catalysis for preparing optically active compounds due to its high efficiency, atom economy and operational simplicity.

As we discussed in the introduction, chiral homodonor bidentated P-donor ligands have played a key role in the success of the enantioselective Rh-catalyzed hydrogenation of functionalized olefins. Research in this area mainly focuses on the search for new chiral ligands that are readily available from cheap/renewable raw materials and which can hydrogenate a wide range of substrates with high ee's. In this respect, ligands derived from the chiral pool have many advantages: they are readily available and highly functionalized, and they have several stereogenic centers. This facilitates the development of chiral ligand libraries in the search for high activities and selectivities for each particular substrate. Other ligands that have also demonstrated their potential utility are heterodonor bidentated P-P' and P-N ligands and monodentated phosphoroamidite ligands. Despite this, the successful use of bidentated P-S and monophosphite ligands for the Rh-catalyzed hydrogenation is scarce. This encourages further research into these ligand types.

Whereas the reduction of olefins containing an adjacent polar group (i.e. dehydroamino acids) by Rh- and Ru- catalysts has a long history, the asymmetric hydrogenation of minimally functionalized olefins is less developed because these substrates have not adjacent polar group to direct the reaction. Iridium complexes with chiral P-N ligands have become established as one of the most efficient catalyst types for the hydrogenation of minimally functionalized olefins. Research focus in the possibility of changing the nature of the N-donor atom in these heterodonor ligands has not been contemplated until very recently. In this respect, our group has recently communicated the first successful application of non-N-donor heterodonor ligands -thioether-phosphite- for asymmetric Ir-catalyzed hydrogenation. Despite this, the use of other thioether-phosphite ligands has not yet been reported. More research is therefore needed to study the possibilities of these types of ligands.

In this chapter, we therefore report the synthesis of two ligand libraries: thioether-phosphite (**L1**-**L8a**-**e**) and furanoside monophosphite (**L9**-**L14a**,**f**,**g**). We

also report their use in the asymmetric hydrogenation reactions. More specifically, in section 3.2 we describe the successful application of thioether-phosphite ligands (**L1**-**L8a**-**e**) in the asymmetric Rh-catalyzed hydrogenation of several α,β-unsaturated carboxylic acid derivatives and enamides. These ligands are efficiently prepared from easily accessible L-(+)-tartaric acid. We found that their effectiveness at transferring the chiral information in the product can be tuned by correctly choosing the ligand components (thioether substituent, substituent at the alkyl backbone chain next to the phosphite moiety and the substituents/configurations in the biaryl phosphite group) and the substrate. High enantioselectivities (ee's up to 96%) were therefore obtained. In next section 3.3, we report the application of a furanoside monophosphite ligand library (**L9**-**L14a**,**f**,**g**). As well as being prepared from commercially available D-(+)-glucose, this ligand library also has the advantage of a flexible ligand scaffold that enables various ligand parameters to be easily tuned. With this ligand library, then, we investigate the effect of systematically varying the configuration of the C-3 carbon atom of the furanoside backbone, the introduction of several alkyl and aryl groups at C-3 and the type of substituents/configurations in the biaryl phosphite moiety. Enantioselectivities up to >99.9% were obtained in the hydrogenation dimethyl itaconate. In section 3.4 we describe the application of previously reported non N-donor heterodonor ligands thioether-phosphite (**L1-L8a-e**; Section 3.2) in the Ir-catalyzed hydrogenation of minimally functionalized olefins. Moderate enantioselectivities were achieved in the reduction of *E*- and *Z*-trisubstituted olefins (ee's up to 70% and 50%, respectively). However, for disubstituted substrate 3,3-dimethyl-2-phenyl-1-butene, excellent enantioselectivities (ee's up to 98%) and activities were achieved at low hydrogen pressure. The asymmetric hydrogenation was also performed using propylene carbonate as an environmentally friendly solvent, which allowed the Ir-catalysts to be reused with no loss in enantiomeric excess.

3.2 Asymmetric Rh-catalyzed hydrogenation using a thioether-phosphite ligand library

Sabina Alegre, Carlota Borràs, Elisabetta Alberico, Montserrat Diéguez, Oscar Pàmies in manuscript to be submitted

Abstract. A modular thioether-phosphite ligand library has been synthesized for the Rh-catalyzed asymmetric hydrogenation of α,β-unsaturated carboxylic acid derivatives and enamides. These ligands can be prepared efficiently from easily accessible L-(+)-tartaric acid. We found that their effectiveness at transferring the chiral information in the product can be tuned by correctly choosing the ligand components (thioether substituent, substituent at the alkyl backbone chain next to the phosphite moiety and the substituents/configurations in the biaryl phosphite group) and the substrate. Enantioselectivities were therefore high (ee's up to 96%).

3.2.1 Introduction

The increasing demand for enantiomerically pure pharmaceuticals, agrochemicals, flavors and other fine chemicals has advanced the field of asymmetric catalytic technologies.[1] Asymmetric hydrogenation utilizing molecular hydrogen to reduce prochiral olefins has become one of the most efficient asymmetric catalytic methods for constructing chiral compounds.[1] Over many years the scope of this reaction has gradually extended in terms of reactant structure and catalyst efficiency.[1] Chiral homodonor P-donor ligands have played a key role in the success of the enantioselective Rh-catalyzed hydrogenation.[1] Research in this area mainly focuses on the search for new chiral ligands that are readily available from cheap/renewable raw materials and which can hydrogenate a wide range of substrates with high ee's. In this respect ligands derived from the chiral pool have many advantages: they are readily available and highly functionalized, and they have several stereogenic centers. This facilitates the development of chiral ligand libraries in the search for high activities and selectivities for each particular substrate.[2]

Heterodonor P,S ligands also have a potential advantage because specific substrate coordination, mediated by two nonequivalent donor atoms, facilitates the transferring of the chiral information from the catalyst to the hydrogenation product for a wide range of substrates.[3] Despite this, their use in asymmetric hydrogenation has been less developed than other heterodonor ligands such as

P,N and P,P' ligands.[1] Among them, thioether-phosphinite ligands have played a dominant role.[4,5,6] In the last decade, a group of less electron rich phosphorus compounds (phosphite and phosphoroamidite ligands) have demonstrated that they are potentially extremely useful in asymmetric hydrogenation.[7] Despite this, to the best of our knowledge, there is only one report on the use of heterodonor thioether-phosphite ligands in this process with moderate results.[5b] More research is therefore needed to study the possibilities offered by thioether-phosphites as a new class of ligands for this process.

For this purpose in this chapter we report the synthesis and application of a new thioether-phosphite ligand library, derived from inexpensive L-(+)-tartaric acid, (**L1**-**L8a**-**e**; Figure 3.2.1) in the Rh-catalyzed asymmetric hydrogenation of α,β-unsaturated carboxylic acid derivatives and enamides. Another advantage of this ligand library design is its highly modular construction which enables a systematic study of the ligand parameters on catalytic performance. With this library we investigate the effect of systematically varying the electronic and steric properties of the thioether group (ligands **L1**-**L7**) and the substituents in the alkyl backbone chain next to the phosphite moiety (ligands **L1** and **L8**). We also study the substituents and configurations in the biaryl phosphite moiety (**a**-**e**). By carefully selecting these elements, we achieved high enantioselectivities and activities in a range of prochiral olefins.

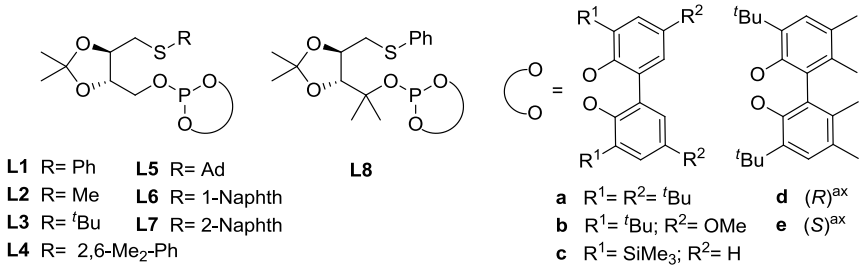


Figure 3.2.1. Thioether-phosphite ligands **L1**-**L8a**-**e**.

3.2.2 Results and discussion

3.2.2.1 Synthesis of ligand library

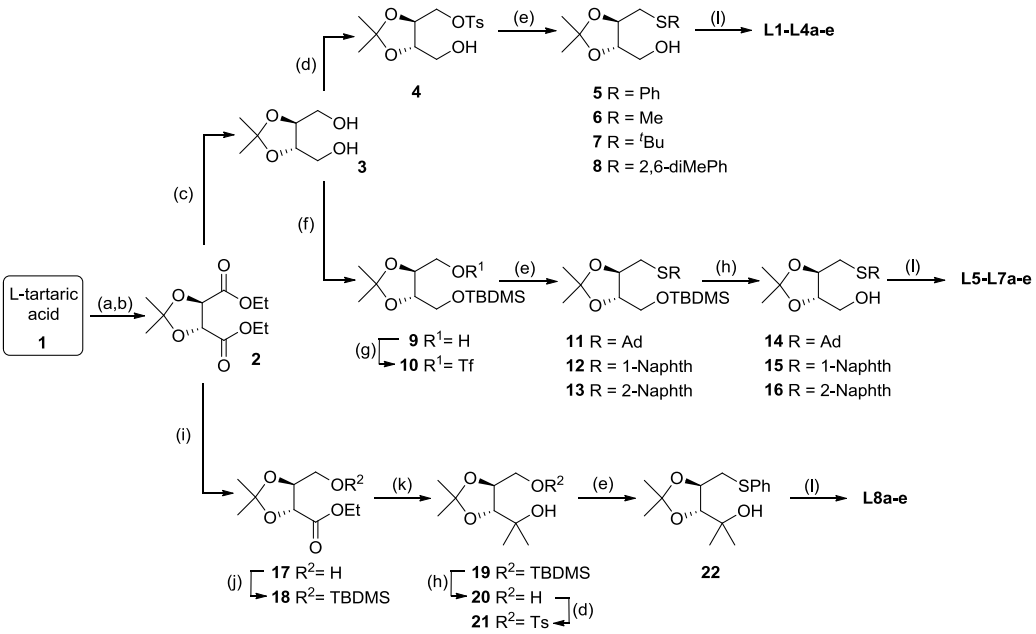
The synthesis of the thioether-phosphite ligands **L1-L8a-e** is straightforward (Scheme 3.2.1). They were efficiently synthesized from the corresponding easily accessible thioether-alcohols **5-8**, **14-16** and **22**. These latter compounds are easily made in few steps from inexpensive natural L-(+)-tartaric

acid **1**. Compounds **2**, **3** and **17** were easily synthesized from **1**.[8,9,10] Compounds **3** and **17** were chosen as intermediates for the preparation of ligands because they will easily allow to incorporate the different substituents at the alkyl backbone chain next to the phosphite moiety. For the preparation of hydroxyl-thioether compounds **5**-**8**, intermediate **3** was treated with 1 equiv of *p*-toluenesulfonyl chloride to produce the desired monotosylated compound **4** (Scheme 3.2.1, step (d)).[11] Subsequent reaction with the corresponding NaSR provided direct access to the corresponding thioether-hydroxyls **5**-**8** (Scheme 3.2.1, step (e)). Therefore, in this step the desired diversity in the electronic and steric properties of the thioether moiety was also attained. However, in this step the incorporation of bulky thioether substituents proceed with poor-to-moderate yields even with long reaction times. Therefore, for the preparation of thioether-hydroxyls **14**-**16**, a new alternative route was developed. Monoprotection of **3** was achieved using 1 equiv of TBDMSCl and NaH in an excellent yield (Scheme 3.2.1, step (f)).[12] Subsequent reaction with triflic anhydride gave access to monotriflate **10** (Scheme 3.2.1, step (g)), which underwent to the corresponding thioether intermediates **11**-**13** on treatment with NaSR (Scheme 3.2.1, step (e)). Finally, the *tert*-butyldimethylsilyl protecting group of compounds **11**-**13** was removed using TBAF to achieve thioether-hydroxyl **14**-**16** (Scheme 3.2.1, step (h)).

For the preparation of hydroxyl-thioether **22**, protection of **17** with TBDMSCl was followed by addition of methyl lithium to achieve compound **19**. Standard deprotection of **19** with TBAF gave access to the corresponding diol **20**. Selective monotosylation of **20** was achieved by treatment with 1 equiv of *p*-toluenesulfonyl chloride. Subsequent reaction with sodium thiophenolate provided direct access to thioether-hydroxyl **22** (Scheme 3.2.1, step (e)).

The last step of the ligand synthesis is common for all of them. Therefore, treating the corresponding thioether-hydroxyl (**5-8**, **14-16** and **22**) with 1.1 equiv of the desired *in situ* formed phosphorochloridite ($ClP(OR)_2$; $(OR)_2$ = **a**-**e**) in the presence of pyridine provided easy access to the desired ligands (Scheme 3.2.1, step (l)).[13] All the ligands were purified on neutral alumina under an argon atmosphere and isolated in moderate-to-good yields as white solids. 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 ligands (see Section 3.2.4). One singlet for each compound was observed in the ^{31}P NMR spectrum. Rapid ring inversions (tropoisomerization) in the biphenyl-phosphorus moieties (**a**-**c**) occurred on the

NMR time scale because the expected diastereoisomers were not detected by low-temperature ^{31}P NMR.[5b]



Scheme 3.2.1. Synthesis of thioether-phosphite ligands **L1**-**L8a**-**e**. (a) EtOH/H_3BO_3;[8] (b) DMP/benzene/PTSA;[9] (c) $LiAlH_4$/Et_2O/THF;[10] (d) ClTs/CH_2Cl_2/Py;[11] (e) NaSR/THF; (f) TBDMS/ NaH/THF;[12] (g) Tf_2O/CH_2Cl_2/Py; (h) TBAF/THF; (i) $NaBH_4$/EtOH; (j) TBDMS/imidazole/DMF; (k) MeLi/THF; (l) $ClP(OR)_2$; $(OR)_2$ = **a**-**e**/Py/toluene.

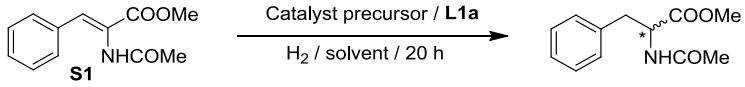
3.2.2.2 Asymmetric hydrogenation of α-dehydroamino acid esters S1-S2

Initially, we evaluated thioether-phosphite ligands **L1**-**L8a**-**e** (Figure 3.2.1) in the Rh-catalyzed asymmetric hydrogenation of benchmark α-dehydroamino acid derivatives methyl 2-acetamidocinnamate **S1** and methyl 2-acetamidoacrylate **S2**. In the first set of experiments we used the Rh-catalyzed hydrogenation of **S1** to evaluate the potential of the new ligands.

We studied the effect of several reaction parameters (i.e. solvent, catalyst preparation, hydrogen pressure and metal source) using the catalyst precursor containing ligand **L1a**. The results, which are given in Table 3.2.1, show that the efficiency of the process depended on the nature of the solvent (entries 1-6). Therefore, the catalytic performance (activity and enantioselectivity) was best when dichloromethane was used (entry 1). On the other hand, while increasing

the temperature has a positive effect on activity, but a negative effect on enantioselectivity (Table 3.2.1, entries 1 vs 7 and 8), increasing the pressure to 30 bar of H_2 has no effect on enantioselectivity (entry 1 vs 10). Activity also increased by increasing the substrate concentration (entry 9 vs 11). The results using *in situ* prepared catalyst precursor, by adding $[Rh(nbd)_2]SbF_6$ to **L1a**, are similar to those achieved using preformed [Rh(cod)**L1a**]SbF_6 catalyst precursor (entry 9 vs 1). Finally, we investigated the effect of different catalysts precursors (entries 11-16). The presence of triflate, CF_3SO_2 and BAr_F as counterions has a negative effect on enantioselectivity (i.e. entries 13-15)

Table 3.2.1 Rh-catalyzed hydrogenation of **S1** using ligand **L1a**. Effect of the reaction parameters[a]



Entry	Solvent	P (bar)	T (°C)	Catalyst precursor	[**S1**] (M)	% Conv[b]	% ee[c]
1	CH_2Cl_2	10	25	[Rh(nbd)(**L1a**)]SbF_6	0.067	76	48 (*R*)
2	THF	10	25	[Rh(nbd)(**L1a**)]SbF_6	0.067	36	15 (*R*)
3	MeOH	10	25	[Rh(nbd)(**L1a**)]SbF_6	0.067	18	0
4	Benzene	10	25	[Rh(nbd)(**L1a**)]SbF_6	0.067	13	18 (*R*)
5	Acetone	10	25	[Rh(nbd)(**L1a**)]SbF_6	0.067	25	38 (*R*)
6	AcOEt	10	25	[Rh(nbd)(**L1a**)]SbF_6	0.067	16	8 (*R*)
7	CH_2Cl_2	10	40	[Rh(nbd)(**L1a**)]SbF_6	0.067	100	45 (*R*)
8	CH_2Cl_2	10	60	[Rh(nbd)(**L1a**)]SbF_6	0.067	100	38 (*R*)
9[d]	CH_2Cl_2	10	25	$[Rh(nbd)_2]SbF_6$	0.067	75	47 (*R*)
10[d]	CH_2Cl_2	30	25	$[Rh(nbd)_2]SbF_6$	0.067	100	46 (*R*)
11[d]	CH_2Cl_2	10	25	$[Rh(nbd)_2]SbF_6$	0.167[e]	100	48 (*R*)
12[d]	CH_2Cl_2	10	25	$[Rh(nbd)_2]PF_6$	0.167[e]	100	46 (*R*)
13[d]	CH_2Cl_2	10	25	$[Rh(nbd)_2]CF_3SO_2$	0.167[e]	100	12 (*R*)
14[d]	CH_2Cl_2	10	25	$[Rh(nbd)_2]BAr_F$	0.167[e]	100	24 (*R*)
15[d]	CH_2Cl_2	10	25	$[Rh(cod)_2]$ BAr_F	0.167[e]	100	27 (*R*)
16[d]	CH_2Cl_2	10	25	$[Rh(cod)_2]BF_4$	0.167[e]	100	45 (*R*)

[a] Catalyst precursor (1 mol%), **S1** (1 mmol), solvent (15 mL). [b] % Conversion measured by GC. [c] Enantiomeric excess measured by GC. [d] Catalyst generated in situ: catalyst precursor (1 mol%), **L1a** (1.1 mol%) and **S1** (1 mmol). [e] CH_2Cl_2 (6 mL).

For the purpose of comparison the rest of ligands were tested under optimized conditions. The results are summarized in Table 3.2.2 and shows that enantioselectivities are highly affected by the thioether substituent, the

substituents in the alkyl backbone chain next to the phosphite moiety and the configuration of the biaryl phosphite moieties. However, the effect of the ligand parameters in activity is less pronounced. In general, full conversion of the desired hydrogenated product was therefore obtained without excess of ligand needed.

Table 3.2.2 Selected results for the Rh-catalyzed hydrogenation of **S1** using the thioether-phosphite ligand library **L1**-**L8a**-**d**[a]

Entry	Ligand	% Conv[b]	% ee[c]
1	**L1a**	100	48 (*R*)
2	**L1b**	100	40 (*R*)
3	**L1c**	100	30 (*R*)
4	**L1d**	64	68 (*R*)
5	**L1e**	100	0
6	**L2a**	92	21 (*R*)
7	**L3a**	100	9 (*R*)
8	**L3d**	100	55 (*R*)
9	**L3e**	100	35 (*S*)
10	**L4a**	82	8 (*S*)
11	**L4d**	96	28 (*S*)
12	**L4e**	95	11 (*R*)
13	**L5d**	100	59 (*R*)
14	**L5e**	100	51 (*S*)
15	**L6d**	100	54 (*R*)
16	**L6e**	100	18 (*S*)
17	**L7d**	100	83 (*R*)
18	**L7e**	100	16 (*S*)
19	**L8a**	100	36 (*R*)
20	**L8d**	100	96 (*R*)
21	**L8e**	100	34 (*S*)

[a] $[Rh(nbd)_2]SbF_6$ (1 mol%), ligand (1.1 mol%), substrate (1 mmol), CH_2Cl_2 (6 mL), 10 bar of H_2, room temperature. [b] % Conversion measured by GC. [c] Enantiomeric excess measured by GC.

We first investigated the effect of the substituents/configurations at the biaryl phosphite moiety with ligands **L1a**-**e**. Although the results indicated that the nature of the substituents at the biaryl phosphite moiety has less impact on enantioselectivities (Table 3.2.2, entries 1-3) than the configuration of the biaryl phosphite moiety (Table 3.2.2, entries 4-5 vs 1-3), enantioselectivities are higher if bulky substituents at the *para* position of the biaryl phosphite groups are present (^{t}Bu > OMe > H; Table 3.2.2, entries 1 vs 2 and 3). In general, ligands containing an

R-biaryl phosphite moiety (**d**) provide therefore higher enantioselectivities than ligands containing an *S*-biaryl group (**e**) (i.e. entry 4 vs 5).

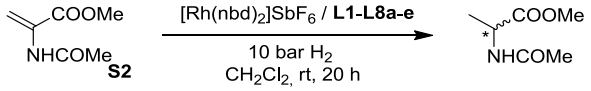
Concerning the effect of the thioether substituent, the results indicated that the presence of an aromatic rather than an alkyl substituent is beneficial in terms of enantioselectivity (i.e. entries 4 vs 8 and 13). The highest enantioselectivity of the series was achieved using a 2-naphthyl thioether substituent (**L7**; Table 3.2.2 entry 17).

Interestingly the introduction of methyl substituents at the alkyl backbone chain next to the phosphite moiety (ligands **L8**) has extremely positive effect on enantioselectivity (i.e. entry 4 vs 20).

To sum up, the best result was obtained with ligand **L8d**, which contains the optimal combination of ligand parameters (100% conversion and 96% of enantioselectivity, entry 20). This result clearly shows the efficiency of highly modular scaffolds in ligand design.

We also screened the phosphite-thioether ligand library **L1**-**L8a**-**e** in the asymmetric reduction of dehydroamino acid derivative **S2**. Substrate **S2** is similar to **S1** but the phenyl group in the latter substrate is lacking, so a different requirement of the ligand parameters may be expected (see Table 3.2.3 for results). Again, enantioselectivities were affected by the thioether substituent, the substituents in the alkyl backbone chain next to the phosphite moiety and the configuration of the biaryl phosphite moieties. However, the effect of these parameters on enantioselectivity was different from their effect on the hydrogenation of substrate **S1**. Enantioselectivity was therefore best with ligand **L8e** (ee's up to 81%). In this respect, the effect on catalytic performance of the substituents in the biaryl phosphite moiety followed the same trend as for the hydrogenation of **S1**. Bulky substituents at the *para* position of the biaryl phosphite groups have a positive effect on enantioselectivities (Table 3.2.3, entries 1-3). The results also indicated a cooperative effect between the configuration of the biaryl phosphite moiety and the substituent in the alkyl backbone chain next to the phosphite moiety. However this effect was different from its effect on the hydrogenation of **S1**. Enantioselectivity was therefore best with ligand **L8e**, with methyl substituents in the alkyl backbone chain next to the phosphite, but in contrast to **S1**, with an *S*-biaryl phosphite group (entry 21). This result again clearly shows the efficiency of using modular scaffolds in ligand design.

Table 3.2.3 Selected results for the Rh-catalyzed hydrogenation of **S2** using the thioether-phosphite ligand library **L1**-**L8a**-**d**[a]



Entry	Ligand	% Conv[b]	% ee[c]
1	**L1a**	100	37 (*R*)
2	**L1b**	100	15 (*R*)
3	**L1c**	100	19 (*S*)
4	**L1d**	100	45 (*R*)
5	**L1e**	100	15 (*R*)
6	**L2a**	100	13 (*R*)
7	**L3a**	100	9 (*S*)
8	**L3d**	100	50 (*S*)
9	**L3e**	100	17 (*R*)
10	**L4a**	100	43 (*S*)
11	**L4d**	100	53 (*S*)
12	**L4e**	100	18 (*R*)
13	**L5d**	100	43 (*S*)
14	**L5e**	100	18 (*R*)
15	**L6d**	100	29 (*R*)
16	**L6e**	100	19 (*R*)
17	**L7d**	99	17 (*R*)
18	**L7e**	100	48 (*R*)
19	**L8a**	100	58 (*R*)
20	**L8d**	100	45 (*R*)
21	**L8e**	100	81 (*S*)

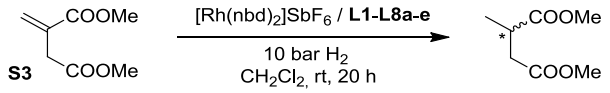
[a] $[Rh(nbd)_2]SbF_6$ (1 mol%), ligand (1.1 mol%), substrate (1 mmol), CH_2Cl_2 (6 mL), 10 bar of H_2, room temperature. [b] % Conversion measured by GC. [c] Enantiomeric excess measured by GC.

3.2.2.3 Asymmetric hydrogenation of dimethyl itaconate S3

We next applied ligand library **L1**-**L8a**-**e** in the Rh-catalyzed asymmetric reduction of dimethyl itaconate **S3**. The results, which are summarized in Table 3.2.4, indicate that the effect of the ligand parameters in enantioselectivity is different from the hydrogenation of α-dehydroamino acid esters **S1-S2**. Although as observed for **S1**-**S2**, the presence of *para* substituents at the biaryl phosphite moiety has a positive effect on enantioselectivity (entries 1-3), the effect of the configuration of the biaryl phosphite moiety depends on the thioether substituent.

Thus, while for ligands **L1**, containing a phenyl thioether substituent, enantioselectivities are better when an *S*-biaryl phosphite is used (entries 4 vs 5), for ligands **L5**, containing bulkier adamantyl thioether substituents, both *R*- and *S*-biaryl moieties led to similar levels of enantioselectivity (entries 13 and 14). Interestingly for the latter ligands, the sense of enantioselectivity is controlled by the configuration of the biaryl phosphite group. As observed for dehydroamino acid derivatives, the introduction of methyl substituents at the alkyl backbone chain next to the phosphite group (ligands **L8**) has a positive effect on enantioselectivity (entries 1, 4-5 vs 19-21, respectively).

Table 3.2.4 Selected results for the Rh-catalyzed hydrogenation of **S3** using the thioether-phosphite ligand library **L1**-**L8a**-**d**[a]



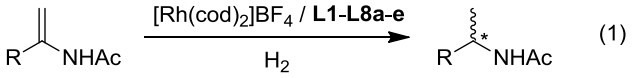
Entry	Ligand	% Conv[b]	% ee[c]
1	**L1a**	100	26 (*S*)
2	**L1b**	100	25 (*S*)
3	**L1c**	100	17 (*S*)
4	**L1d**	100	5 (*S*)
5	**L1e**	100	18 (*S*)
6	**L2a**	100	10 (*S*)
7	**L3a**	100	8 (*R*)
8	**L3d**	100	36 (*S*)
9	**L3e**	100	18 (*R*)
10	**L4a**	100	51 (*R*)
11	**L4d**	100	17 (*S*)
12	**L4e**	100	24 (*R*)
13	**L5d**	100	52 (*S*)
14	**L5e**	100	53 (*R*)
15	**L6d**	100	25 (*S*)
16	**L6e**	100	29 (*S*)
17	**L7d**	100	39 (*S*)
18	**L7e**	100	43 (*S*)
19	**L8a**	100	51 (*S*)
20	**L8d**	100	67 (*S*)
21	**L8e**	100	75 (*S*)

[a] $[Rh(nbd)_2]SbF_6$ (1 mol%), ligand (1.1 mol%), substrate (1 mmol), CH_2Cl_2 (6 mL), 10 bar of H_2, room temperature. [b] % Conversion measured by GC. [c] Enantiomeric excess measured by GC.

In summary, the highest enantioselectivity (ee's up to 75%) was achieved using ligand **L8e**, which contain the optimal combination of ligand parameters.

3.2.2.3 Asymmetric hydrogenation of enamides S4-S8

We subsequently applied ligand library **L1**-**L8a**-**e** in the Rh-catalyzed asymmetric reduction of several enamides (Equation 1). Enamides are an important class of substrates because their reductions give rise to optically active secondary amines, which are useful building blocks for the synthesis of fine chemicals.[14]

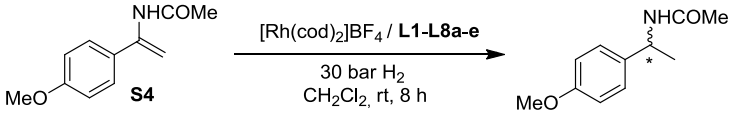


(1)

S4 R= 4-OMe-C_6H_4
S5 R= 4-F-C_6H_4
S6 R= 4-Me-C_6H_4
S7 R= C_6H_5
S8 R= 2-Naphthyl

In a first set of experiments, we used *N*-(1-(4-methoxyphenyl)vinyl)-acetamide **S4** as substrate to assess the potential of the ligand library **L1**-**L8a**-**e** under standard reaction conditions[15] (i.e. $[Rh(cod)_2]BF_4$ as catalyst precursor, 30 bar H_2 at rt). The results, which are summarized in Table 3.2.5, indicate that again enantioselectivities are highly affected by a subtle balance of the thioether substituent, the substituent at the alkyl backbone chain next to the phosphite moiety as well as the configuration of the biaryl phosphite moiety. However, the effect of these parameters is different from the hydrogenation of **S1**-**S3**. Thus, for instance, although the presence of an *R*-biaryl phosphite group led to higher enantioselectivities (entries 4 vs 5), enantioselectivity is hardly affected by the different substituents at the biaryl phosphite group (entries 1-3). Once again, the introduction of methyl substituents at the alkyl chain next to the phosphite moiety has a positive effect on enantioselectivity (i.e. entry 4 vs 20). To sum up, the best enantioselectivities (ee's up to 84%) were obtained using Rh-**L8d** catalyst precursor (entry 20).

Table 3.2.5 Selected results for the Rh-catalyzed hydrogenation of **S4** using the thioether-phosphite ligand library **L1**-**L8a**-**d**[a]

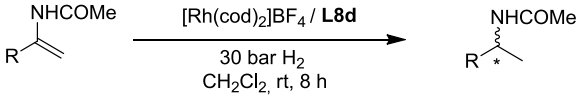


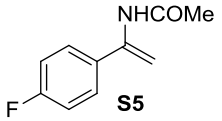
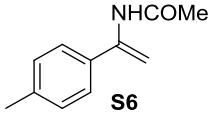
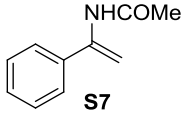
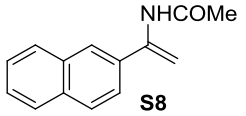
Entry	Ligand	% Conv[b]	% ee[c]
1	**L1a**	100	32 (*R*)
2	**L1b**	100	30 (*R*)
3	**L1c**	100	31 (*R*)
4	**L1d**	100	54 (*R*)
5	**L1e**	100	31 (*S*)
6	**L2a**	100	15 (*R*)
7	**L3a**	100	33 (*S*)
8	**L3d**	100	14 (R)
9	**L3e**	100	29 (S)
10	**L4a**	100	19 (*S*)
11	**L4d**	100	8 (*R*)
12	**L4e**	100	19 (*S*)
13	**L5d**	100	52 (*R*)
14	**L5e**	100	30 (*S*)
15	**L6d**	100	59 (*R*)
16	**L6e**	100	29 (*S*)
17	**L7d**	100	25 (*R*)
18	**L7e**	100	19 (*S*)
19	**L8a**	100	13 (*R*)
20	**L8d**	100	84 (*R*)
21	**L8e**	100	11 (*S*)

[a] $[Rh(cod)_2]BF_4$ (1 mol%), ligand (1.1 mol%), substrate (0.5 mmol), CH_2Cl_2 (6 mL), 30 bar of H_2, room temperature. [b] % Conversion measured by GC. [c] Enantiomeric excess measured by GC.

To further investigate the catalytic efficiency of the Rh/**L8d** catalytic system, we tested it in the Rh-catalyzed hydrogenation of other enamides with different aryl substituents. The results are summarized in Table 3.2.6. We found that conversion is hardly affected by the presence of either electron-donating or electron-withdrawing groups at the *para* positions of the aryl group. However, enantioselectivities are best when electron-withdrawing groups are present (i.e. 85% (*S*) for *N*-(1-(4-fluorophenyl)vinyl)-acetamide **S5**; Table 3.2.6, entry 1).

Table 3.2.6 Selected results for the Rh-catalyzed hydrogenation of enamides **S5**-**S8** using the Rh/**L8d** catalytic system[a]



Entry	Ligand	% Conv[b]	% ee[c]
1	 **S5**	100	85 (*R*)
2	 **S6**	100	77 (*R*)
3	 **S7**	100	80 (*R*)
4	 **S8**	100	79 (*R*)

[a] $[Rh(cod)_2]BF_4$ (1 mol%), ligand (1.1 mol%), substrate (0.5 mmol), CH_2Cl_2 (6 mL), 30 bar of H_2, room temperature. [b] % Conversion measured by GC. [c] Enantiomeric excess measured by GC.

3.2.3 Conclusions

A modular thioether-phosphite ligand library has been synthesized for the Rh-catalyzed asymmetric hydrogenation of α,β-unsaturated carboxylic acid derivatives and enamides. These ligands can be prepared efficiently from easily accessible L-(+)-tartaric acid. The results indicate that enantioselectivity is mainly affected by the substituents in both the thioether group and at the alkyl backbone chain next to the phosphite moiety, and the configuration of the biaryl phosphite moiety. However, the effect of these parameters depends on each substrate class. By carefully selecting the ligand components, full conversions and high enantioselectivities have been achieved in the reduction of several α-dehydroamino acid esters (up to 96% ee), dimethyl itaconate (up to 75% ee), and a range of enamides (up to 85% ee).

3.2.4 Experimental Section

3.2.4.1 General Considerations

All syntheses were performed by using standard Schlenk techniques under an argon atmosphere. Solvents were purified by standard procedures. Phosphorochloridites are easily prepared in one step from the corresponding biaryls.[16] Compounds **2**,[9] **3**,[10] **4**,[11] **5**[11] and **9**[12] were prepared as previously described. Methyl (*Z*)-*N*-acetylaminocinnamate **S1**[17] and enamides **S4**-**S8**[18] were prepared following literature procedures. All other reagents were used as commercially available. ^{1}H, $^{13}C\{^{1}H\}$, $^{31}P\{^{1}H\}$ NMR spectra experiments were recorded using a 400 MHz spectrometer. Chemical shifts are relative to that of $SiMe_4$ (^{1}H and ^{13}C) as internal standard or H_3PO_4 (^{31}P) as external standard. ^{1}H and ^{13}C assignments were done based on ^{1}H-^{1}H gCOSY and ^{1}H-^{13}C gHSQC experiments. Elemental analyses were carried out by the "Service Central d'Analyses du CNRS" in Lyon using LECO SC 144 microanalyzer.

3.2.4.2 Typical procedure for the preparation of thioether-phosphite ligands L1-L8a-e.

The corresponding phosphorochloridite (1.1 mmol) produced *in situ* was dissolved in toluene (5 mL) and pyridine (0.3 mL, 3.9 mmol) was added. The corresponding thioether-hydroxyl compound (1 mmol) was azeotropically dried with toluene (3 x 2 mL) and then dissolved in toluene (5 mL) to which pyridine (0.3 mL, 3.9 mmol) was added. The alcohol solution was transferred slowly to the solution of phosphorochloridite. The reaction mixture was stirred at 80 ºC for 90 min, and the pyridine salts were removed by filtration. Evaporation of the solvent gave a white foam, which was purified by flash chromatography in alumina (toluene/NEt_3= 100/1) to produce the corresponding ligand as a white solid.

L1a: Yield: 413 mg, 65 %. ^{31}P NMR (400 MHz, C_6D_6) δ: 135.7 (s). ^{1}H NMR (C_6D_6), δ: 1.27 (s, 9H, CH_3, ^{t}Bu), 1.28 (s, 9H, CH_3, ^{t}Bu), 1.29 (s, 3H, CH_3), 1.32 (s, 3H, CH_3), 1.57 (s, 9H, CH_3, ^{t}Bu), 1.59 (s, 9H, CH_3, ^{t}Bu), 2.88 (dd, 1H, $^{2}J_{H-H}$= 13.6 Hz, $^{3}J_{H-H}$= 6.4 Hz, CH_2-S), 3.03 (dd, 1H, $^{2}J_{H-H}$= 13.6 Hz, $^{3}J_{H-H}$= 5.6 Hz, CH_2-S), 3.93-3.96 (m, 1H, C*H*CH_2O), 4.02 (m, 1H, C*H*CH_2S), 4.08-4.11 (m, 2H, CH_2-O), 6.87-7.60 (m, 9H, CH=). ^{13}C NMR (C_6D_6), δ: 26.9 (CH_3), 27.1 (CH_3), 30.8 (CH_3, ^{t}Bu), 30.9 (CH_3, ^{t}Bu), 31.2 (CH_3, ^{t}Bu), 34.3 (C, ^{t}Bu), 35.3 (C, ^{t}Bu), 35.3 (C, ^{t}Bu), 36.5 (CH_2-S), 64.6 (CH_2-O), 76.5 (*C*HCH_2S), 79.7 (d, *C*HCH_2O, J_{C-P}= 3.8 Hz), 109.4 (CMe_2), 124.1 (CH=), 125.3 (C), 125.7 (CH=), 126.7 (CH=), 128.1 (CH=), 128.7 (CH=), 128.9 (CH=), 129.0 (CH=), 133.2

(C), 136.4 (C), 140.1 (C), 140.2 (C), 146.5 (C), 146.6 (C). Anal. calcd (%) for $C_{41}H_{57}O_5PS$: C 71.07, H 8.29, S. 4.63. Found: C 71.22, H 8.33, S. 4.52

L1b: Yield: 294 mg, 46 %. ^{31}P NMR (400 MHz, C_6D_6) δ: 134.3 (s). ^{1}H NMR (C_6D_6), δ: 1.24 (s, 3H, CH_3), 1.27 (s, 3H, CH_3), 1.45 (s, 9H, CH_3, ^{t}Bu), 1.48 (s, 9H, CH_3, ^{t}Bu), 2.83 (dd, 1H, $^{2}J_{H-H}$= 13.6 Hz, $^{3}J_{H-H}$= 6.4 Hz, CH_2-S), 3.02 (dd, 1H, $^{2}J_{H-H}$= 13.6 Hz, $^{3}J_{H-H}$= 5.6 Hz, CH_2-S), 3.31 (s, 6H, CH_3-O), 3.90-3.92 (m, 1H, C*H*CH_2O), 3.93-3.97 (m, 1H, C*H*CH_2S), 3.98-4.02 (m, 1H, CH_2-O), 4.12 (m, 1H, CH_2-O), 6.64-7.21 (m, 9H, CH=). ^{13}C NMR (C_6D_6), δ: 26.9 (CH_3), 27.0 (CH_3), 30.6 (CH_3, ^{t}Bu), 35.1 (C, ^{t}Bu), 35.2 (C, ^{t}Bu), 36.6 (CH_2-S), 54.7 (CH_3-O), 64.6 (CH_2-O), 76.2 (*C*HCH_2S), 79.8 (d, *C*HCH_2O, J_{C-P}= 3.0 Hz), 109.4 (CMe_2), 112.9 (CH=), 114.5 (CH=), 125.2 (C), 125.9 (CH=), 128.1 (C), 128.8 (CH=), 128.9 (CH=), 129.1 (CH=), 133.8 (C), 136.3 (C), 137.4 (C), 142.2 (C), 142.3 (C), 156.0 (C). Anal. calcd (%) for $C_{35}H_{45}O_7PS$: C, 65.60; H, 7.08; S, 5.00. Found: C, 65.81; H, 7.14; S, 4.79.

L1c: Yield: 366 mg, 60 %. ^{31}P NMR (400 MHz, C_6D_6) δ: 134.5 (s). ^{1}H NMR (C_6D_6), δ: 0.0 (s, 9H, CH_3, $SiMe_3$), 0.03 (s, 9H, CH_3, $SiMe_3$), 0.88 (s, 3H, CH_3), 0.92 (s, 3H, CH_3), 2.48 (dd, 1H, $^{2}J_{H-H}$= 13.2 Hz, $^{3}J_{H-H}$= 5.6 Hz, CH_2-S), 2.64 (dd, 1H, $^{2}J_{H-H}$= 13.6 Hz, $^{3}J_{H-H}$= 4.8 Hz, CH_2-S), 3.50-3.54 (m, 1H, CH_2-O), 3.54-3.56 (m, 1H, C*H*CH_2O), 3.56-3.60 (m, 1H, C*H*CH_2S), 3.67-3.71 (m, H, CH_2-O), 6.52-7.03 (m, 11H, CH=). ^{13}C NMR (C_6D_6), δ: 0.0 (CH_3-Si), 27.2 (CH_3), 27.4 (CH_3), 36.9 (CH_2-S), 64.8 (CH_2-O), 76.7 (*C*HCH_2S), 79.9 (d, *C*HCH_2O, J_{C-P}= 3.1 Hz), 109.7 (CMe_2), 125.0 (CH=), 125.6 (C), 126.1 (CH=), 128.4 (CH=), 129.0 (CH=), 129.2 (CH=), 129.5 (C), 131.2 (CH=), 131.3 (CH=), 131.9 (CH=),132.5 (C), 135.5 (CH=), 135.6 (CH=), 136.6 (C), 155.0 (C), 155.1 (C). Anal. calcd (%) for $C_{31}H_{41}O_5PSSi_2$: C, 60.75; H, 6.74; S, 5.23. Found: C, 60.94; H, 6.79; S, 5.06.

L1d: Yield: 342 mg, 54 %. ^{31}P NMR (400 MHz, C_6D_6) δ: 128.7 (s). ^{1}H NMR (C_6D_6), δ: 1.25 (s, 3H, CH_3), 1.27 (s, 3H, CH_3), 1.52 (s, 9H, CH_3, ^{t}Bu), 1.54 (s, 9H, CH_3, ^{t}Bu), 1.64 (s, 3H, CH_3), 1.73 (s, 3H, CH_3), 2.02 (s, 3H, CH_3), 2.04 (s, 3H, CH_3), 2.80 (dd, 1H, $^{2}J_{H-H}$= 13.6 Hz, $^{3}J_{H-H}$= 6 Hz, CH_2-S), 2.97 (dd, 1H, $^{2}J_{H-H}$= 13.6 Hz, $^{3}J_{H-H}$= 5.2 Hz, CH_2-S), 3.53-3.59 (m, 1H, CH_2-O), 3.84-3.88 (m, 1H, C*H*CH_2O), 3.94-3.99 (m, 1H, C*H*CH_2S), 4.17-4.23 (m, 1H, CH_2-O), 6.84-7.22 (m, 7H, CH=). ^{13}C NMR (C_6D_6), δ: 16.1 (CH_3), 16.3 (CH_3), 20.0 (CH_3), 26.9 (CH_3), 27.0 (CH_3), 30.9 (CH_3, ^{t}Bu), 31.2 (CH_3, ^{t}Bu), 34.5 (C, ^{t}Bu), 34.6 (C, ^{t}Bu), 36.5 (CH_2-S), 64.4 (CH_2-O), 76.4 (*C*HCH_2S), 79.8 (d, *C*HCH_2O, J_{C-P}= 3.1 Hz), 109.3 (CMe_2), 125.8 (CH=), 127.8 (CH=), 127.9 (CH=), 128.1 (CH=), 128.7 (CH=), 128.9 (CH=), 129.0 (CH=),131.1 (C), 131.5 (C), 131.7 (C), 132.3 (C), 134.5 (C), 134.9 (C), 136.5 (C), 137.0 (C), 137.4 (C), 138.1 (C), 145.8 (C). Anal. calcd (%) for $C_{37}H_{49}O_5PS$: C, 69.78; H, 7.76; S, 5.04. Found: C, 70.01; H, 7.82; S, 4.65.

L1e: Yield: 317 mg, 50 %. ^{31}P NMR (400 MHz, C_6D_6) δ: 126.1 (s). ^{1}H NMR (C_6D_6), δ: 1.19 (s, 3H, CH_3), 1.24 (s, 3H, CH_3), 1.52 (s, 9H, CH_3, ^{t}Bu), 1.54 (s, 9H, CH_3, ^{t}Bu), 1.63 (s, 3H, CH_3), 1.72 (s, 3H, CH_3), 2.01 (s, 3H, CH_3), 2.03 (s, 3H, CH_3), 2.82 (dd, 1H, $^{2}J_{H-H}$= 13.6 Hz, $^{3}J_{H-H}$= 6.4 Hz, CH_2-S), 2.96 (dd, 1H, $^{2}J_{H-H}$= 13.2 Hz, $^{3}J_{H-H}$= 4.8 Hz, CH_2-S), 3.56-3.61 (m, 1H, CH_2-O), 3.83-3.88 (m, 1H, C*H*CH_2O), 3.90-3.95 (m, 1H, C*H*CH_2S), 4.13-4.19 (m, 1H, CH_2-O), 6.85-7.23 (m, 7H, CH=). ^{13}C NMR (C_6D_6), δ: 16.1 (CH_3), 16.4 (CH_3), 20.0 (CH_3), 26.7 (CH_3), 27.0 (CH_3), 30.9 (CH_3, ^{t}Bu), 31.2 (C, ^{t}Bu), 36.4 (CH_2-S), 64.4 (CH_2-O), 76.2 (*C*HCH_2S), 79.6 (d, *C*HCH_2O, J_{C-P}= 3 Hz), 109.3 (CMe_2), 125.7 (CH=), 128.1 (CH=), 128.2 (CH=), 128.8 (CH=), 128.9 (CH=), 129.0 (CH=), 131.0 (C), 131.5 (C), 131.6 (C), 132.3 (C), 134.4 (C), 135.0 (C), 136.5 (C), 136.9 (C), 137.4 (C), 138.1 (C), 145.8 (C). Anal. calcd (%) for $C_{37}H_{49}O_5PS$: C, 69.78; H, 7.76; S, 5.04. Found: C, 70.12; H, 7.84; S, 4.63.

L2a: Yield: 322 mg, 51 %. ^{31}P NMR (400 MHz, C_6D_6) δ: 135.4 (s). ^{1}H NMR (C_6D_6), δ: 1.23 (s, 9H, CH_3, ^{t}Bu), 1.24 (s, 9H, CH_3, ^{t}Bu), 1.28 (s, 3H, CH_3), 1.28 (s, 3H, CH_3), 1.53 (s, 9H, CH_3, ^{t}Bu), 1.55 (s, 9H, CH_3, ^{t}Bu), 1.79 (s, 3H, CH_3), 2.36 (dd, 1H, $^{2}J_{H-H}$= 14 Hz, $^{3}J_{H-H}$= 6 Hz, CH_2-S), 2.46 (dd, 1H, $^{2}J_{H-H}$= 13.6 Hz, $^{3}J_{H-H}$= 5.2 Hz, CH_2-S), 3.78-3.83 (m, 1H, C*H*CH_2O), 3.93-3.98 (m, 1H, C*H*CH_2S), 4.00-4.02 (m, 2H, CH_2-O), 6.95-7.54 (m, 4H, CH-Ar).^{13}C NMR (C_6D_6), δ: 16.1 (CH_3), 26.9 (CH_3), 27.0 (CH_3), 30.9 (2CH_3, ^{t}Bu), 31.1 (CH_3, ^{t}Bu), 31.2 (CH_3, ^{t}Bu), 34.3 (2C, ^{t}Bu), 35.3 (2C, ^{t}Bu), 36.5 (CH_2-S), 64.4 (CH_2-O), 77.5 (*C*HCH_2S), 79.5 (d, *C*HCH_2O, J_{C-P}= 3. Hz), 109.0 (CMe_2), 124.1 (CH-Ar), 125.2 (C-Ar), 126.6 (CH-Ar), 128.1 (CH-Ar), 128.9 (CH-Ar),133.1 (C-Ar), 133.2 (C-Ar), 140.0 (C-Ar), 140.1 (C-Ar), 146.4 (C-Ar), 146.5 (C-Ar), 146.6 (C-Ar). Anal. calcd (%) for $C_{36}H_{55}O_5PS$: C, 68.54; H, 8.79; S, 5.08. Found: C, 68.81; H, 8.84; S, 4.81.

L3a: Yield: 376 mg, 56 %. ^{31}P NMR (400 MHz, C_6D_6) δ: 135.0 (s). ^{1}H NMR (C_6D_6), δ: 1.09 (s, 9H, CH_3, ^{t}Bu), 1.23 (s, 9H, CH_3, ^{t}Bu), 1.24 (s, 9H, CH_3, ^{t}Bu),1.28 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 1.54 (s, 3H, CH_3, ^{t}Bu), 1.56 (s, 9H, CH_3, ^{t}Bu), 2.57 (dd, 1H, $^{2}J_{H-H}$= 12.8 Hz, $^{3}J_{H-H}$= 7.2 Hz, CH_2-S), 2.71 (dd, 1H, $^{2}J_{H-H}$= 12.8 Hz, $^{3}J_{H-H}$= 5.2 Hz, CH_2-S), 3.83-3.87 (m, 1H, C*H*CH_2O), 3.94-4.00 (m, 1H, C*H*CH_2S), 4.01-4.08 (m, 2H, CH_2-O), 6.95-7.53 (m, 4H, CH=). ^{13}C NMR (C_6D_6), δ: 26.9 (CH_3), 27.2 (CH_3), 30.5 (CH_3, ^{t}Bu), 30.9 (CH_3, ^{t}Bu), 31.2 (CH_3, ^{t}Bu), 31.4 (CH_2-S), 34.3 (C, ^{t}Bu), 35.3 (C, ^{t}Bu), 41.6 (C, ^{t}Bu), 64.6 (CH_2-O), 77.2 (*C*HCH_2S), 80.0 (d, *C*HCH_2O, J_{C-P}= 3.9 Hz), 109.0 (CMe_2), 124.0 (CH=), 125.2 (C), 126.6 (CH=), 128.1 (CH=),128.9 (CH=), 133.1 (C), 140.0 (C), 146.3 (C), 146.7 (C). Anal. calcd (%) for $C_{39}H_{61}O_5PS$: C, 69.61; H, 9.14; S, 4.76. Found: C, 70.02; H, 9.11; S, 4.51.

L3d: Yield: 321 mg, 52 %. ^{31}P NMR (400 MHz, C_6D_6) δ: 128.4 (s). ^{1}H NMR (C_6D_6), δ: 1.09 (s, 9H, CH_3, ^{t}Bu), 1.30 (s, 6H, CH_3), 1.54 (s, 9H, CH_3, ^{t}Bu), 1.56 (s, 9H, CH_3, ^{t}Bu), 1.64 (s, 3H, CH_3), 1.75 (s, 3H, CH_3), 2.02 (s, 3H, CH_3), 2.06 (s, 3H, CH_3), 2.56 (dd, 1H, $^2J_{H-H}$= 12.8 Hz, $^3J_{H-H}$= 6.8 Hz, CH_2-S), 2.69 (dd, 1H, $^2J_{H-H}$= 13.2 Hz, $^3J_{H-H}$= 6 Hz, CH_2-S), 3.58-3.64 (m, 1H, CH_2-O), 3.78-3.82 (m, 1H, C*H*CH_2O), 3.97-4.02 (m, 1H, C*H*CH_2S), 4.26-4.32 (m, 1H, CH_2-O), 6.95-7.18 (m, 2H, CH=). ^{13}C NMR (C_6D_6), δ: 16.1 (CH_3), 16.3 (CH_3), 20.0 (CH_3), 26.9 (CH_3), 27.1 (CH_3), 30.5 (CH_3, ^{t}Bu), 31.0 (CH_3, ^{t}Bu), 31.2 (CH_3, ^{t}Bu), 31.3 (CH_2-S), 34.5 (C, ^{t}Bu), 34.6 (C, ^{t}Bu), 41.6 (C, ^{t}Bu), 64.3 (CH_2-O), 77.5 (*C*HCH_2S), 80.0 (d, *C*HCH_2O, J_{C-P}= 3.1 Hz), 109.0 (CMe_2), 128.2 (CH=), 128.9 (CH=), 131.1 (C), 131.4 (C), 131.7 (C), 132.2 (C), 134.3 (C), 134.9 (C), 137.4 (C), 138.1 (C), 145.7(C), 145.8 (C). Anal. calcd (%) for $C_{35}H_{53}O_5PS$: C, 68.15; H, 8.66; S, 5.20. Found: C, 68.44; H, 8.60; S, 5.09.

L3e: Yield: 388 mg, 63 %. ^{31}P NMR (400 MHz, C_6D_6) δ: 125.8 (s). ^{1}H NMR (C_6D_6), δ: 1.10 (s, 9H, CH_3, ^{t}Bu), 1.25 (s, 3H, CH_3), 1.27 (s, 3H, CH_3), 1.53 (s, 9H, CH_3, ^{t}Bu), 1.55 (s, 9H, CH_3, ^{t}Bu), 1.62 (s, 3H, CH_3), 1.72 (s, 3H, CH_3), 2.00 (s, 3H, CH_3), 2.06 (s, 3H, CH_3), 2.55 (dd, 1H, $^2J_{H-H}$= 12.8 Hz, $^3J_{H-H}$= 6.4 Hz, CH_2-S), 2.70 (dd, 1H, $^2J_{H-H}$= 12.8 Hz, $^3J_{H-H}$= 5.2 Hz, CH_2-S), 3.57-3.62 (m, 1H, CH_2-O), 3.81-3.86 (m, 1H, C*H*CH_2O), 3.93-3.98 (m, 1H, C*H*CH_2S), 4.19-4.28 (m, 1H, CH_2-O), 6.94-7.18 (m, 2H, CH-Ar). ^{13}C NMR (C_6D_6), δ: 16.1 (CH_3), 16.3 (CH_3), 20.0 (CH_3), 26.7 (CH_3), 27.1 (CH_3), 30.5 (CH_3, ^{t}Bu), 30.9 (CH_3, ^{t}Bu), 31.2 (CH_3, ^{t}Bu), 31.3 (CH_3, ^{t}Bu), 31.4 (CH_2-S), 34.5 (C, ^{t}Bu), 34.6 (C, ^{t}Bu), 41.5 (C, ^{t}Bu), 64.4 (CH_2-O), 77.1 (*C*HCH_2S), 79.8 (d, *C*HCH_2O, J_{C-P}= 3.9 Hz), 109.0 (CMe_2), 128.2 (CH=), 128.9 (CH=), 131.0 (C), 131.4 (C), 131.7 (C), 132.3 (C), 134.3 (C), 134.9 (C), 137.4 (C), 138.1 (C), 145.7(C), 146.1 (C). Anal. calcd (%) for $C_{35}H_{53}O_5PS$: C, 68.15; H, 8.66; S, 5.20. Found: C, 68.37; H, 8.61; S, 5.11.

L4a: Yield: 462 mg, 64 %. ^{31}P NMR (400 MHz, C_6D_6) δ: 134.9 (s). ^{1}H NMR (C_6D_6), δ: 1.31 (s, 9H, CH_3, ^{t}Bu), 1.31 (s, 9H, CH_3, ^{t}Bu), 1.32 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 1.60 (s, 9H, CH_3, ^{t}Bu), 1.61 (s, 9H, CH_3, ^{t}Bu), 2.15 (s, 3H, CH_3), 2.52 (s, 3H, CH_3), 2.73-2.76 (m, 2H, CH_2-S), 3.89-3.92 (m, 1H, C*H*CH_2O), 3.98-4.03 (m, 1H, C*H*CH_2S), 4.05 (m, 2H, CH_2-O), 6.95-7.63 (m, 7H, CH=).^{13}C NMR (C_6D_6), δ: 21.8 (CH_3-Ar), 22.6 (CH_3-Ar), 27.5 (CH_3), 27.8 (CH_3), 31.6 (CH_3, ^{t}Bu), 31.9 (CH_3, ^{t}Bu), 35.0 (C, ^{t}Bu), 36.0 (C, ^{t}Bu), 38.8 (CH_2-S), 65.0 (CH_2-O), 77.9 (*C*HCH_2S), 80.2 (d, *C*HCH_2O, J_{C-P}= 3.8 Hz), 110.0 (CMe_2), 124.8 (CH=), 126.0 (CH=), 127.4 (CH=), 128.1 (CH=), 128.3 (CH=), 128.6 (CH=), 129.6 (CH=), 133.9 (C), 134.2 (C), 138.1(C), 140.9 (C), 143.6 (C), 147.2 (C), 147.3 (C). Anal. calcd (%) for $C_{43}H_{61}O_5PS$: C, 71.63; H, 8.53; S, 4.45. Found: C, 71.84; H, 8.58; S, 4.21.

L4d: Yield: 315 mg, 47 %. ^{31}P NMR (400 MHz, C_6D_6) δ: 125.4 (s). ^{1}H NMR (C_6D_6), δ: 1.24 (s, 3H, CH_3), 1.26 (s, 3H, CH_3), 1.51 (s, 9H, CH_3, ^{t}Bu), 1.54 (s, 9H, CH_3, ^{t}Bu), 1.64 (s, 3H, CH_3), 1.72 (s, 3H, CH_3), 2.44 (s, 6H, CH_3), 2.62 (m, 2H, CH_2-S), 3.48-3.53(m, 1H, CH_2-O), 3.76-3.81 (m, 1H, C*H*CH_2O), 3.88-3.93 (m, 1H, C*H*CH_2S), 4.13-4.19 (m, 1H, CH_2-O), 6.86-7.18 (m, 5H, CH=). ^{13}C NMR (C_6D_6), δ: 16.1 (CH_3), 16.3 (CH_3), 20.0 (CH_3), 21.8 (CH_3), 26.7 (CH_3), 27.0 (CH_3), 30.9 (CH_3, ^{t}Bu), 31.2 (CH_3, ^{t}Bu), 34.5 (C, ^{t}Bu), 38.0 (CH_2-S), 64.1 (CH_2-O), 77.2 (*C*HCH_2S), 79.5 (d, *C*HCH_2O, $J_{C\text{-}P}$= 3 Hz), 109.2 (CMe_2), 127.8 (CH=), 128.0 (CH=), 128.1 (CH=), 128.2 (CH=), 128.9 (C), 131.1 (C), 131.5 (C), 131.6 (C), 131.7 (C), 132.3 (C), 133.6 (C), 134.4 (C), 134.9 (C), 136.9(C), 138.1 (C), 142.8 (C), 145.8 (C). Anal. calcd (%) for $C_{39}H_{53}O_5PS$: C, 70.45; H, 8.03; S, 4.82. Found: C, 70.82; H, 8.11; S, 4.67.

L4e: Yield: 297 mg, 45 %. ^{31}P NMR (400 MHz, C_6D_6) δ: 128.0 (s). ^{1}H NMR (C_6D_6), δ: 1.16 (s, 3H, CH_3), 1.19 (s, 3H, CH_3), 1.46 (s, 18H, CH_3, ^{t}Bu), 1.57 (s, 3H, CH_3), 1.68 (s, 3H, CH_3), 1.96 (s, 3H, CH_3), 2.00 (s, 3H, CH_3), 2.42 (s, 6H, CH_3), 2.61 (m, 2H, CH_2-S), 3.41-3.46 (m, 1H, CH_2-O), 3.70-3.75 (m, 1H, C*H*CH_2O), 3.84-3.89 (m, 1H, C*H*CH_2S), 4.06-4.12 (m, 1H, CH_2-O), 6.84-7.11 (m, 5H, CH=). ^{13}C NMR (C_6D_6), δ: 16.1 (CH_3), 16.3 (CH_3), 20.0 (CH_3), 21.9 (CH_3), 26.6 (CH_3), 27.1 (CH_3), 30.9 (CH_3, ^{t}Bu), 31.2 (CH_3, ^{t}Bu), 34.5 (C, ^{t}Bu), 34.6 (C, ^{t}Bu), 38.1 (CH_2-S), 64.0 (CH_2-O), 77.0 (*C*HCH_2S), 79.4 (d, *C*HCH_2O, $J_{C\text{-}P}$= 3.8 Hz), 109.2 (CMe_2), 128.0 (CH=), 128.1 (CH=), 128.2 (CH=), 128.9 (CH=), 131.0 (C), 131.5 (C), 131.6 (C), 132.4 (C), 133.6 (C), 134.4 (C), 135.0 (C), 136.9 (C), 137.0 (C), 138.0 (C), 142.8 (C), 145.6 (C), 146.0 (C). Anal. calcd (%) for $C_{39}H_{53}O_5PS$: C, 70.45; H, 8.03; S, 4.82. Found: C, 70.84; H, 8.09; S, 4.54.

L5d: Yield: 381 mg, 62 %. ^{31}P NMR (400 MHz, C_6D_6) δ: 128.6 (s). ^{1}H NMR (C_6D_6), δ: 1.37 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 1.47 (m, 6H, CH_2, Ad), 1.61 (s, 9H, CH_3, ^{t}Bu), 1.63 (s, 9H, CH_3, ^{t}Bu), 1.69 (s, 3H, CH_3), 1.76 (m, 6H, CH_2, Ad), 1.80 (m, 6H, CH, Ad, CH_3), 2.06 (s, 3H, CH_3), 2.10 (s, 3H, CH_3), 2.60 (dd, 1H, $^{2}J_{H\text{-}H}$= 12.8 Hz, $^{3}J_{H\text{-}H}$= 6.8 Hz, CH_2-S), 2.81 (dd, 1H, $^{2}J_{H\text{-}H}$= 13.2 Hz, $^{3}J_{H\text{-}H}$= 5.6 Hz, CH_2-S), 3.67-3.72 (m, 1H, CH_2-O), 3.86-3.90 (m, 1H, C*H*CH_2O), 4.05-4.10 (m, 1H, C*H*CH_2S), 4.39-4.45 (m, 1H, CH_2-O), 6.99-7.25 (m, 2H, CH=). ^{13}C NMR (C_6D_6), δ: 16.9 (CH_3), 17.1 (CH_3), 20.7 (CH_3), 20.8 (CH_3), 27.7 (CH_3), 27.9 (CH_3), 29.5 (CH_2-S), 30.3 (CH, Ad), 31.8 (CH_3, ^{t}Bu), 31.9 (CH_3, ^{t}Bu), 35.3 (C, ^{t}Bu), 35.4 (C, ^{t}Bu), 36.7 (CH_2, Ad), 44.0 (CH_2, Ad), 44.6 (C, Ad), 65.1 (CH_2-O), 78.2 (*C*HCH_2S), 81.0 (d, *C*HCH_2O, $J_{C\text{-}P}$= 3.1 Hz), 109.7 (CMe_2), 129.6 (CH=), 131.9 (C), 132.2 (C), 132.5 (C), 132.9 (C), 135.1 (C), 135.6 (C), 137.7 (C), 138.2 (C), 138.9 (C), 146.6 (C). Anal. calcd (%) for $C_{41}H_{59}O_5PS$: C, 70.86; H, 8.56; S, 4.61. Found: C, 71.13; H, 8.61; S, 4.37.

L5e: Yield: 331 mg, 54 %. ^{31}P NMR (400 MHz, C_6D_6) δ: 125.8 (s). ^{1}H NMR (C_6D_6), δ: 1.32 (s, 3H, CH_3), 1.39 (s, 3H, CH_3), 1.51 (m, 6H, CH_2, Ad),1.61 (s, 9H, CH_3, ^{t}Bu), 1.63 (s, 9H, CH_3, ^{t}Bu), 1.68 (s, 3H, CH_3), 1.78 (s, 3H, CH_3),1.79 (m, 6H, CH_2, Ad), 1.82 (m, 3H, CH, Ad), 2.05 (s, 3H, CH_3), 2.12 (s, 3H, CH_3), 2.61 (dd, 1H, $^2J_{H-H}$= 13.2 Hz, $^3J_{H-H}$= 7.2 Hz, CH_2-S), 2.83 (dd, 1H, $^2J_{H-H}$= 12.4 Hz, $^3J_{H-H}$= 4.8 Hz, CH_2-S), 3.72-3.76 (m, 1H, CH_2-O), 3.93-4.02 (m, 2H, C*H*CH_2O, C*H*CH_2S), 4.30-4.35 (m, 1H, CH_2-O), 6.99-7.27 (m, 2H, CH=). ^{13}C NMR (C_6D_6), δ: 16.1 (CH_3), 16.4 (CH_3), 20.0 (CH_3), 20.1 (CH_3), 26.8 (CH_3), 27.2 (CH_3), 28.8 (CH_2-S), 29.6 (CH, Ad), 30.9 (CH_3, ^{t}Bu), 31.3 (CH_3, ^{t}Bu), 34.6 (C, ^{t}Bu), 34.7 (C, ^{t}Bu), 36.0 (CH_2, Ad), 43.3 (CH_2, Ad), 43.9 (C, Ad), 64.7 (CH_2-O), 77.3 (*C*HCH_2S), 80.2 (d, *C*HCH_2O, J_{C-P}= 4 Hz), 109.0 (CMe_2), 128.1 (CH=), 128.9 (CH=), 131.1 (C), 131.4 (C), 131.7 (C), 132.9 (C), 134.4 (C), 134.9 (C), 136.9 (C), 138.1 (C), 145.8 (C), 146.6 (C). Anal. calcd (%) for $C_{41}H_{59}O_5PS$: C, 70.86; H, 8.56; S, 4.61. Found: C, 71.24; H, 8.62; S, 4.29.

L6d: Yield: 344 mg, 56 %. ^{31}P NMR (400 MHz, C_6D_6) δ: 128.6 (s). ^{1}H NMR (C_6D_6), δ: 1.30 (s, 3H, CH_3), 1.31 (s, 3H, CH_3), 1.52 (s, 9H, CH_3, ^{t}Bu), 1.58 (s, 9H, CH_3, ^{t}Bu), 1.67 (s, 3H, CH_3), 1.75 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 2.06 (s, 3H, CH_3), 2.89 (dd, 1H, $^2J_{H-H}$= 8.8 Hz, $^3J_{H-H}$= 6 Hz, CH_2-S), 3.05 (dd, 1H, $^2J_{H-H}$= 13.2 Hz, $^3J_{H-H}$= 6 Hz, CH_2-S), 3.56-3.62 (m, 1H, CH_2-O), 3.89-3.93 (m, 1H, C*H*CH_2O), 4.06-4.10 (m, 1H, C*H*CH_2S), 4.23-4.30 (m, 1H, CH_2-O), 6.99-8.54 (m, 9H, CH=). ^{13}C NMR (C_6D_6), δ: 16.8 (CH_3), 17.0 (CH_3), 20.7 (CH_3), 27.6 (CH_3), 27.8 (CH_3), 31.6 (CH_3, ^{t}Bu), 31.9 (CH_3, ^{t}Bu), 35.2 (CH_2-S), 37.8 (C, ^{t}Bu), 65.0 (CH_2-O), 77.0 (*C*HCH_2S), 80.7 (d, *C*HCH_2O, J_{C-P}= 2.3 Hz), 110.0 (CMe_2), 125.8 (CH=), 126.0 (CH=), 126.2 CH=), 126.8 (CH=), 127.0 (CH=), 127.9 (CH=), 128.8 (CH=), 129.2 (CH=), 129.6 (CH=), 131.8 (C), 132.2 (C), 132.4 (C), 133.0 (C), 133.7 (C), 134.2 (C), 134.8 (C), 135.2 (C), 135.7 (C), 137.7 (C), 138.1 (C), 138.8 (C), 146.4 (C). Anal. calcd (%) for $C_{41}H_{51}O_5PS$: C, 71.69; H, 7.48; S, 4.67. Found: C, 71.98; H, 7.56; S, 4.47.

L6e: Yield: 331 mg, 54 %. ^{31}P NMR (400 MHz, C_6D_6) δ: 126.2 (s). ^{1}H NMR (C_6D_6), δ: 1.25 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 1.55 (s, 9H, CH_3, ^{t}Bu), 1.56 (s, 9H, CH_3, ^{t}Bu), 1.66 (s, 3H, CH_3), 1.76 (s, 3H, CH_3), 2.02 (s, 3H, CH_3), 2.04 (s, 3H, CH_3), 2.94 (dd, 1H, $^2J_{H-H}$= 12.8 Hz, $^3J_{H-H}$= 5.6 Hz, CH_2-S), 3.05 (dd, 1H, $^2J_{H-H}$= 12.8 Hz, $^3J_{H-H}$= 6 Hz, CH_2-S), 3.62-3.67 (m, 1H, CH_2-O), 3.92-3.96 (m, 1H, C*H*CH_2O), 4.03-4.08 (m, 1H, C*H*CH_2S), 4.21-4.27 (m, 1H, CH_2-O), 7.00-8.58 (m, 9H, CH=). ^{13}C NMR (C_6D_6), δ: 16.8 (CH_3), 17.1 (CH_3), 20.7 (CH_3), 27.5 (CH_3), 27.8 (CH_3), 31.6 (CH_3, ^{t}Bu), 31.9 (CH_3, ^{t}Bu), 35.2 (C, ^{t}Bu), 35.3 (C, ^{t}Bu), 37.8 (CH_2-S), 65.1 (CH_2-O), 77.1 (*C*HCH_2S), 80.4 (d, *C*HCH_2O, J_{C-P}= 3.8 Hz), 110.1 (CMe_2), 125.8 (CH=), 126.0 (CH=), 126.2 (CH=), 126.8 (CH=), 127.0 (CH=), 127.9 (CH=), 128.9 (CH=), 129.2 (CH=), 129.6 (CH=),131.8 (C),

132.3 (C), 133.1 (C), 133.7 (C), 134.4 (C), 134.8 (C), 135.2 (C), 135.7 (C), 137.7 (C), 138.2 (C), 138.8 (C), 146.4 (C), 146.7 (C). Anal. calcd (%) for $C_{41}H_{51}O_5PS$: C, 71.69; H, 7.48; S, 4.67. Found: C, 71.94; H, 7.55; S, 4.43.

L7d: Yield: 270 mg, 60 %. ^{31}P NMR (400 MHz, C_6D_6) δ: 126.2 (s). ^{1}H NMR (C_6D_6), δ: 1.25 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 1.55 (s, 9H, CH_3, ^{t}Bu), 1.56 (s, 9H, CH_3, ^{t}Bu), 1.66 (s, 3H, CH_3), 1.76 (s, 3H, CH_3), 2.02 (s, 3H, CH_3), 2.04 (s, 3H, CH_3), 2.94 (dd, 1H, $^2J_{H\text{-}H}$= 12.8 Hz, $^3J_{H\text{-}H}$= 5.6 Hz, CH_2-S), 3.05 (dd, 1H, $^2J_{H\text{-}H}$= 12.8 Hz, $^3J_{H\text{-}H}$= 6 Hz, CH_2-S), 3.62-3.67 (m, 1H, CH_2-O), 3.92-3.96 (m, 1H, C*H*CH_2O), 4.03-4.08 (m, 1H, C*H*CH_2S), 4.21-4.27 (m, 1H, CH_2-O), 7.00-8.58 (m, 9H, CH=). ^{13}C NMR (C_6D_6), δ: 16.8 (CH_3), 17.1 (CH_3), 20.7 (CH_3), 27.5 (CH_3), 27.8 (CH_3), 31.6 (CH_3, ^{t}Bu), 31.9 (CH_3, ^{t}Bu), 35.2 (C, ^{t}Bu), 35.3 (C, ^{t}Bu), 37.8 (CH_2-S), 65.1 (CH_2-O), 77.1 (*C*HCH_2S), 80.4 (d, *C*HCH_2O, $J_{C\text{-}P}$= 3.8 Hz), 110.1 (CMe_2), 125.8 (CH=), 126.0 (CH=), 126.2 (CH=), 126.8 (CH=), 127.0 (CH=), 127.9 (CH=), 128.9 (CH=), 129.2 (CH=), 129.6 (CH=),131.8 (C), 132.3 (C), 133.1 (C), 133.7 (C), 134.4 (C), 134.8 (C), 135.2 (C), 135.7 (C-Ar), 137.7 (C), 138.2 (C), 138.8 (C), 146.4 (C), 146.7 (C). Anal. calcd (%) for $C_{41}H_{51}O_5PS$: C, 71.69; H, 7.48; S, 4.67. Found: C, 71.87; H, 7.54; S, 4.39.

L7e: Yield: 234 mg, 52 %. ^{31}P NMR (400 MHz, C_6D_6) δ: 126.4 (s). ^{1}H NMR (C_6D_6), δ: 1.25 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 1.56 (s, 9H, CH_3, ^{t}Bu), 1.57 (s, 9H, CH_3, ^{t}Bu), 1.66 (s, 3H, CH_3), 1.75 (s, 3H, CH_3), 2.02 (s, 3H, CH_3), 2.04 (s, 3H, CH_3), 3.00 (dd, 1H, $^2J_{H\text{-}H}$= 13.6 Hz, $^3J_{H\text{-}H}$= 5.6 Hz, CH_2-S), 3.11 (dd, 1H, $^2J_{H\text{-}H}$= 13.6 Hz, $^3J_{H\text{-}H}$= 5.2 Hz, CH_2-S), 3.63-3.68 (m, 1H, CH_2-O), 3.94-3.99 (m, 1H, C*H*CH_2O), 4.04-4.09 (m, 1H, C*H*CH_2S), 4.22-4.28 (m, 1H, CH_2-O), 6.99-7.74 (m, 9H, CH=). ^{13}C NMR (C_6D_6), δ: 16.1 (CH_3), 16.3 (CH_3), 19.9 (CH_3), 20.0 (CH_3), 26.7 (CH_3), 27.0 (CH_3), 30.9(CH_3, ^{t}Bu), 31.2 (CH_3, ^{t}Bu), 34.5 (C, ^{t}Bu), 34.6 (C, ^{t}Bu), 36.4 (CH_2-S), 64.4 (CH_2-O), 76.4 (*C*HCH_2S), 79.6 (d, *C*HCH_2O, $J_{C\text{-}P}$= 3.8 Hz), 109.4 (CMe_2), 125.2 (CH=), 125.4 (CH=), 126.3 (CH=), 126.7 (CH=), 127.1 (CH=), 127.2 (CH=), 128.2 (CH=), 128.4 (CH=), 128.9 (CH=),131.0 (C), 131.6 (C), 131.7 (C), 131.8 (C), 132.4 (C), 134.0 (C), 134.1 (C),134.4 (C), 135.0 (C), 137.0 (C), 137.4 (C), 138.1 (C), 145.7 (C). Anal. calcd (%) for $C_{41}H_{51}O_5PS$: C, 71.69; H, 7.48; S, 4.67. Found: C, 71.94; H, 7.57; S, 4.34.

L8a: Yield: 312 mg, 55 %. ^{31}P NMR (400 MHz, C_6D_6) δ: 150.4 (s). ^{1}H NMR (C_6D_6), δ: 1.15 (s, 3H, CH_3), 1.22 (s, 9H, CH_3, ^{t}Bu), 1.23 (s, 9H, CH_3, ^{t}Bu), 1.27 (s, 3H, CH_3), 1.50 (s, 3H, CH_3), 1.53 (s, 9H, CH_3, ^{t}Bu), 1.56 (s, 9H, CH_3, ^{t}Bu), 1.65 (s, 3H, CH_3), 2.57 (dd, 1H, $^2J_{H\text{-}H}$= 14.8 Hz, $^3J_{H\text{-}H}$= 7.6 Hz, CH_2-S), 3.07 (dd, 1H, $^2J_{H\text{-}H}$= 14.8 Hz, $^3J_{H\text{-}H}$= 2.4 Hz, CH_2-S), 3.88-3.91 (m, 1H, C*H*CMe_2O), 4.22-4.28 (m, 1H, C*H*CH_2S), 6.71-7.57 (m, 9H, CH=). ^{13}C NMR (C_6D_6), δ: 24.0 (CH_3), 26.7 (CH_3), 27.2 (CH_3), 28.1 (CH_3), 30.9 (CH_3, ^{t}Bu), 31.1 (CH_3, ^{t}Bu), 31.2 (CH_3, ^{t}Bu), 34.3 (C, ^{t}Bu), 35.1 (C, ^{t}Bu), 35.2 (C, ^{t}Bu),

36.0 (CH_2-S), 76.4 (*C*HCH$_2$S), 79.9 (*C*Me$_2$O), 84.5 (d, *C*HCMe$_2$O, $J_{C\text{-}P}$= 1 Hz), 109.0 (CMe_2), 123.8 (CH=),124.1 (CH=), 124.7 (CH=), 127.0 (CH=), 128.0 (CH=), 128.1 (CH=), 128.4 (CH=), 128.7 (CH=), 128.9 (CH=), 130.3 (C), 135.3 (C), 137.2 (C), 139.9 (C), 146.4 (C). Anal. calcd (%) for $C_{43}H_{61}O_5PS$: C, 71.63; H, 8.53; S, 4.45. Found: C, 72.02; H, 8.61; S, 4.21.

L8d: Yield: 360 mg, 62%. ^{31}P NMR (400 MHz, C_6D_6) δ: 142.4 (s). ^{1}H NMR (C_6D_6), δ: 1.21 (s, 3H, CH_3), 1.29 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 1.57 (s, 9H, CH_3, ^{t}Bu), 1.59 (s, 9H, CH_3, ^{t}Bu), 1.68 (s, 3H, CH_3), 1.75 (s, 3H, CH_3), 1.76 (s, 3H, CH_3), 1.84 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 2.07 (s, 3H, CH_3), 2.62 (dd, 1H, $^2J_{H\text{-}H}$= 14.8 Hz, $^3J_{H\text{-}H}$= 6.8 Hz, CH_2-S), 2.93 (dd, 1H, $^2J_{H\text{-}H}$= 14.8 Hz, $^3J_{H\text{-}H}$= 2.8 Hz, CH_2-S), 4.06 (d, 1H, $^3J_{H\text{-}H}$= 4 Hz, C*H*CMe$_2$O), 4.20-4.25 (m, 1H, C*H*CH$_2$S), 6.87-7.33 (m, 7H, CH=). ^{13}C NMR (C_6D_6), δ: 16.1 (CH_3), 16.5 (CH_3), 20.0 (CH_3), 23.6 (CH_3), 26.8 (CH_3), 27.1 (CH_3), 27.9 (CH_3), 30.9 (CH_3, ^{t}Bu), 31.6 (CH_3, ^{t}Bu), 34.3 (C, ^{t}Bu), 34.6 (C, ^{t}Bu), 36.4 (CH_2-S), 76.5 (*C*HCH$_2$S), 79.9 (d, *C*Me$_2$O, $J_{C\text{-}P}$= 11.4 Hz), 84.4 (*C*HCMe$_2$O), 108.8 (CMe_2), 124.9 (CH=),125.9 (CH=), 128.0 (CH=), 128.1 (CH=), 128.4 (CH=), 128.5 (CH=), 128.9 (CH=), 131.1 (C), 131.8 (C), 131.7 (C), 132.2(C), 132.3 (C), 134.7 (C), 135.1 (C), 137.3 (C),137.6 (C), 138.0 (C). Anal. calcd (%) for $C_{39}H_{53}O_5PS$: C, 70.45; H, 8.03; S, 4.82. Found: C, 70.89; H, 8.11; S, 4.58.

L8e: Yield: 323 mg, 57%. ^{31}P NMR (400 MHz, C_6D_6) δ: 143.4 (s). ^{1}H NMR (C_6D_6), δ: 1.08 (s, 3H, CH_3), 1.31 (s, 3H, CH_3), 1.51 (s, 9H, CH_3, ^{t}Bu), 1.54 (s, 3H, CH_3), 1.57 (s, 3H, CH_3), 1.64 (s, 3H, CH_3), 1.65 (s, 9H, CH_3, ^{t}Bu), 1.69 (s, 3H, CH_3), 2.04 (s, 3H, CH_3), 2.14 (s, 3H, CH_3), 2.41 (dd, 1H, $^2J_{H\text{-}H}$= 14.8 Hz, $^3J_{H\text{-}H}$= 9.6 Hz, CH_2-S), 2.94 (dd, 1H, $^2J_{H\text{-}H}$= 14.8 Hz, $^3J_{H\text{-}H}$= 1.6 Hz, CH_2-S), 3.76 (d, 1H, $^3J_{H\text{-}H}$= 8.8 Hz, C*H*CMe$_2$O), 4.16-4.21 (m, 1H, C*H*CH$_2$S), 6.74-7.23 (m, 7H, CH=). ^{13}C NMR (C_6D_6), δ: 16.2 (CH_3), 16.4 (CH_3), 20.0 (CH_3), 20.1 (CH_3), 23.8 (CH_3), 26.4 (CH_3), 27.2 (CH_3), 28.5 (CH_3), 31.1 (CH_3, ^{t}Bu), 31.7 (CH_3, ^{t}Bu), 34.3 (C, ^{t}Bu), 34.4 (C, ^{t}Bu), 34.6 (CH_2-S), 75.0 (*C*HCH$_2$S), 79.5 (d, *C*Me$_2$O, $J_{C\text{-}P}$= 9.9 Hz), 84.3 (*C*HCMe$_2$O), 108.4 (CMe_2), 124.1 (CH=),125.3 (CH=), 126.8 (CH=), 128.1 (CH=), 128.7 (CH=), 128.9 (CH=), 131.0 (C), 132.4 (C), 134.7 (C), 135.3 (C), 136.5 (C), 137.2 (C), 137.3 (C), 137.4 (C), 144.5 (C), 145.9 (C). Anal. calcd (%) for $C_{39}H_{53}O_5PS$: C, 70.45; H, 8.03; S, 4.82. Found: C, 70.74; H, 8.09; S, 4.59.

3.2.4.3. General procedure for the preparation of thioether-alcohols 6-8 and 22

To a cooled (-15 °C) suspension of the desired thiolate sodium salt (10.2 mmol) in THF (20 mL), a solution of **4** or **21** (3.2 mmol) in THF (10 mmol) was added. The reaction mixture was stirred at room temperature for minimum 48 h

and quenched with water. The THF was removed under reduced pressure. The aqueous phase was extracted with CH_2Cl_2 (3 x 25 mL), dried with $MgSO_4$ and the solvent was evaporated. The crude was purified by flash chromatography (AcOEt/EP= 1/2) to produce the desired thioether-alcohols as white solids.

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

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

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

2-((4R,5R)-2,2-Dimethyl-5-((phenylthio)methyl)-1,3-dioxolan-4-yl)propan-2-ol **22**. Yield: 0.77 g, 70 %. ^{1}H NMR ($CDCl_3$), δ: 1.15 (s, 3H, CH_3), 1.24 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 2.01 (b, 1H, OH), 3.13 (dd, 1H, $^2J_{H-H}$= 12 Hz, $^3J_{H-H}$= 8 Hz, CH_2-S), 3.3 (dd, 1H, $^2J_{H-H}$ = 16 Hz, $^3J_{H-H}$ = 4 Hz, CH_2-S), 3.76 (d, 1H, $^2J_{H-H}$ = 8 Hz, C*H*CMe_2O), 4.18-4.23 (m, 1H, C*H*CH_2S), 7.17-7.41 (m, 5H, CH=). ^{13}C NMR ($CDCl_3$), δ: 25.2 (CH_3), 27.0 (CH_3), 27.1 (CH_3), 27.3 (CH_3), 38.8 (CH_2-S), 69.8 (*C*Me_2OH), 75.7 (*C*HCH_2S), 85.9 (*C*HCMe_2O), 109.2 (CMe_2), 126.3 (CH=), 128.9 (CH=), 129.6 (CH=), 146.4 (C).

3.2.4.4. General procedure for the preparation of compounds 11-13

Compound **9** (890 mg, 3.2 mmol) was azeotropically dried with toluene (3 x 2 mL) and then dissolved in CH_2Cl_2 (20 mL) to which pyridine (0.56 mL, 6.8 mmol) was added. The alcohol solution was cooled to -15 °C and Tf_2O (0.78 mL, 4.5 mmol) was added slowly over 2 min. The reaction mixture was stirred at -15 °C for 2 h and quenched with water. The aqueous phase was extracted with diethyl ether (3 x 50 mL), dried with $MgSO_4$ and the solvents were removed at room temperature. To the crude product, petroleum ether (25 mL) was added and the insoluble impurities were removed by filtration. Evaporation of the solvent provided the desired monotriflate **10** in 93% yield (1.22 g), which was used without further purification in the next step.

To a suspension of NaH (385 mg, 9.6 mmol) in THF (5 mL) a solution of the desired thiol (0.94 g, 5.6 mmol) in THF (15 mL) was added. After 2 min, the suspension was cooled to -78 °C and a solution of **10** (1.22 g, 3.0 mmol) in THF (20 mL) was added. After 90 min, water (25 mL) was added and the THF was evaporated. The solution was extracted with CH_2Cl_2 (3 x 50 mL), dried with $MgSO_4$ and the solvents were evaporated. The crude was purified by flash chromatography (AcOEt/EP= 1/19) to produce the desired compounds as white solids.

*((4S,5R)-5-((Adamantan-1-ylthio)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanol (tert-butyl) dimethylsilane **11**.* Yield: 0.83 g, 66 %. ^{1}H NMR ($CDCl_3$), δ: 0.06 (s, 6H, CH_3-Si), 0.89 (s, 9H, CH_3, Si^{t}Bu),1.37 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 1.65 (m, 6H, CH_2, Ad), 1.85 (m, 6H, CH_2, Ad), 2.02 (m, 3H, CH, Ad), 2.77 (d, 1H, $^2J_{H-H}$= 6.4 Hz, CH_2-S), 3.77-3.83 (m, 3H, CH_2-O, C*H*CH_2O), 4.03 (m, 1H, C*H*CH_2S).

*tert-Butyl(((4S,5R)-2,2-dimethyl-5-((naphthalen-1-ylthio)methyl)-1,3-dioxolan-4-yl)methoxy)dimethylsilane **12**.* Yield: 0.83 g, 67 %. ^{1}H NMR ($CDCl_3$), δ: 0.01 (s, 6H, CH_3-Si), 0.84 (s, 9H, CH_3, Si^{t}Bu),1.49 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 3.25 (dd, 1H, $^2J_{H-H}$= 12 Hz, $^3J_{H-H}$= 8 Hz, CH_2-S), 3.31 (dd, 1H, $^2J_{H-H}$= 12 Hz, $^3J_{H-H}$= 4 Hz, CH_2-S), 3.74 (dd, 1H, $^2J_{H-H}$= 8 Hz, $^3J_{H-H}$= 4 Hz, CH_2-O), 3.83 (dd, 1H, $^2J_{H-H}$= 8 Hz, $^3J_{H-H}$= 4 Hz, CH_2-O), 3.92-3.96 (m, 1H, C*H*CH_2O), 4.17-4.22 (m, 1H, C*H*CH_2S), 7.41-8.47 (m, 7H, CH=).

*tert-Butyl(((4S,5R)-2,2-dimethyl-5-((naphthalen-2-ylthio)methyl)-1,3-dioxolan-4-yl)methoxy)dimethylsilane **13**.* Yield: 0.78 g, 63 %.^{1}H NMR ($CDCl_3$), δ: 0.01 (s, 6H, CH_3-Si), 0.84 (s, 9H, CH_3, Si^{t}Bu),1.39 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 3.27 (dd, 1H, $^2J_{H-H}$= 13.6 Hz, $^3J_{H-H}$= 6.8 Hz, CH_2-S), 3.34 (dd, 1H, $^2J_{H-H}$= 13.2 Hz, $^3J_{H-H}$= 4.8 Hz, CH_2-S), 3.74 (dd, 1H, $^2J_{H-H}$= 10.8 Hz, $^3J_{H-H}$= 6 Hz, CH_2-O), 3.83 (dd, 1H, $^2J_{H-H}$= 10.8

Hz, $^{3}J_{H-H}$= 4.4 Hz, CH_2-O), 3.91-3.95 (m, 1H, C*H*CH_2O), 4.15-4.20 (m, 1H, C*H*CH_2S), 7.40-7.78 (m, 7H, CH=).^{13}C NMR ($CDCl_3$), δ: -5.2 (CH_3-Si), 18.5 (C-Si), 26.0 (CH_3, Si^{t}Bu), 27.2 (CH_3), 27.5 (CH_3), 37.0 (CH_2-S), 63.9 (CH_2-O), 77.2 (*C*HCH_2S), 80.8 (*C*HCH_2O), 109.6 (CMe_2), 125.9 (CH=), 126.7 (CH=), 127.1 (CH=), 127.2 (CH=), 127.5 (CH=), 127.9 (CH=), 128.6 (C).

3.2.4.5. General procedure for the preparation of thioether-alcohols 14-16

The desired compound **11-13** (1.27 mmol) was dissolved in THF (5 mL) to which TBAF (3.8 mL of 1M in THF, 3.8 mmol) was added slowly. The reaction mixture was stirred at room temperature for 90 min and quenched with diethyl ether (25 mL). The organic phase was washed with HCl 1M, brine and water, dried with $MgSO_4$ and evaporated. The crude was purified by flash chromatography (AcOEt/EP= 1/3) to produce the desired thioether-alcohols as white solids.

((4S,5R)-5-((Adamantan-1-ylthio)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanol **14.** Yield: 241 mg, 63 %. ^{1}H NMR ($CDCl_3$), δ: 1.34 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 1.60-1.62 (m, 6H, CH_2, Ad), 1.78-1.79 (m, 6H, CH_2, Ad), 1.97 (m, 3H, CH, Ad), 2.51 (m, 1H, OH), 2.60 (dd, 1H, $^{2}J_{H-H}$= 12.8 Hz, $^{3}J_{H-H}$= 7.6 Hz, CH_2-S), 2.81 (dd, 1H, $^{2}J_{H-H}$= 12.8 Hz, $^{3}J_{H-H}$= 5.6 Hz, CH_2-S), 3.62-3.69 (m, 1H, CH_2-O), 3.77-3.83 (m, 2H, CH_2-O, C*H*CH_2O), 3.89-3.94 (m, 1H, C*H*CH_2S). ^{13}C NMR ($CDCl_3$), δ: 27.0 (CH_3), 27.1 (CH_3), 28.5 (CH_2-S), 29.5 (CH, Ad), 36.1 (CH_2, Ad), 43.3 (CH_2, Ad), 53.4 (C, Ad), 62.6 (CH_2-O), 76.8 (*C*HCH_2S), 81.7 (*C*HCH_2O), 109.0 (CMe_2).

((4S,5R)-2,2-dimethyl-5-((naphthalen-1-ylthio)methyl)-1,3-dioxolan-4-yl)methanol **15.** Yield: 255 mg, 66 %. ^{1}H NMR ($CDCl_3$), δ: 1.40 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 2.84 (b, 1H, OH), 3.13 (dd, 1H, $^{2}J_{H-H}$= 13.2 Hz, $^{3}J_{H-H}$= 5.6 Hz, CH_2-S), 3.27 (dd, 1H, $^{2}J_{H-H}$= 13.2 Hz, $^{3}J_{H-H}$= 5.6 Hz, CH_2-S), 3.64 (m, 1H, CH_2-O), 3.80 (m, 1H, CH_2-O), 3.95-3.99 (m, 1H, C*H*CH_2O), 4.10 (m, 1H, C*H*CH_2S), 7.34-8.41 (m, 7H, CH=).^{13}C NMR ($CDCl_3$), δ: 27.1 (CH_3), 27.2 (CH_3), 37.1 (CH_2-S), 62.5 (CH_2-O), 75.7 (*C*HCH_2S), 81.3 (*C*HCH_2O), 109.5 (CMe_2), 124.9 (CH=), 125.6 (CH=), 126.3 (CH=), 126.6 (CH=), 127.6 (CH=), 128.4 (CH=), 128.6 (CH=), 132.7 (C), 133.9 (C).

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

125.8 (CH=), 126.6 (CH=), 127.1 (CH=), 127.2 (CH=), 127.7 (CH=), 128.6 (CH=), 131.8 (C), 132.8 (C), 133.7 (C).

3.2.4.6. Preparation of compounds 17-21

(4R,5S)-Ethyl-5-(hydroxymethyl)-2,2-dimethyl-1,3-dioxolane-4-carboxylate **17.** To a stirred solution of compound **2** (10 g, 40.6 mmol) in ethanol (40 mL), with cooling (ice-bath), was added, portionwise, $NaBH_4$ (922 mg, 24.4 mmol) over a **1** hour period. The resulting mixture was then stirred at room temperature for a further 30 min. After, the ethanol was removed under reduced pressure. To the crude product was added water and extracted in ethyl acetate (3 x 25 mL), dried with $MgSO_4$ and dried in the rotavapor. The crude was purified by flash chromatography on silica (Et_2O/EP= 1/1) afforded diester **2**. Further elution (Et_2O/EP= 3/1) afforded the desired compound **17** Yield: 2.7 g, 33 %. ^{1}H NMR ($CDCl_3$), δ: 1.27 (m, 3H, CH_3, Et), 1.39 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 2.40 (b, 1H, OH), 3.69-3.72 (m, 1H, CH_2-O), 3.89-3.92 (m, 1H, CH_2-O), 4.17-4.24 (m, 3H, C*H*CH_2O, CH_2, Et), 4.38-4.42 (m, 1H, C*H*COOEt). ^{13}C NMR ($CDCl_3$), δ: 14.1 (CH_3, Et), 25.5 (CH_3), 26.7 (CH_3), 61.5 (CH_2, Et), 61.8 (CH_2-O), 74.8 (*C*HCOOEt), 79.2 (*C*HCH_2O), 111.3 (CMe_2), 170.8 (C=O). Further elution with ethyl acetate (100%) afforded diol **3**.

(4R,5S)-Ethyl-5-(((tert-butyldimethylsilyl)oxy)methyl)-2,2-dimethyl-1,3-dioxolane-4-carboxylate **18**. Compound **17** (1.8 g, 8.8 mmol), tert-butyldimethylsilyl chloride (1.59 g, 10.6 mmol) and imidazole (1.5 g, 22 mmol) were stirred together in dry DMF (4.5 mL) at room temperature for 1 h. The crude product was extracted in Et_2O (3 x 25 mL), dried with $MgSO_4$ and dried in the rotavapor. The crude was purified by flash chromatography (Et_2O/EP= 1/10) to produce **18** as an oil. Yield: 2.1 g, 75 %. ^{1}H NMR ($CDCl_3$), δ: 0.00 (s, 6H, CH_3-Si), 0.82 (s, 9H, CH_3, Si^{t}Bu), 1.21 (m, 3H, CH_3, Et), 1.36 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 3.71 (dd, 1H, $^2J_{H\text{-}H}$= 8 Hz, $^3J_{H\text{-}H}$= 4 Hz, CH_2-O), 3.8 (dd, 1H, $^2J_{H\text{-}H}$= 12 Hz, $^3J_{H\text{-}H}$= 4 Hz, CH_2-O), 4.11-4.18 (m, 3H, C*H*CH_2O, CH_2, Et), 4.38 (d, 1H, $^2J_{H\text{-}H}$= 4 Hz, CHCOOEt). ^{13}C NMR ($CDCl_3$), δ: -5.4 (CH_3-Si), -5.3 (CH_3-Si), 14.1 (CH_3, Et), 18.3 (C-Si), 25.8 (CH_3, Si^{t}Bu), 25.9 (CH_3), 26.8 (CH_3), 61.2 (CH_2, Et), 62.6 (CH_2-O), 75.2 (*C*HCOOEt), 79.7 (*C*HCH_2O), 111.2 (CMe_2), 170.9 (C=O).

2-((4R,5S)-5-(((tert-Butyldimethylsilyl)oxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)propan-2-ol **19**. To a solution of compound **18** (2.1 g, 6.5 mmol) in dry stirred THF (16.5 mL) under nitrogen, at -60 ^{o}C was added methyllithium (as a complex with LiBr, 11 mL of 1.5 mol dm^{-3}, solution in diethyl ether, 16.2 mmol)

dropwise. The resulting mixture was stirred at -60 °C for 0.5 h, then was warmed to room temperature and quenched with water. The crude product was extracted in Et_2O (3 x 25 mL), dried with $MgSO_4$ and dried in the rotavapor. The crude was purified by flash chromatography (Et_2O/EP= 1/4) to produce **19** as an oil. Yield: 1.1 g, 52 %. ^{1}H NMR ($CDCl_3$), δ: 0.06 (s, 6H, CH_3-Si), 0.88 (s, 9H, CH_3, Si^{t}Bu), 1.19 (s, 3H, CH_3), 1.22 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 1.39 (s, 3H, CH_3), 2.82 (b, 1H, OH), 3.70-3.79 (m, 3H, CH_2, C*H*-CH_2), 3.93-3.97 (m, 1H, C*H*-CMe_2).^{13}C NMR ($CDCl_3$), δ: -5.5 (CH_3-Si), -5.4 (CH_3-Si), 18.3 (C-Si), 25.8 (CH_3, Si^{t}Bu), 25.9 (CH_3), 26.1(CH_3), 27.0 (CH_3), 27.1 (CH_3), 64.3 (CH_2), 69.5 (CMe_2), 77.3 (*C*H-CH_2), 84.7(*C*H-CMe_2), 108.5 (CMe_2).

2-((4R,5S)-5-(Hydroxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)propan-2-ol **20**. Compound **19** (500 mg, 1.6 mmol) was dissolved in THF (5 mL) to which TBAF (5 mL, 5 mmol) was added slowly. The reaction mixture was stirred at room temperature for 90 min. The THF was removed under reduced pressure. The crude product was purified by flash chromatography (AcOEt/EP= 2/1) to produce **20** as a white solid. Yield: 265 mg, 85 %. ^{1}H NMR ($CDCl_3$), δ: 1.21 (s, 3H, CH_3), 1.28 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 2.08 (b, 2H, 2OH), 3.65-3.84 (m, 3H, CH_2, C*H*-CH_2), 4.07-4.11 (m, 1H, C*H*-CMe_2).^{13}C NMR ($CDCl_3$), δ: 25.7 (CH_3), 26.3 (CH_3), 27.1 (CH_3), 27.2 (CH_3), 63.4 (CH_2), 69.8 (C-O), 77.4 (*C*H-CH_2), 83.5 (*C*H-CMe_2), 108.8 (CMe_2).

((4S,5R)-5-(2-Hydroxypropan-2-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl 4-methylbenzenesulfonate **21**. To a solution of compound **20** (100 mg, 0.52 mmol) in anhydrous pyridine (0.3 mL) at 0 °C, a solution of tosylchloride (100.2 mg, 0.52 mmol) in dichloromethane (2 mL) was added dropwise. The reaction mixture was stirred overnight at room temperature and quenched with water. The crude product was extracted in CH_2Cl_2 (3 x 20 ml), then washed with Copper sulphate and water, finally dried with $MgSO_4$ and dried in the rotavapor. The crude was purified by flash chromatography (AcOEt/EP= 1/1) to produce **21** as white solid. Yield: 148 mg, 82 %. ^{1}H NMR ($CDCl_3$), δ: 1.12 (s, 3H, CH_3), 1.23 (s, 3H, CH_3), 1.32 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 1.95 (b, 1H, OH), 2.45 (s, 3H, CH_3, OTs), 3.74 (d, 1H, $^2J_{H-H}$= 7.6 Hz, C*H*-CMe_2), 4.08 (dd, 1H, $^2J_{H-H}$= 10.8 Hz, $^3J_{H-H}$= 4.8 Hz, CH_2), 4.13-4.16 (m, 1H, C*H*-CH_2), 4.23 (dd, 1H, $^2J_{H-H}$= 10.8 Hz, $^3J_{H-H}$= 2.8 Hz, CH_2), 7.33-7.81 (m, 4H, CH=). ^{13}C NMR ($CDCl_3$), δ: 21.6 (CH_3, OTs), 25.1 (CH_3), 26.7 (CH_3), 27.1 (CH_3), 69.6 (C-O), 70.1 (CH_2), 74.7 (*C*H-CH_2), 82.4 (*C*HCMe_2), 109.7(CMe_2), 128.0 (CH=), 129.8 (CH=), 132.7 (C), 145.0 (C).

3.2.4.7 Preparation of $[Rh(nbd)(L1a)]SbF_6$

To a solution of $[Rh(nbd)_2]SbF_6$ (69 mg, 0.131 mmol) in dichloromethane (2 mL), a solution of ligand **L1a** (100 mg, 0.144 mmol) in dichloromethane (4 mL) was added dropwise. The reaction mixture was stirred at room temperature for 2 hours. Then, the solvent was removed and hexane (10 mL) was added. The orange/yellow precipitate was filtered and washed with cold hexane to afford the desired complex. Yield: 100 mg, 86%.

3.2.4.8 General procedure for the asymmetric hydrogenation

In a typical run, $[Rh(nbd)_2]SbF_6$ (5.2 mg, 0.01 mmol), the corresponding ligand (0.011 mmol) and the corresponding substrate (1 mmol) were dissolved in dichloromethane (6 mL). The reaction mixture was then placed in the autoclave and the autoclave was purged five times with hydrogen gas. Then, it was pressurized to the desired pressure. After the desired reaction time, the autoclave was depressurized and the solvent evaporated off. The residue was dissolved in Et_2O (2 mL) and filtered through a short celite plug. The enantiomeric excess was determined by chiral GC and conversions were determined by GC and confirmed by ^1H NMR. The enantiomeric excesses of hydrogenated products were determined using the conditions previously described.[19]

3.2.5. Acknowledgements

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3.3 Rh-catalyzed asymmetric hydrogenation using a furanoside monophosphite second-generation ligand library. Scope and limitations.

Sabina Alegre, Elisabetta Alberico, Montserrat Diéguez, Oscar Pàmies in manuscript submitted to *Tetrahedron: Asymmetry*

Abstract. We have expanded the ligand design of one of the most successful monophosphite ligands in Rh-catalyzed hydrogenation by introducing several substituents at C-3 position of the furanoside backbone. These new furanoside monophosphite ligands have been evaluated in the Rh-catalyzed asymmetric hydrogenation of α,β-unsaturated carboxylic acid derivatives and enamides. The results show that the effect of introducing a substituent at C-3 of the furanoside backbone on enantioselectivity depends on the configuration at both C-3 of the furanoside backbone and at the binaphthyl group as well as the substrate. Thus, the new ligands afforded high-to-excellent enantioselectivities in the reduction of carboxylic acid derivatives (ee's up to >99.9%) and moderate ee's (up to 67%) in the hydrogenation of enamides.

3.3.1 Introduction

Asymmetric hydrogenation of functionalized prochiral olefins catalyzed by chiral transition metal complexes has been widely used in stereoselective organic synthesis and some processes have found industrial applications.[1] Many chiral ligands, mainly P- and N- containing ligands with either C_2- or C_1-symmetry, have been successfully applied.[1] During long time, it has generally been accepted that enantioselective hydrogenation was more effective in the presence of bidentated ligands.[1] Less attention was therefore paid to catalysts containing monodentated ligands in this process. However, in 2000, the group of Reetz obtained excellent enantioselectivities with catalyst precursors containing monophosphite ligands, derived from D-(+)-mannitol, in the hydrogenation of dimethyl itaconate.[2] Since then, other successful monodentated ligands have been developed.[3] Research in this field has been mainly centered in the selection/design of new chiral ligands prepared from readily available cheap/renewable raw materials. For this purpose, carbohydrates are particularly advantageous thanks to their low price and easy modular constructions.[4] In this respect, the groups of Reetz[3d] and Zheng[3e-g] have independently reported the successful use of furanoside ligands **L15** and **L16**, derived from D-(+)-glucose, in the Rh-catalyzed asymmetric hydrogenation of a range of carboxylic acid derivatives, enamides and vinyl carboxylates (Figure 3.3.1).

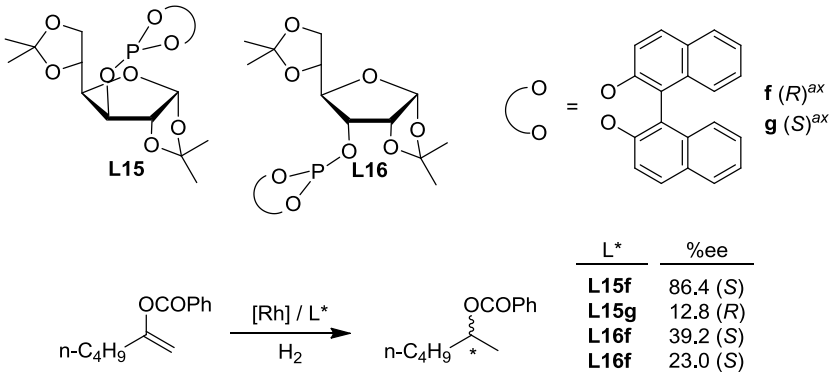


Figure 3.3.1. Furanoside monophosphite ligands **L15**-**L16f**-**g**. As example, the enantioselectivities achieved in the asymmetric hydrogenation of a vinyl carboxylate are shown.

Following our interest in carbohydrates as an inexpensive and highly modular chiral source for preparing ligands,[4] and encouraged by the results of monophosphite ligands **L15** and **L16** in asymmetric hydrogenation,[3d-g] we here report the development and application of new furanoside monophosphite ligands **L9**-**L14a**,**f**,**g** (Figure 3.3.2) in the Rh-catalyzed enantioselective hydrogenation of carboxylic acid derivatives and enamides. These ligands differ from the previously monophosphite ligands **L15** and **L16** in the introduction of new substituents with different electronic and steric properties at C-3 of the sugar backbone. With this library we therefore fully investigated the effects of systematically varying the configuration of the C-3 carbon atom of the sugar backbone (**L9**-**L10**), the electronic and steric hindrance of the new substituent at C-3 (**L10**-**L14**) and the substituents/configuration of the biaryl phosphite moieties (**a**,**f**,**g**).

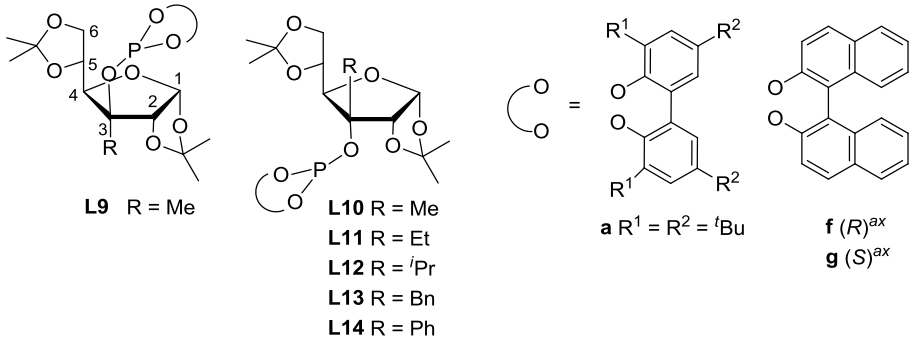
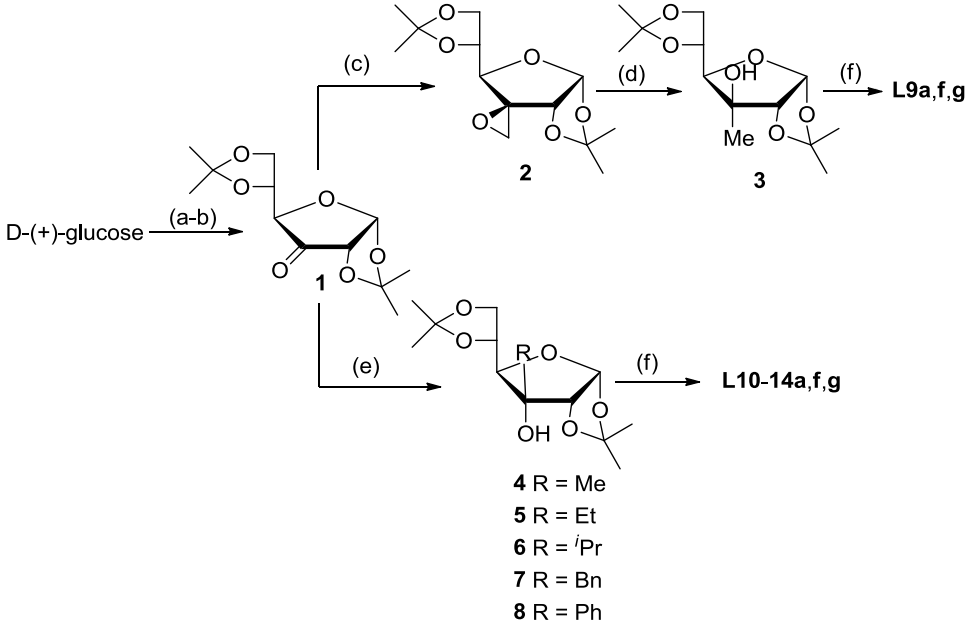


Figure 3.3.2. Furanoside monophosphite ligand library **L9**-**L14a**,**f**,**g**.

3.3.2 Results and discussion

3.3.2.1 Synthesis of monophosphite ligand library

The sequence of ligand synthesis is illustrated in Scheme 3.3.1. Ligands **L9**-**L14a**,**f**,**g** were synthesized very efficiently from the corresponding easily accessible ketone sugar derivative **1** (Scheme 3.3.1). Compound **1** is easily made in two steps from D-(+)-glucose. This compound was chosen as intermediate for the preparation of ligands because it will easily allow incorporating the various elements that will enable us to study the configuration of C-3. For the preparation of alcohol **3**, compound **1** was treated with trimethylsulfonium iodide and potassium *tert*-butoxide to produce the desired epoxide **2**[5] and then reduced with $LiAlH_4$ [6] (Scheme 3.3.1, steps (c,d)). For the preparation of alcohols **4**-**8**, intermediate **1** was treated with the corresponding Grignard reagent (Scheme 3.3.1, step (e)).[7]



Scheme 3.3.1. Synthesis of monophosphite ligands **L9**-**L14a**,**f**,**g**. Reagents: (a) acetone/I_2;[8] (b) PCC/NaOAc/CH_2Cl_2;[9] (c) KO^{t}Bu/Me_3SOI/^{t}BuOH;[5] (d) $LiAlH_4$/Et_2O;[6] (e) RMgX/THF or Et_2O;[7] (f) $ClP(OR)_2$; $(OR)_2$ = **a**,**f**,**g**/Py/toluene.

The last step of the ligand synthesis is common for all of them. Therefore, treating the corresponding alcohols **3**-**8** with 1.1 equiv of the desired *in situ* formed phosphorochloridite ($ClP(OR)_2$; $(OR)_2$ = **a**,**f**,**g**) in the presence of pyridine provided

easy access to the desired ligands (Scheme 3.3.1, step (f)).[10] All ligands were purified on neutral alumina under an argon atmosphere and isolated in moderate-to-good yields as white solids. 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. One singlet for each compound was observed in the ^{31}P NMR spectrum. Rapid ring inversions (tropoisomerization) in the biphenyl-phosphorus moieties **a** occurred in the NMR timescale since the expected diastereoisomers were not detected by low-temperature phosphorus NMR.[11]

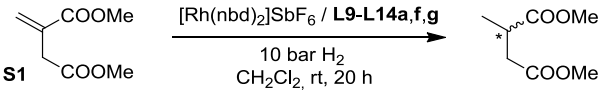
3.3.2.2 Asymmetric hydrogenation of dimethyl itaconate S1

Initially, we evaluated furanoside monophosphite ligands **L9**-**L14a**,**f**,**g** (Figure 3.3.2) in the Rh-catalyzed asymmetric hydrogenation of dimethyl itaconate **S1**, which is used as a model substrate. The catalysts were prepared *in situ* by adding the corresponding ligands to the catalyst precursor $[Rh(nbd)_2]SbF_6$. For the purpose of comparison, we have chosen the reaction conditions previously selected for the hydrogenation using ligands **L15**-**L16** (i.e. 10 bar of H_2, dichloromethane as solvent, 1 mol% catalyst precursor, ligand-to-rhodium ratio of 2.2 and room temperature).

The results, which are summarized in Table 3.3.1, indicated that catalytic activity is almost suppressed using bulky biaryl substituents (i.e. ligands **L9**-**L10a** and **L15**-**L16a**; entries 1, 4, 11 and 14). We also found that enantioselectivities are highly affected by the substituents/configuration at the C-3 of the furanoside backbone and the configuration of the binaphthyl group. The results indicated that the effect of introducing the new substituent at C-3 on enantioselectivity depends on the configuration at both C-3 of the furanoside backbone and at the binaphthyl moiety. Thus, for glucofuranoside ligands **L15**, the introduction of a methyl substituent at C-3 (ligands **L9**) had a positive effect on enantioselectivity if an *S*-binaphthyl group (**g**) is present (ligand **L9g**, ee's up to >99.9%, entry 3 vs 13). However, the presence of a methyl substituent at C-3 in combination with an *R*-biaryl group (**f**) had a negative effect on enantioselectivity (ligand **L9f**; entry 2 vs 12). On the other hand for allofuranoside ligands **L16**, enantioselectivities decreased considerably when introducing a substituent at C-3, regardless the configuration at the binaphthyl group (ligands **L10**-**L13**; entries 5, 7-9 vs 15 and entry 6 vs 16). However, with ligand **L14f**, with a phenyl substituent, we obtained similar enantioselectivities than with previously reported ligand **L16f** (entry 10 vs 15).

In summary, the best result (ee's up to >99.9%) was obtained with ligand **L9g** (Table 3.3.1, entry 3), which contains the optimal combination of ligand parameters (substituent at C-3 and configuration at both C-3 position of the furanoside ring and at biaryl group). When this latter result is compared with the enantioselectivity obtained with its corresponding Rh/**L15g** catalytic system, we can conclude that introducing a methyl group at C-3 into ligand **L15g** is advantageous. This result is among the best that have been reported.[1]

Table 3.3.1 Selected results for the Rh-catalyzed hydrogenation of **S1** using the furanoside monophosphite ligand library **L9**-**L14a**,**f**,**g**[a]

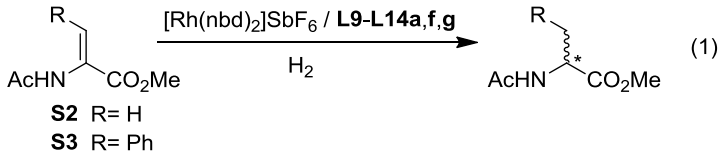


Entry	Ligand	% Conv[b]	% ee[c]
1	**L9a**	<5	nd
2	**L9f**	100	86 (*R*)
3	**L9g**	100	>99.9 (*S*)
4	**L10a**	<5	nd
5	**L10f**	100	33 (*R*)
6	**L10g**	100	15 (*S*)
7	**L11f**	100	4 (*R*)
8	**L12f**	100	52 (*R*)
9	**L13f**	100	12 (*R*)
10	**L14f**	100	93 (*S*)
11	**L15a**	<5	nd
12	**L15f**	100	92.8 (*R*)[d]
13	**L15g**	100	99.1 (*S*)[d]
14	**L16a**	<5	nd
15	**L16f**	100	93.6 (*R*)[d]
16	**L16g**	100	77.5 (*S*)[d]

[a] $[Rh(nbd)_2]SbF_6$ (1 mol%), ligand (1.1 mol%), **S1** (1 mmol), CH_2Cl_2 (6 mL), 10 bar of H_2, room temperature. [b] % Conversion measured by GC. [c] Enantiomeric excess measured by GC. [d] Data from ref. 3e.

3.3.2.3 Asymmetric hydrogenation of α-dehydroamino acid esters S2-S3

We also screened the monophosphite ligands **L9**-**L14a**,**f**,**g** in the asymmetric reduction of some benchmark α-dehydroamino acid derivatives (Equation 1).



S2 R= H
S3 R= Ph

The results achieved in the hydrogenation of methyl 2-acetamidoacrylate **S2**, which are summarized in Table 3.3.2, showed again that the presence of bulky biaryl substituents (**a**) has a detrimental effect on catalytic activity (i.e. ligands **L9**-**L10a** and **L15**-**L16a**; entries 1, 4, 11 and 14).

Table 3.3.2 Selected results for the Rh-catalyzed hydrogenation of **S2** using the furanoside monophosphite ligand library **L9**-**L14a**,**f**,**g**[a]

Entry	Ligand	% Conv[b]	% ee[c]
1	**L9a**	<5	nd
2	**L9f**	100	23 (*S*)
3	**L9g**	100	85 (*S*)
4	**L10a**	<5	nd
5	**L10f**	100	32 (*R*)
6	**L10g**	100	45 (*S*)
7	**L11f**	100	29 (*R*)
8	**L12f**	100	10 (*R*)
9	**L13f**	100	34 (*R*)
10	**L14f**	100	58 (*R*)
11	**L15a**	<5	nd
12	**L15f**	100	87.9 (*S*)[d]
13	**L15g**	100	79.9 (*R*)[d]
14	**L16a**	<5	nd
15	**L16f**	100	26.5 (*R*)[d]
16	**L16g**	100	5.5 (*S*)[d]

[a] $[Rh(nbd)_2]SbF_6$ (1 mol%), ligand (1.1 mol%), **S2** (1 mmol), CH_2Cl_2 (6 mL), 10 bar of H_2, room temperature. [b] % Conversion measured by GC. [c] Enantiomeric excess measured by GC. [d] Data from ref. 3f.

As for **S1**, the effect of introducing the new substituent at C-3 on enantioselectivity depends on the configuration at both C-3 of the furanoside backbone and at the binaphthyl moiety. For glucofuranoside ligands, this led again to a matched combination for glucofuranoside ligand **L9g**, containing an *S*-binaphthyl moiety (entry 3 vs 13); and a mismatched combination for **L9f** with an *R*-biaryl group (entry 2 vs 12). However, the effect of the substituents for allofuranoside ligands is slightly different than for **S1**. Thus, regardless the

configuration of the binaphthyl group, the introduction of a new substituent at C-3 has in general a positive effect on enantioselectivity (i.e entries 5-6 vs 15-16, respectively). Again, for the allofuranoside ligands, the highest enantioselectivity was achieved using ligand **L14f** (ee's increased from 26.5% to 58% by introducing a phenyl substituent at C-3; entry 10 vs 15).

To sum up, the results show again that the introduction of a methyl substituent at C-3 in glucofuranoside ligand containing an *S*-binaphthyl moiety has a positive effect on enantioselectivity (ligand **L9g**; ee's increased from 79.9% to 85%; Table 3.3.2, entry 3 vs 13).

We next applied ligands **L9**-**L14a**,**f**,**g** in the hydrogenation of methyl 2-acetamidocinnamate **S3**. The results, which are shown in Table 3.3.3, followed the same trends as for the hydrogenation of **S2**. Again, the introduction of a methyl substituent in glucofuranoside ligand **L15g** led to higher enantioselectivities (ligand **L9g**; ee's increased from 68% to 84%; Table 3.3.3., entry 3 vs 12).

Table 3.3.3 Selected results for the Rh-catalyzed hydrogenation of **S3** using the furanoside monophosphite ligand library **L9**-**L14a**,**f**,**g**[a]

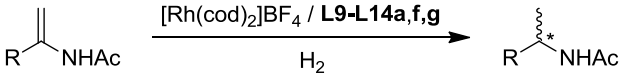
Entry	Ligand	% Conv[b]	% ee[c]
1	**L9a**	<5	nd
2	**L9f**	100	25 (*S*)
3	**L9g**	100	84 (*S*)
4	**L10a**	<5	nd
5	**L10f**	100	38 (*R*)
6	**L10g**	100	43 (*S*)
7	**L11f**	100	64 (*R*)
8	**L12f**	100	7 (*R*)
9	**L13f**	100	35 (*S*)
10	**L14f**	100	73 (*R*)
11	**L15f**	100	84 (*S*)
12	**L15g**	100	68 (*R*)
13	**L16f**	100	30 (*R*)
14	**L16g**	100	7 (*S*)

[a] $[Rh(nbd)_2]SbF_6$ (1 mol%), ligand (1.1 mol%), **S3** (1 mmol), CH_2Cl_2 (6 mL), 10 bar of H_2, room temperature. [b] % Conversion measured by GC. [c] Enantiomeric excess measured by GC.

3.3.2.3 Asymmetric hydrogenation of enamides S4-S8

To expand the utility of monophosphite ligands **L9**-**L14a**,**f**,**g** and further investigate the influence of the introduction of a new substituent at C-3 of the

furanoside backbone, we examined the Rh-catalyzed enantioselective hydrogenation of several 1,1-disubstituted-α-arylenamides (Equation 2). The hydrogenation of this substrate class gives access to chiral secondary amines, which are highly valuable intermediates for preparing chiral pharmaceutical and agricultural products.[12]



S4 R= C_6H_5
S5 R= 4-F-C_6H_4
S6 R= 4-Me-C_6H_4
S7 R= 4-OMe-C_6H_4
S8 R= 2-Naphthyl

First, we used *N*-(1-phenylvinyl)-acetamide **S4** as substrate to study the potential of the ligand library. The results are summarized in Table 3.3.4.

Table 3.3.4 Selected results for the Rh-catalyzed hydrogenation of **S4** using the furanoside monophosphite ligand library **L9**-**L14a**,**f**,**g**[a]

Entry	Ligand	% Conv[b]	% ee[c]
1	**L9a**	<5	nd
2	**L9f**	100	54 (*S*)
3	**L9g**	100	24 (*R*)
4	**L10a**	<5	nd
5	**L10f**	100	32 (*R*)
6	**L10g**	100	44 (*S*)
7	**L11f**	100	29 (*R*)
8	**L12f**	100	18 (*R*)
9	**L13f**	100	26 (*R*)
10	**L14f**	100	58 (*R*)
11	**L15a**	<5	nd
12	**L15f**	100	93.9 (*S*)[d]
13	**L15g**	100	85.5 (*R*)[d]
14	**L16a**	<5	nd
15	**L16f**	100	49.1 (*R*)[d]
16	**L16g**	100	87.1 (*S*)[d]

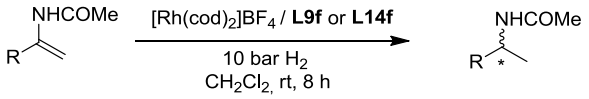
[a] $[Rh(nbd)_2]SbF_6$ (1 mol%), ligand (1.1 mol%), **S2** (1 mmol), CH_2Cl_2 (6 mL), 10 bar of H_2, room temperature. [b] % Conversion measured by GC. [c] Enantiomeric excess measured by GC. [d] Data from ref. 3e.

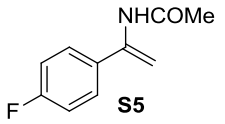
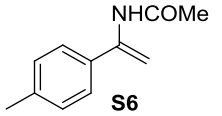
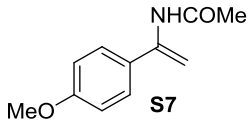
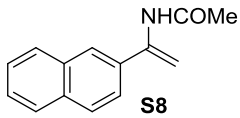
In general, catalytic activity and enantioselectivity are affected by the same parameters than for substrates **S1**-**S3**. However, in all cases except for ligand **L14f** (entry 10 vs 15), the introduction of a substituent at C-3 has a negative effect on enantioselectivity (i.e. entries 2-3 vs 12-13, and entries 5-6 vs 15-16).

Nevertheless, both enantiomers of the hydrogenation product can be obtained in similar moderate enantioselectivities using ligands **L9f** and **L14f** (ee's up to 58%; entries 2 and 10).

To further investigate the catalytic efficiency of the Rh/**L9f** and Rh/**L14f** catalytic systems, we tested them in the Rh-catalyzed hydrogenation of other enamides with different aryl substituents. The results, which are given in Table 3.3.5, indicated that catalytic performance (activity and enantioselectivity) is hardly affected by the presence of either electron-donating or electron-withdrawing groups at the *para* positions of the aryl group. However, the highest enantioselectivity was achieved using *N*-(1-(2-naphthyl)vinyl)-acetamide **S8** as substrate (ee's up to 67%; Table 3.3.5, entries 7 and 8).

Table 3.3.5 Selected results for the Rh-catalyzed hydrogenation of enamides **S5**-**S8** using the Rh/**L9f** and Rh/**L14f** catalytic system[a]



Entry	Ligand	Ligand	% Conv[b]	% ee[c]
1	 **S5**	**L9f**	100	53 (*S*)
2		**L14f**	100	57 (*R*)
3	 **S6**	**L9f**	100	59 (*S*)
4		**L14f**	100	61 (*R*)
5	 **S7**	**L9f**	100	56 (*S*)
6		**L14f**	100	59 (*R*)
7	 **S8**	**L9f**	100	64 (*S*)
8		**L14f**	100	67 (*R*)

[a] $[Rh(cod)_2]BF_4$ (1 mol%), ligand (1.1 mol%), substrate (0.5 mmol), CH_2Cl_2 (6 mL), 30 bar of H_2, room temperature. [b] % Conversion measured by GC. [c] Enantiomeric excess measured by GC.

3.3.3 Conclusions

We have expanded the ligand design of one of the most successful monophosphite ligands in Rh-catalyzed hydrogenation by introducing several substituents at C-3 position of the furanoside backbone. These new furanoside monophosphite ligands have been evaluated in the Rh-catalyzed asymmetric hydrogenation of α,β-unsaturated carboxylic acid derivatives and enamides. The general tendency is that the effect of introducing these new substituents on enantioselectivity depends on the configuration at both C-3 of the furanoside backbone and at the binaphthyl moiety as well as the substrate. Thus, for α,β-unsaturated carboxylic acids, enantioselectivities improved when introducing a methyl substituent at C-3 in glucofuranoside ligand containing an *S*-binaphthyl group (ligand **L9g**). Enantioselectivities could be therefore increased to >99.9% ee and 85% ee in the asymmetric reduction of dimethyl itaconate and dehydroamino acid derivatives, respectively. However, in the reduction of enamides, the introduction of substituents at C-3 of the furanoside backbone has a negative effect on enantioselectivity. Only moderate enantioselectivities could be therefore achieved for this substrate class (ee's up to 67%).

3.3.4 Experimental Section

3.3.4.1 General Considerations

All syntheses were performed by using standard Schlenk techniques under an argon atmosphere. Solvents were purified by standard procedures. Phosphorochloridites are easily prepared in one step from the corresponding biaryls.[13] Compounds **3**[5,6] and **4**-**8**[7] were prepared as previously reported. Monophosphite ligands **L15**-**L16a**,**f**,**g** were prepared as previously described.[3d,14] Methyl (*Z*)-*N*-acetylaminocinnamate **S3**[15] and enamides **S4**-**S8**[16] were prepared following literature procedures. All other reagents were used as commercially available. ^{1}H, $^{13}C\{1H\}$, $^{31}P\{1H\}$ NMR spectra experiments were recorded using a 400 MHz spectrometer. Chemical shifts are relative to that of $SiMe_4$ (^{1}H and ^{13}C) as internal standard or H_3PO_4 (^{31}P) as external standard. ^{1}H and ^{13}C assignments were done based on ^{1}H-^{1}H gCOSY and ^{1}H-^{13}C gHSQC experiments. Elemental analyses were carried out by the "Service Central d'Analyses du CNRS" in Lyon using LECO SC 144 microanalyzer.

3.3.4.2 Typical procedure for the preparation of monophosphite ligands

The corresponding phosphorochloridite (1.1 mmol) produced in situ was dissolved in toluene (5 mL) before the addition of pyridine (0.18 mL, 2.3 mmol). Alcohol (1 mmol) was azeotropically dried with toluene (3 x 1 mL) and then dissolved in toluene (5 mL), to which pyridine (0.18 mL, 2.3 mmol) was added. The phosphorochloridite solution was transferred slowly to the solution of alcohol. The reaction mixture was warmed to 80 ^{o}C and stirred for 4 h, after which 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.

L9a: Yield: 415 mg (58%). ^{31}P NMR (C_6D_6), δ: 150.8 (s, 1P). ^{1}H NMR (C_6D_6), δ: 1.05 (s, 3H, CH_3), 1.19 (s, 3H, CH_3), 1.23 (s, 9H, CH_3, ^{t}Bu), 1.26 (s, 9H, CH_3, ^{t}Bu), 1.31 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 1.48 (s, 9H, CH_3, ^{t}Bu), 1.53 (s, 9H, CH_3, ^{t}Bu), 1.94 (s, 3H, CH_3), 3.69 (dd, 1H, H-6' , $^{2}J_{6'-6}$ = 8.4 Hz, $^{3}J_{6'-5}$ = 6.0 Hz), 3.97 (dd, 1H, H-6, $^{2}J_{6-6'}$ = 8.4 Hz, $^{3}J_{6-5}$ = 6.0 Hz), 4.13 (dd, 1H, H-4, $^{3}J_{4-5}$ = 2.4 Hz, $^{3}J_{4-P}$ = 6.4 Hz), 4.42 (m, 1H, H-5), 4.71 (dd, 1H, H-2, $^{3}J_{2-1}$ = 3.6 Hz, J_{2-P} = 4.0 Hz), 5.87 (d, 1H, H-1, $^{3}J_{1-2}$ = 3.6 Hz), 7.29 (m, 2H, CH=), 7.54 (m, 2H, CH=). ^{13}C NMR (C_6D_6), δ: 19.1 (d, CH_3, J_{C-P} = 11.5 Hz), 25.3 (CH_3), 26.1 (CH_3), 26.5 (CH_3), 26.6 (CH_3), 30.8 (CH_3, ^{t}Bu), 30.9 (CH_3, ^{t}Bu), 31.0 (CH_3, ^{t}Bu), 31.1 (CH_3, ^{t}Bu), 34.2 (C, ^{t}Bu), 35.1 (C, ^{t}Bu), 35.2 (C, ^{t}Bu), 66.6 (C-6), 72.7 (C-5), 84.5 (C-4), 86.7 (d, C-3, J_{C-P} = 8.4 Hz), 87.2 (C-2), 104.7 (C-1), 108.7 (CMe_2), 111.9 (CMe_2), 123.9 (CH=), 124.1 (CH=), 126.7 (CH=), 126.9 (CH=), 140.1 (C), 140.3 (C), 146.1 (C), 146.2 (C), 146.5 (C), 146.6 (C). Anal. Calcd for $C_{41}H_{61}O_8P$: C, 69.08; H, 8.62. Found: C, 69.12; H, 8.61.

L9f: Yield: 389 mg (65%). ^{31}P NMR (C_6D_6), δ: 150.7 (s, 1P). ^{1}H NMR (C_6D_6), δ: 1.09 (s, 3H, CH_3), 1.14 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 1.37 (s, 3H, CH_3), 1.96 (d, 3H, CH_3, J_{3-P} = 1.2 Hz), 3.79 (dd, 1H, H-6' , $^{2}J_{6'-6}$ = 8.4 Hz, $^{3}J_{6'-5}$ = 6.0 Hz), 3.99 (dd, 1H, H-6, $^{2}J_{6-6'}$ = 8.4 Hz, $^{3}J_{6-5}$ = 6.0 Hz), 4.13 (dd, 1H, H-4, $^{3}J_{4-5}$ = 2.8 Hz, $^{3}J_{4-P}$ = 7.6 Hz), 4.37 (m, 1H, H-5), 4.66 (dd, 1H, H-2, $^{3}J_{2-1}$ = 3.6 Hz, J_{2-P} = 1.6 Hz), 5.94 (d, 1H, H-1, $^{3}J_{1-2}$ = 3.6 Hz), 6.86–7.63 (m, 12H, CH=). ^{13}C NMR (C_6D_6), δ: 19.3 (d, CH_3, J_{C-P} = 16.0 Hz), 25.3 (CH_3), 26.7 (CH_3), 27.0 (CH_3), 27.3 (CH_3), 67.6 (C-6), 73.1 (C-5), 84.7 (C-4), 87.3 (d, C-3, J_{C-P} = 3.2 Hz), 87.6 (C-2), 105.3 (C-1), 109.4 (CMe_2), 112.8 (CMe_2), 122.1 (CH=), 122.4 (CH=), 125.2 (CH=), 125.3 (CH=), 126.7 (CH=), 127.4 (CH=), 127.5 (CH=), 128.7 (CH=), 129.9 (CH=), 130.7 (CH=), 131.7 (C), 132.1 (C), 133.2 (C), 133.5 (C), 148.2 (C), 148.4 (C). Anal. Calcd for $C_{33}H_{33}O_8P$: C, 67.34; H, 5.65. Found: C, 67.36; H, 5.68.

L9g: Yield: 415 mg (70%). ^{31}P NMR (C_6D_6), δ: 151.9 (s, 1P). ^{1}H NMR (C_6D_6), δ: 0.94 (s, 3H, CH_3), 1.29 (s, 3H, CH_3), 1.32 (s, 3H, CH_3), 1.39 (s, 3H, CH_3), 2.03 (s, 3H,

CH_3), 3.87 (dd, 1H, H-6' , $^2J_{6'-6}$ = 8.8 Hz, $^3J_{6'-5}$ = 6.0 Hz), 4.06 (m, 2H, H-6 and H-4), 4.48 (m, 1H, H-5), 4.51 (m, 1H, H-2), 5.71 (d, 1H, H-1, $^3J_{1-2}$ = 3.6 Hz), 6.83–7.69 (m, 12H, CH=). ^{13}C NMR (C_6D_6), δ: 18.9 (d, CH_3, J_{C-P} = 15.3 Hz), 25.2 (CH_3), 26.0 (CH_3), 26.7 (CH_3), 26.8 (CH_3), 67.5 (C-6), 72.7 (C- 5), 84.3 (C-4), 86.7 (C-2), 87.0 (b, C-3), 104.7 (C-1), 109.2 (CMe_2), 112.3 (CMe_2), 121.6 (CH=), 122.4 (CH=), 124.9 (CH=), 125.3 (CH=), 126.3 (CH=), 126.4 (CH=), 126.9 (CH=), 127.2 (CH=), 128.3 (CH=), 128.9 (CH=), 129.5 (CH=), 130.4 (CH=), 131.4 (C), 131.8 (C), 132.8 (C), 133.1 (C), 147.8 (C), 148.1 (C). Anal. Calcd for $C_{33}H_{33}O_8P$: C, 67.34; H, 5.65. Found: C, 67.29; H, 5.63.

L10a: Yield: 552 mg (77%). ^{31}P NMR (C_6D_6), δ: 146.9 (s, 1P). ^{1}H NMR (C_6D_6), δ: 1.09 (s, 3H, CH_3), 1.10 (s, 3H, CH_3), 1.21 (s, 3H, CH_3), 1.23 (s, 9H, CH_3, ^{t}Bu), 1.25 (s, 9H, CH_3, ^{t}Bu), 1.30 (s, 3H, CH_3), 1.48 (s, 3H, CH_3), 1.59 (s, 9H, CH_3, ^{t}Bu), 1.63 (s, 9H, CH_3, ^{t}Bu), 3.75 (dd, 1H, H-6' , $^2J_{6'-6}$ = 8.0 Hz, $^3J_{6'-5}$ = 6.8 Hz), 3.93 (dd, 1H, H-6, $^2J_{6-6'}$ = 8.0 Hz, $^3J_{6-5}$ = 6.4 Hz), 4.07 (m, 1H, H-5), 4.13 (d, 1H, H-2, $^3J_{2-1}$ = 3.6 Hz), 4.59 (d, 1H, H-4, $^3J_{4-5}$ = 4.4 Hz), 5.36 (d, 1H, H-1, $^3J_{1-2}$ = 3.6 Hz), 7.29 (m, 2H, CH=), 7.56 (m, 2H, CH=). ^{13}C NMR (C_6D_6), δ: 21.0 (d, CH_3, J_{C-P} = 9.6 Hz), 25.2 (CH_3), 26.3 (CH_3), 26.4 (CH_3), 26.8 (CH_3), 31.0 (CH_3, ^{t}Bu), 31.2 (CH_3, ^{t}Bu), 31.3 (CH_3, ^{t}Bu), 31.5 (CH_3, ^{t}Bu), 34.2 (C, ^{t}Bu), 34.3 (C, ^{t}Bu), 35.2 (C, ^{t}Bu), 35.5 (C, ^{t}Bu), 65.7 (C-6), 73.6 (C-5), 80.6 (d, C-4, J_{C-P} = 5.3 Hz), 82.7 (C-2), 83.8 (C-3), 103.6 (C-1), 108.6 (CMe_2), 112.9 (CMe_2), 123.7 (CH=), 124.0 (CH=), 126.5 (CH=), 126.9 (CH=), 133.4 (C), 134.0 (C), 140.1 (C), 140.5 (C), 146.0 (C), 146.2 (C), 146.4 (C). Anal. Calcd for $C_{41}H_{61}O_8P$: C, 69.08; H, 8.62. Found: C, 69.05; H, 8.60.

L10f: Yield: 441 mg (75%). ^{31}P NMR (C_6D_6), δ: 150.9 (s, 1P). ^{1}H NMR (C_6D_6), δ: 1.20 (s, 3H, CH_3), 1.24 (s, 3H, CH_3), 1.28 (s, 3H, CH_3), 1.29 (s, 3H, CH_3), 1.56 (s, 3H, CH_3), 3.99 (m, 4H, H-6' , H-6, H-5 and H-2), 4.57 (dd, 1H, H-4, $^3J_{4-5}$ = 3.2 Hz, J_{4-P} = 8.0 Hz), 5.38 (d, 1H, H-1, $^3J_{1-2}$ = 4.0 Hz), 6.91–7.81 (m, 12H, CH=). ^{13}C NMR (C_6D_6), δ: 20.5 (d, CH_3, J_{C-P} = 5.3 Hz), 25.3 (CH_3), 26.4 (CH_3), 26.6 (CH_3), 26.7 (CH_3), 67.6 (C-6), 73.6, 79.5 (d, C-4, J_{C-P} = 9.9 Hz), 83.4 (d, C-3, J_{C-P} = 5.3 Hz), 84.3, 103.7 (C-1), 109.6 (CMe_2), 113.1 (CMe_2), 121.9 (CH=), 122.8 (CH=), 124.6 (CH=), 126.0 (CH=), 126.2 (CH=), 127.4 (CH=), 128.1 (CH=), 128.3 (CH=), 129.1 (CH=), 130.1 (CH=), 131.2 (C), 131.6 (C), 132.9 (C), 133.2 (C), 148.4 (C), 148.6 (C). Anal. Calcd for $C_{33}H_{33}O_8P$: C, 67.34; H, 5.65. Found: C, 67.41; H, 5.68.

L10g: Yield: 322 mg (55%). ^{31}P NMR (C_6D_6), δ: 149.1 (s, 1P). ^{1}H NMR (C_6D_6), δ: 1.08 (s, 3H, CH_3), 1.20 (s, 3H, CH_3), 1.29 (s, 3H, CH_3), 1.37 (s, 3H, CH3), 2.67 (s, 3H, CH_3), 3.87 (d, 1H, H-2, $^3J_{2-1}$ = 3.6 Hz), 3.99 (m, 3H, H-6' , H-6 and H-5), 4.65 (dd, 1H, H-4, $^3J_{4-5}$ = 4.0 Hz, J_{4-P} = 7.2 Hz), 5.29 (d, 1H, H-1, $^3J_{1-2}$ = 3.6 Hz), 6.91–7.81 (m, 12H, CH=). ^{13}C NMR (C_6D_6), δ: 20.5 (d, CH_3, J_{C-P} = 3.8 Hz), 26.1 (CH_3), 27.0 (CH_3), 27.2

(CH_3), 27.3 (CH_3), 68.5 (C-6), 74.3, 80.2 (d, C-4, J_{C-P} = 12.2 Hz), 84.0 (d, C-3, J_{C-P} = 2.2 Hz), 84.9 (C-2), 104.2 (C-1), 110.5 (CMe_2), 113.5 (CMe_2), 123.7 (CH=), 125.4 (CH=), 125.5 (CH=), 126.9 (CH=), 127.6 (CH=), 127.9 (CH=), 128.1 (CH=), 128.9 (CH=), 129.0 (CH=), 129.1 (CH=), 129.6 (CH=), 129.9 (CH=), 130.7 (C), 132.0 (C), 132.3 (C), 133.6 (C), 133.9 (C), 149.3 (C), 149.6 (C). Anal. Calcd for $C_{33}H_{33}O_8P$: C, 67.34; H, 5.65. Found: C, 67.39; H, 5.69.

L11f: Yield: 458 mg (76%). ^{31}P NMR (C_6D_6), δ: 148.7 (s, 1P). ^{1}H NMR (C_6D_6), δ: 0.73 (m, 3H, CH_3, Et), 1.19 (m, 1H, CH_2, Et), 1.22 (s, 3H, CH_3), 1.31 (s, 3H, CH_3), 1.51 (s, 3H, CH_3), 1.63 (s, 3H, CH_3), 1.89 (m, 1H, CH_2, Et), 4.02 (m, 2H, H-6' and H-6), 4.08 (m, 1H, H-5), 4.28 (d, 1H, H-2, $^{3}J_{2-1}$ = 3.6 Hz), 4.79 (dd, 1H, H-4, $^{3}J_{4-5}$ = 5.2 Hz, J_{4-P} = 8.4 Hz), 5.39 (d, 1H, H-1, $^{3}J_{1-2}$ = 4.0 Hz), 6.92–7.79 (m, 12H, CH=). ^{13}C NMR (C_6D_6), δ: 7.1 (CH_3, Et), 21.0 (b, CH_2, Et), 24.9 (CH_3), 25.1 (CH_3), 26.5 (CH_3), 26.6 (CH_3), 68.1 (C-6), 73.0 (C-5), 79.8 (d, C-4, J_{C-P} = 12.4 Hz), 80.1 (C-2), 86.2 (C-3), 103.7 (C-1), 109.6 (CMe_2), 112.9 (CMe_2), 121.9 (CH=), 123.0 (CH=), 124.5 (CH=), 126.0 (CH=), 126.1 (CH=), 127.0 (CH=), 127.1 (CH=), 128.1 (CH=), 128.3 (CH=), 128.9 (CH=), 130.0 (CH=), 131.2 (C), 131.5 (C), 132.9 (C), 133.2 (C), 148.7 (C), 148.8 (C). Anal. Calcd for $C_{34}H_{35}O_8P$: C, 67.77; H, 5.85. Found: C, 67.74; H, 5.86.

L12f: Yield: 336 mg (55%). ^{31}P NMR (C_6D_6), δ: 147.6 (s, 1P). ^{1}H NMR (C_6D_6), δ: 0.62 (d, 3H, CH_3, ^{i}Pr, $^{3}J_{H-H}$ = 7.2 Hz), 0.76 (d, 3H, CH_3, ^{i}Pr, $^{3}J_{H-H}$ = 7.2 Hz), 1.24 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 1.58 (s, 3H, CH_3), 1.68 (s, 3H, CH_3), 2.34 (m, 1H, CH, ^{i}Pr), 4.07 (m, 2H, H-6' and H-6), 4.25 (m, 1H, H-5), 4.30 (d, 1H, H-2, $^{3}J_{2-1}$ = 4.0 Hz), 4.93 (dd, 1H, H-4, $^{3}J_{4-5}$ = 8.0 Hz, J_{4-P} = 9.2 Hz), 5.47 (d, 1H, H-1, $^{3}J_{1-2}$ = 4.0 Hz), 6.92–7.80 (m, 12H, CH=). ^{13}C NMR (C_6D_6), δ: 17.6 (CH_3, ^{i}Pr), 18.4 (CH_3, ^{i}Pr), 25.9 (CH3), 27.2 (CH_3), 27.3 (CH_3), 31.4(CH_2, ^{i}Pr), 69.4 (C-6), 73.5 (C-5), 79.2 (C-2), 82.0 (d, C-4, J_{C-P} = 16.7 Hz), 89.5 (C-3), 105.1 (C-1), 110.7 (CMe_2), 113.4 (CMe_2), 122.6 (CH=), 123.8 (CH=), 125.2 (CH=), 126.0 (CH=), 126.7 (CH=), 126.8 (CH=), 127.7 (CH=), 127.8 (CH=), 128.9 (CH=), 129.0 (CH=), 129.6 (CH=), 130.7 (CH=), 131.9 (C), 132.2 (C), 133.7 (C), 134.0 (C), 149.6 (C), 149.7 (C). Anal. Calcd for $C_{35}H_{37}O_8P$: C, 68.17; H, 6.05. Found: C, 68.21; H, 6.08.

L13f: Yield: 351 mg (53%). ^{31}P NMR (C_6D_6), δ: 147.5 (s, 1P). ^{1}H NMR (C_6D_6), δ: 1.05 (s, 3H, CH_3), 1.37 (s, 3H, CH_3), 1.58 (s, 3H, CH_3), 1.72 (s, 3H, CH_3), 2.40 (m, 1H, CH_2-Ph), 3.35 (m, 1H, CH_2-Ph), 3.78 (dd, 1H, H-6' , $^{2}J_{6-6'}$ = 8.8 Hz, $^{3}J_{6-5}$ = 6.8 Hz), 4.06 (m, 1H, H-6), 4.21 (m, 1H, H-5), 4.39 (d, 1H, H-2, $^{3}J_{2-1}$ = 3.6 Hz), 5.03 (dd, 1H, H-4, $^{3}J_{4-5}$ = 5.6 Hz, J_{4-P} = 8.0 Hz), 5.62 (d, 1H, H-1, $^{3}J_{1-2}$ = 3.6 Hz), 6.82–7.76 (m, 17H, CH=). ^{13}C NMR (C_6D_6), δ: 25.0 (CH_3), 25.4 (CH_3), 26.0 (CH_3), 26.4 (CH_3), 38.2 (CH_2-Ph), 68.5 (C-6), 72.8 (C-5), 78.2 (d, C-4, J_{C-P} = 7.5 Hz), 80.2 (C-2), 85.9 (C-3), 103.3 (C-

1), 109.9 (CMe_2), 113.1 (CMe_2), 121.8 (CH=), 122.7 (CH=), 123.5 (C), 124.6 (CH=), 125.3 (CH=), 126.2 (CH=), 126.3 (CH=), 127.0 (CH=), 127.1 (CH=), 128.1 (CH=), 128.9 (CH=), 129.6 (C), 130.1 (C), 130.9 (CH=), 131.1 (C), 131.6 (C), 132.8 (C), 133.2 (C), 134.9 (C), 148.6 (C), 148.8 (C). Anal. Calcd for $C_{39}H_{37}O_8P$: C, 70.47; H, 5.61. Found: C, 70.45; H, 5.63.

L14f: Yield: 441 mg (68%). ^{31}P NMR (C_6D_6), δ: 146.9 (s, 1P). ^1H NMR (C_6D_6), δ: 1.15 (s, 3H, CH_3), 1.24 (s, 3H, CH_3), 1.54 (s, 3H, CH_3), 1.69 (s, 3H, CH_3), 3.43 (dd, 1H, H-6' , $^2J_{6-6'}$ = 7.6 Hz, $^3J_{6-5}$ = 5.6 Hz), 3.81 (m, 1H, H-5), 3.85 (m, 1H, H-6), 4.55 (d, 1H, H-2, $^3J_{2-1}$ = 3.6 Hz), 5.21 (t, 1H, H-4, J = 7.2 Hz), 5.75 (d, 1H, H-1, $^3J_{1-2}$ = 3.6 Hz), 6.89–7.71 (m, 17H, CH=). ^{13}C NMR (C_6D_6), δ: 25.1 (CH_3), 26.4 (CH_3), 26.5 (CH_3), 26.6 (CH_3), 66.4 (C-6), 73.5 (C-5), 80.1 (d, C-4, J_{C-P} = 16.9 Hz), 84.5 (C-2), 87.8 (C-3), 104.9 (C-1), 109.2 (CMe_2), 113.3 (CMe_2), 121.9 (CH=), 122.5 (CH=), 123.6 (C), 124.5 (CH=), 124.7 (CH=), 125.3 (CH=), 126.2 (CH=), 126.3 (CH=), 127.0 (CH=), 127.2 (CH=), 128.2 (CH=), 128.3 (CH=), 128.9 (CH=), 129.3 (C), 130.3 (C), 131.2 (CH=), 131.6 (C), 132.8 (C), 133.5 (C), 137.5 (C), 138.2 (C), 148.5 (C), 148.8 (C). Anal. Calcd for $C_{38}H_{35}O_8P$: C, 70.15; H, 5.42. Found: C, 70.11; H, 5.38.

3.3.4.3 Asymmetric hydrogenation

In a typical run, $[Rh(nbd)_2]SbF_6$ (5.2 mg, 0.01 mmol), the corresponding ligand (0.022 mmol, 2.2 equivalents) were dissolved in dichloromethane (6 mL) and the resulting solution stirred at room temperature for 30 minutes. The catalyst solution was then transferred to a steel autoclave equipped with a glass liner already containing the substrate (1 mmol). The autoclave was purged five times with hydrogen gas. Then, it was pressurized to the desired pressure. After the desired reaction time, the autoclave was depressurized and the solvent evaporated off. The residue was dissolved in Et_2O (2 mL) and filtered through a short celite plug. The enantiomeric excess was determined by chiral GC and conversions were determined by GC and confirmed by ^1H NMR. The enantiomeric excesses of hydrogenated products were determined using the conditions previously described.[17]

3.3.5. Acknowledgements

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UNIVERSITAT ROVIRA I VIRGILI
SCREENING OF MODULAR SUGAR DERIVED PHOSPHITE-BASED LIGAND LIBRARIES FOR M-CATALYZED REACTIONS. A GREEN APPROACH TO CATALYSTS DISCOVERY
Sabina Alegre Aragonés
Dipòsit Legal: T.194-2014

3.4 Asymmetric Ir-catalyzed hydrogenation of minimally functionalized olefins using a thioether-phosphite ligand library derived from L-(+)-tartaric acid.

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

Abstract. Thioether-phosphite ligands prepared from readily available L-(+)-tartaric acid were applied to the Ir-catalyzed asymmetric hydrogenation of minimally functionalized olefins. Our results show that the enantioselectivity is dependent on the ligand parameters (thioether substituent, substituent at the alkyl backbone chain next to the phosphite moiety and the substituents/configurations in the biaryl phosphite group) as well as the substrate structure. Moderate enantioselectivities were achieved in the reduction of *E*- and *Z*-trisubstituted olefins (ee's up to 70% and 50%, respectively). However, for disubstituted substrate 3,3-dimethyl-2-phenyl-1-butene, excellent enantioselectivities (ee's up to 98%) and activities were achieved at low hydrogen pressure. For the latter substrate, the sense of enantioselectivity is controlled by the configuration of the biaryl phosphite group which allows the preparation of both enantiomers of the hydrogenation product. The asymmetric hydrogenation was also performed using propylene carbonate as an environmentally friendly solvent, which allowed the Ir-catalysts to be reused with no loss in enantiomeric excess.

3.4.1 Introduction

Metal-catalyzed asymmetric reactions have become one of the most powerful tools for the production of enantiomerically pure compounds. The large number and permanently growing number of chemical processes suitable for asymmetric catalysis, as well as the large variety of substrate to which they can be applied represent a permanent need for the discovery of new catalysts.[1] The performance of catalytic enantioselective reactions largely depends on appropriate chiral ligands being selected for the catalyst structure. Most of the research in this area, then, has focused on finding new series of efficient chiral ligands. Although many thousands of chiral ligands have been prepared and tested, very few of them have been found to have a general scope.[1]

Because of its high efficiency, atom economy and operational simplicity, asymmetric hydrogenation that uses molecular hydrogen to reduce prochiral olefins has become one of the most reliable catalytic methods for preparing optically active compounds.[1] The first asymmetric hydrogenation reactions were reported in 1968 independently by Horner and Knowles.[2] In 1977, Knowles introduced the bidentate P-stereogenic phosphine ligand DIPAMP, which allowed the stereoselective hydrogenation of α-acylaminoacrylates with up to 96% ee.[3] This process was used as a key step in the synthesis of Dopa, the first industrially applied asymmetric hydrogenation.[4] In the meantime, a wide range of other ligands have been developed for not only Rh- but also Ru-catalyzed processes.[1] Nevertheless, the asymmetric hydrogenation of minimally functionalized alkenes was a challenge for a long time because these substrates have no adjacent polar group to direct the reaction.[5]

In 1977, Crabtree described the first homogeneous achiral iridium catalyst which allowed the reduction of a wide range of minimally functionalized, also highly substituted, alkenes.[6] On the basis of this pioneering work, Pfaltz et al. developed a new class of hydrogenation Ir-catalysts with chiral P,N ligands (PHOX ligands).[7] Since then, most of the research has been devoted to develop new P,N chiral ligands.[5] The first successful P,N ligands contained a phosphine or phosphinite moiety as P-donor group and either an oxazoline, oxazole, thiazole or pyridine as *N*-donor group.[8,9] However, these iridium-phosphine/phosphinite,N catalysts were still highly substrate-dependent and the development of efficient chiral ligands that tolerate a broader range of substrates remained a challenge. Some years ago we discovered that the presence of biaryl-phosphite moieties in these P,N-ligands provides greater substrate versatility than previous Ir-phosphine/phosphinite,N catalyst systems.[10] Although the number of substrates that can be successfully reduced increased, there is still an important substrate classes that give unsatisfactory results with known catalysts. More research is therefore needed to find more versatile ligand systems that can be synthesized on an efficient and modular synthetic route using simple starting materials.

In this respect, research focus in the possibility of changing the nature of the N-donor atom in these heterodonor ligands has not been contemplated until very recently.[11,12] Thus, we have recently communicated the first successful application of non-N-donor heterodonor ligands – thioether-phosphite – for asymmetric Ir-catalyzed hydrogenation of model trisubstituted and terminal minimally functionalized olefins.[11] Despite this success, the use of other thioether-

phosphite ligands has not yet been reported and a systematic study of the possibilities offered by thioether-phosphorus as new ligands for this process is still needed. For this purpose in this chapter we report the synthesis and application of new Ir-complexes modified with a chiral thioether-phosphite ligand library derived from L-(+)-tartaric acid (**L1**-**L8a**-**e**; Figure 3.4.1). The modular ligand design allowed us to systematically investigate the effect of varying: (a) the electronic and steric properties of the thioether group (ligands **L1**-**L7**); (b) the substituents in the alkyl backbone chain next to the phosphite moiety (ligands **L1** and **L8**); and (c) the substituents/configurations in the biaryl phosphite moiety (**a**-**e**). By carefully selecting these elements, we achieved moderate-to-high enantioselectivities and activities in a range of minimally functionalized olefins.

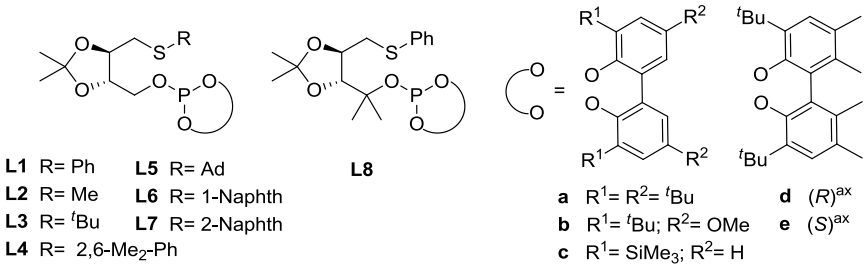
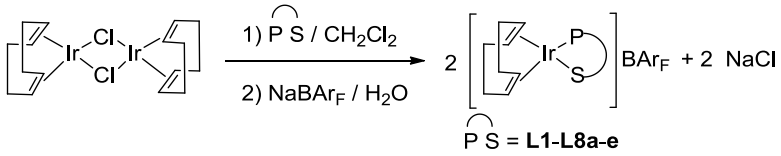


Figure 3.4.1. Thioether-phosphite ligands **L1**-**L8a**-**e**.

3.4.2 Results and discussion

3.4.2.1 Synthesis of the Ir-catalyst precursors

The catalyst precursors were made by refluxing a dichloromethane solution of the appropriate ligand (**L1**-**L8a**-**e**) in the presence of 0.5 equivalent of $[Ir(\mu\text{-}Cl)cod]_2$ for 1 h and then exchanging the counterion with sodium tetrakis[3,5-bis(trifluoromethyl)-phenyl]borate ($NaBAr_F$) (1 equiv), in the presence of water (Scheme 3.4.2.1). All complexes were isolated as air-stable red-orange solids and were used without further purification. The complexes were characterized by elemental analysis and ^{1}H, ^{13}C, and ^{31}P NMR spectroscopy. The spectral assignments were based on information from ^{1}H-^{1}H and ^{13}C-^{1}H correlation measurements and were as expected for these iridium complexes.



Scheme 3.4.2.1 Synthesis of catalyst precursors [Ir(cod)(P-S)]BAr_F (P-S = **L1**-**L8a**-**e**).

3.4.2.2 Asymmetric hydrogenation of trisubstituted olefins S1-S2

In a first set of experiments we used the Ir-catalyzed hydrogenation of substrate *E*-2-(4-methoxyphenyl)-2-butene **S1** to study the potential of thioether-phosphite ligands **L1**-**L8a**-**e**. Substrate **S1** was chosen as a model for the hydrogenation of trisubstituted olefins because it has been reduced with a wide range of ligands, which enable the efficiency of the various ligand systems to be compared directly.[5] The results, which are summarized in Table 3.4.1, indicate that enantioselectivities are highly affected by a subtle balance of the thioether substituent, the substituent at the alkyl backbone chain next to the phosphite moiety as well as the configuration of the biaryl phosphite moiety.

Using ligands **L1a**-**e**, we investigated the effect of the substituents/configuration at the biaryl phosphite moiety. The results indicated that although the nature of the substituents at the biaryl phosphite moiety has little impact on the catalytic performance (Table 3.4.1, entries 1-3), enantioselectivity is highly affected by the configuration of the biaryl phosphite moiety (entries 4-5 vs 1-3). In general, ligands containing an *R*-biaryl phosphite moiety (**d**) provide higher enantioselectivities than ligands containing an S-biaryl group (**e**) (i.e. entry 4 vs 5).

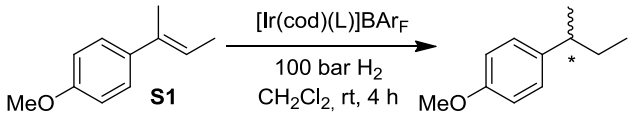
The results also indicate that enantioselectivity is affected by the thioether substituent. The presence of an aromatic rather than an alkyl substituent is beneficial in terms of enantioselectivity (*i.e.* entries 4 vs 6, 8 and 13). The highest enantioselectivity of the series was achieved using bulky 2,6-dimethylphenyl thioether substituent (**L4**; Table 3.4.1 entries 11 and 12).

We also found that introducing methyl substituents at the alkyl backbone chain next to the phosphite moiety (ligands **L8**) has a negative effect on enantioselectivity (*i.e.* entry 4 vs 20). This contrast with the highly positive effect observed in the Rh-catalyzed hydrogenation of functionalized olefins (Chapter 3.2).

In summary the best results were achieved with ligands **L4d**-**e**, which contains the optimal combination of ligand parameters (ee's up to 70%, entries 11

and 12). Interestingly, they provide opposite enantiomers of the hydrogenation product.

Table 3.4.1 Selected results for the Ir-catalyzed hydrogenation of **S1** using the thioether-phosphite ligand library **L1**-**L8a**-**e**[a]



Entry	Ligand	% Conv[b]	% ee[b]
1	**L1a**	99	6 (*R*)
2	**L1b**	100	5 (*R*)
3	**L1c**	100	6 (*R*)
4	**L1d**	100	66 (*R*)
5	**L1e**	99	29 (*S*)
6	**L2a**	100	19 (*R*)
7	**L3a**	100	0
8	**L3d**	100	33 (*R*)
9	**L3e**	99	10 (*S*)
10	**L4a**	95	25 (*S*)
11	**L4d**	100	69 (*R*)
12	**L4e**	100	70 (*S*)
13	**L5d**	100	21 (*R*)
14	**L5e**	99	11 (*R*)
15	**L6d**	100	50 (*R*)
16	**L6e**	98	31 (*S*)
17	**L7d**	100	60 (*R*)
18	**L7e**	100	35 (*S*)
19	**L8a**	100	25 (*S*)
20	**L8d**	100	27 (*R*)
21	**L8e**	100	36 (*S*)
22[c]	**L4e**	96	67 (*S*)
23[d]	**L4e**	74	65 (*S*)
24[e]	**L4e**	48	70 (*S*)

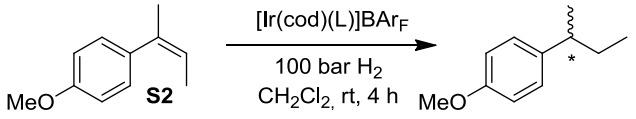
[a] Reactions carried out using 0.5 mmol of **S1** and 2 mol% of Ir-catalyst precursor.[b] Conversion and enantiomeric excesses determined by chiral GC. [c] Reaction carried out at 75 bar of H_2. [d] Reaction carried out at 50 bar of H_2. [e] Reaction carried out at 0.5 mol% of Ir-catalyst precursor.

Not only can the effect of the structural parameters on catalytic performance be controlled, but also the reaction parameters. Therefore, we next

studied the effect of the hydrogen pressure on the catalytic outcome. The results show a small decrease in enantioselectivity when the hydrogen pressure is lowered (Table 3.4.1, entries 12 vs 22 and 23). We also performed the reaction at low catalyst loading (0.5 mol%) using Ir-**L4e** catalysts (entry 24). The result shows that enantioselectivity was maintained (70% (*S*) ee).

In order to assess the potential of thioether-phosphite ligands **L1**-**L8a**-**e** for the more demanding *Z*-isomers, which are usually hydrogenated less enantioselectively than the corresponding *E*-isomers, we choose *Z*-2-(4-methoxyphenyl)-2-butene **S2** as a model.[5]

Table 3.4.2 Selected results for the Ir-catalyzed hydrogenation of **S2** using the thioether-phosphite ligand library **L1**-**L8a**-**e**[a]



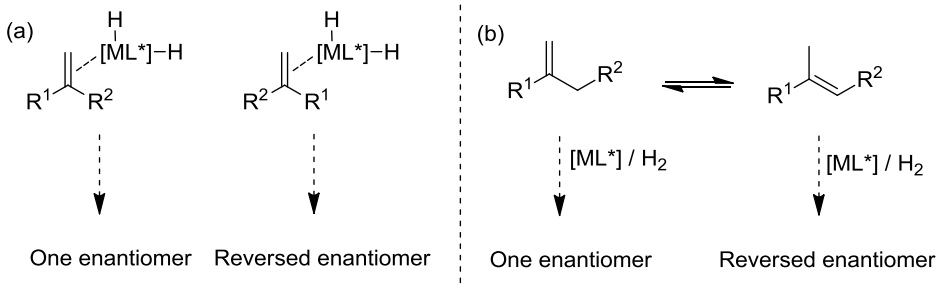
Entry	Ligand	% Conv[b]	% ee[b]
1	**L1a**	82	7 (*R*)
2	**L1b**	86	6 (*R*)
3	**L1c**	95	6 (*R*)
4	**L1d**	88	2 (*S*)
5	**L1e**	70	15 (*R*)
6	**L2a**	100	0
7	**L3a**	100	3 (*S*)
8	**L3d**	100	1 (*R*)
9	**L3e**	100	11 (*R*)
10	**L4a**	98	12 (*R*)
11	**L4d**	83	12 (*S*)
12	**L4e**	81	4 (*R*)
13	**L5d**	100	3 (*S*)
14	**L5e**	100	14 (*R*)
15	**L6d**	100	4 (*S*)
16	**L6e**	80	6 (*R*)
17	**L7d**	94	6 (*S*)
18	**L7e**	100	8 (*R*)
19	**L8a**	75	8 (*S*)
20	**L8d**	70	50 (*S*)
21	**L8e**	100	18 (*R*)

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

Disappointingly, low-to-moderate enantioselectivities were obtained (Table 3.4.2, ee's up to 50%). In contrast to the hydrogenation of **S1**, ligand **L8d** contains the optimal combination of ligand parameters (entry 20). This suggests that for this more demanding substrate the presence of methyl substituents in the alkyl backbone chain next to the phosphite moiety has a positive effect on enantioselectivity.

3.4.2.3 Asymmetric hydrogenation of disubstituted olefin S3

To further study the potential of the thioether-phosphite ligand library **L1**-**L8a**-**e**, we also screened it in the Ir-catalyzed hydrogenation of more demanding terminal olefins. Enantioselectivity is more difficult to control in these substrates than in trisubstituted olefins. There are two main reasons for this:[5d,e] a) the two substituents in the substrate can easily exchange positions in the chiral environment formed by the catalysts, thus reversing the face selectivity (Scheme 3.4.1(a)); and b) the terminal double bond can isomerize to form the more stable internal *E*-alkene, which usually leads to the predominant formation of the opposite enantiomer of the hydrogenated product (Scheme 3.4.1(b)). Few known catalytic systems provide high enantioselectivities for these substrates, and those that do are usually limited in substrate scope.[5e, 13 , 14] In contrast to the hydrogenation of trisubstituted olefins, the enantioselectivity in the reduction of terminal alkenes is highly pressure dependent. Therefore, hydrogenation at an atmospheric pressure of H_2 gave, in general, significantly higher ee values than at higher pressures.[13a]

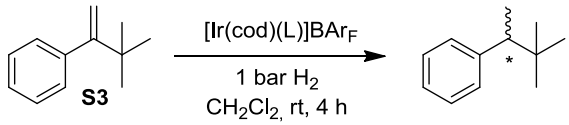


Scheme 3.4.1

As a model substrate, we have chosen the 3,3-dimethyl-2-phenyl-1-butene **S3** as a model substrate to assess the potential of the new ligand library. The results are summarized in Table 3.4.3. We were able to fine-tune the ligand

parameters to produce high activities and enantioselectivities (ee's up to 98%) in the hydrogenation of this substrate using low hydrogen pressures (1 bar).

Table 3.4.3 Selected results for the Ir-catalyzed hydrogenation of **S3** using the thioether-phosphite ligand library **L1**-**L8a**-**e**[a]



Entry	Ligand	% Conv[b]	% ee[b]
1	**L1a**	94	14 (*S*)
2	**L1b**	97	16 (*S*)
3	**L1c**	75	19 (*S*)
4	**L1d**	100	94 (*S*)
5	**L1e**	65	93 (*R*)
6	**L2a**	100	20 (*S*)
7	**L3a**	55	23 (*S*)
8	**L3d**	100	90 (S)
9	**L3e**	96	88 (*R*)
10	**L4a**	81	39 (*R*)
11	**L4d**	85	92 (*S*)
12	**L4e**	66	93 (*R*)
13	**L5d**	55	90 (*S*)
14	**L5e**	31	89 (*R*)
15	**L6d**	100	91 (*S*)
16	**L6e**	58	93 (*R*)
17	**L7d**	100	96 (*S*)
18	**L7e**	64	98 (*R*)
19	**L8a**	100	6 (*R*)
20	**L8d**	100	94 (*S*)
21	**L8e**	100	96 (*R*)

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

Although, enantioselectivities were slightly affected by the thioether substituent and the substituents in the alkyl backbone chain next to the phosphite moiety, enantioselectivity is mainly controlled by the configuration of the biaryl phosphite group (i.e. entries 1-5). Therefore, in contrast to the hydrogenation of

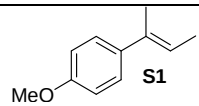
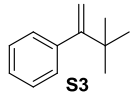
trisubstituted substrates, ligands containing enantiopure bulky *R*- and *S*-biaryl moieties (**d** and **e**) led to excellent enantioselectivities. Interestingly, the sense of enantioselectivity is controlled by the configuration of the biaryl phosphite moiety. Both enantiomers of the hydrogenation product can be therefore obtained in high enantioselectivities (ee's up to 98%).

In summary, enantioselectivities were best using the Ir-catalysts precursors containing thioether-phosphite ligands **L7d** and **L7e**. These results, which again clearly show the efficiency of using modular scaffolds in the ligand design, are among the best that have been reported for this demanding substrate.[5e]

3.4.2.4 Recycling experiments using propylene carbonate as solvent

Encouraged by the results obtained so far, we decided to go one step further and study the recycling of our catalyst systems. For a practical application, catalyst recycling is an extremely important topic because of the very high price of iridium. Propylene carbonate (PC) allows catalysts to be repeatedly recycled by a simple two phase extraction with an apolar solvent.[15] Moreover, PC is an extremely attractive solvent because of its high boiling point, low toxicity and environmentally friendly synthesis.[15,16]

Table 3.4.4. Recycling experiments with catalyst precursors [Ir(cod)(**L4e**)]BAr_F and [Ir(cod)(**L7d**)]BAr_F in PC[a]

Cycle	Substrate	% Conv (h)[b]	% ee[b]
1[c]	 **S1**	100 (4)	70 (*S*)
2[c]		87 (4)	69 (*S*)
3[c]		76 (8)	68 (*S*)
4[c]		82 (12)	69 (*S*)
1[d]	 **S3**	100 (4)	96 (S)
2[d]		96 (4)	95 (S)
3[d]		94 (6)	95 (S)
4[d]		91 (12)	95 (S)

[a] Reactions carried out using 0.5 mmol of substrate and 2 mol% of Ir-catalyst precursor. [b] Conversion and enantiomeric excesses determined by chiral GC. [c] Reaction carried out at 125 bar. [d] Reaction carried out at 50 bar.

To study whether the new Ir-P,S catalytic systems developed in this study can be efficiently recycled using PC, substrates **S1** and **S3** were hydrogenated with catalyst precursors [Ir(cod)(**L4e**)]BAr_F and [Ir(cod)(**L7d**)]BAr_F, respectivelly (Table

3.4.4). We were pleased to see that these catalysts can be used in PC up to four times with no significant losses in enantioselectivity, although the reaction time increased. This is probably due to the iridium catalyst partially passing into the hexane phase[15a] and/or the formation of inactive triiridium hydride clusters.[6b,17]

3.4.3 Conclusions

A thioether-phosphite ligand library, derived from L-(+)-tartaric acid, was tested in the asymmetric Ir-catalyzed hydrogenation of several model minimally functionalized alkenes. Our results show that catalytic performance depended strongly on the ligand parameters (the thioether substituent, the substituents/configuration in the biaryl phosphite moiety and the substituent at the alkyl chain next to the phosphite moiety) as well as the substrate. While for trisubstituted olefins only moderate enantioselectivities were achieved (ee's up to 70%), the hydrogenation of more challenging disubstituted substrate 3,3-dimethyl-2-phenyl-1-butene **S3** led to excellent enantioselectivities (ee's up to 98%). For the latter substrate, the presence of atropoisomeric chiral biaryl moieties is crucial for the high enantioselectivities achieved. Moreover, the sense of enantioselectivity is controlled by the configuration of the biaryl phosphite group which gives access to both enantiomers of the hydrogenation product in excellent enantiocontrol. The asymmetric hydrogenation was also performed using propylene carbonate as solvent, which allowed the Ir-catalysts to be reused with no loss of enantioselectivity.

3.4.4 Experimental Section

3.4.4.1 General Considerations

All syntheses were performed by using standard Schlenck techniques under an argon atmosphere. Solvents were purified by standard procedures. The synthesis of ligands **L1-L8a-e** has been previously described in Chapter 3.2. All other reagents were used as commercially available**.**

3.4.4.2 Typical procedure for the preparation of [Ir(cod)(L)]BAr_F (L =L1-L8a-e)

The corresponding ligand (0.037 mmol) was dissolved in CH_2Cl_2 (2 mL) and $[Ir(\mu\text{-}Cl)(cod)]_2$ (12.5 mg, 0.0185 mmol) was added. The reaction was refluxed at 50 °C for 1 hour. After 5 min at room temperature, $NaBAr_F$ (38.6 mg, 0.041 mmol)

and water (2 mL) were added and the reaction mixture was stirred vigorously for 30 min at room temperature. The phases were separated and the aqueous phase was extracted twice with CH_2Cl_2. The combined organic phases were dried with $MgSO_4$, filtered through a plug of celite and the solvent was evaporated to give the products as red-orange solids.

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

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

[Ir(cod)(**L1c**)]BAr_F: ^{31}P NMR (400 MHz, $CDCl_3$) δ: 102.6 (s). ^{1}H NMR ($CDCl_3$), δ: 0.40 (s, 9H, CH_3, $SiMe_3$), 0.56 (s, 9H, CH_3, $SiMe_3$),1.19 (s, 3H, CH_3), 1.21 (s, 3H, CH_3), 1.73 (m, 2H, CH_2, COD), 1.98 (m, 2H, CH_2, COD), 2.15 (m, 4H, $2CH_2$, COD), 3.63-3.85 (m, 3H, CH_2-O, CH_2-S), 3.95-4.06 (m, 3H, CH_2-S, CH= COD, C*H*CH_2S), 4.06 (m, 1H, C*H*CH_2O), 4.38 (m, 2H, CH=, COD), 4.74 (m, 1H, CH=, COD), 7.18-7.63 (m, 23H, CH=). ^{13}C NMR ($CDCl_3$), δ: 0.0 ($SiMe_3$), 0.9 ($SiMe_3$), 26.3 (CH_3), 26.4 (CH_3), 26.9 (CH_2, COD), 29.6 (CH_2, COD), 30.1 (CH_2, COD), 34.3 (CH_2, COD), 48.0 (CH_2-S), 69.1 (d, CH_2-O, $J_{C\text{-}P}$= 13 Hz), 69.7 (CH=, COD), 74.2 (CH=, COD), 77.1 (*C*HCH_2S), 79.5

(*C*HCH$_2$O), 103.4 (CH=, COD), 110.5 (CMe$_2$), 117.3-152.4 (aromatic carbons) , 161. 6 (q, C-B, BAr$_F$, $^1J_{C-B}$= 50 Hz).

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

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

[Ir(cod)(**L2a**)]BAr$_F$: ^{31}P NMR (400 MHz, CDCl$_3$) δ: 103.4 (s). ^{1}H NMR (CDCl$_3$), δ: 1.24 (s, 6H, CH$_3$), 1.33 (s, 18H, CH$_3$, ^{t}Bu), 1.48 (s, 9H, CH$_3$, ^{t}Bu), 1.57 (s, 9H, CH$_3$, ^{t}Bu), 2.11 (m, 8H, CH$_2$, COD), 2.5 (s, 3H, CH$_3$), 3.43 (m, 2H, CH$_2$-S), 3.84-3.99 (m, 2H, CH$_2$-O, C*H*CH$_2$S), 4.15 (m, 1H, CH=, COD), 4.22 (m, 1H, C*H*CH$_2$O), 4.52 (m, 1H, CH=, COD), 5.09 (m, 2H, CH=, COD), 7.15-7.69 (m, 16H, CH=).^{13}C NMR (CDCl$_3$), δ: 19.7 (CH$_3$), 26.6 (CH$_3$), 26.7 (CH$_3$), 28.7 (CH$_2$, COD), 29.8 (CH$_2$, COD), 30.3 (CH$_2$, COD), 31.5 (CH$_3$, ^{t}Bu), 31.6 (CH$_3$, ^{t}Bu), 31.8 (CH$_3$, ^{t}Bu), 33.2 (CH$_2$, COD), 35.0 (C, ^{t}Bu), 35.6 (C, ^{t}Bu), 35.7 (C, ^{t}Bu), 44.5 (CH$_2$-S), 68.1 (d, CH$_2$-O, J_{C-P}= 12.4 Hz), 72.2 (CH=, COD), 74.8 (CH=, COD), 77.1 (*C*HCH$_2$S), 77.4 (*C*HCH$_2$O), 99.8 (CH=, COD), 100.9

(CH=, COD), 110.9 (CMe_2), 117.6- 149.6 (aromatic carbons), 161.8 (q, C-B, BAr_F, $^1J_{C-B}$= 49 Hz).

[Ir(cod)(**L3a**)]BAr_F: ^{31}P NMR (400 MHz, $CDCl_3$) δ: 104.1 (s). ^{1}H NMR ($CDCl_3$), δ: 1.29 (s, 6H, CH_3), 1.35 (s, 9H, CH_3, ^{t}Bu), 1.36 (s, 9H, CH_3, ^{t}Bu), 1.44 (s, 9H, CH_3, ^{t}Bu), 1.63 (s, 18H, CH_3, ^{t}Bu), 1.73 (m, 2H, CH_2, COD), 1.86 (m, 2H, CH_2, COD), 2.01 (m, 2H, $2CH_2$, COD), 2.25 (m, 2H, $2CH_2$, COD), 3.27 (dd, 1H, $^2J_{H-H}$= 15.2 Hz, $^3J_{H-H}$= 3.2 Hz, CH_2-S), 3.50-3.56 (m, 1H, CH_2-O), 3.62 (dd, 1H, $^2J_{H-H}$= 12.4 Hz, $^3J_{H-H}$= 2.8 Hz, CH_2-S), 3.80-3.86 (m, 1H, CH_2-O), 3.96-4.02 (m, 1H, C*H*CH_2O), 4.04-4.07 (m, 1H, C*H*CH_2S), 4.56(m, 2H, CH=, COD), 5.56 (m, 1H, CH=, COD), 6.02 (m, 1H, CH=, COD), 7.18-7.72 (m, 16H, CH=). ^{13}C NMR ($CDCl_3$), δ: 26.6 (CH_3), 27.7(CH_2, COD), 29.9(CH_2, COD), 30.9 (CH_3, ^{t}Bu), 31.1 (CH_3, ^{t}Bu), 31.5 (CH_3, ^{t}Bu), 32.5 (CH_2, COD), 33.9 (CH_2, COD), 35.0 (C, ^{t}Bu), 35.5 (C, ^{t}Bu), 35.7 (C, ^{t}Bu), 36.3 (CH_2-S), 66.5 (CH_2-O), 71.1 (CH=, COD), 71.7 (CH=, COD), 76.3 (*C*HCH_2S), 78.0 (*C*HCH_2O), 93.9 (CH=, COD), 98.6 (CH=, COD), 110.4 (CMe_2), 117.6-149.8 (aromatic carbons), 161.6 (q, C-B, BAr_F, $^1J_{C-B}$= 49 Hz).

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

[Ir(cod)(**L3e**)]BAr_F: ^{31}P NMR (400 MHz, $CDCl_3$) δ: 98.6 (s). ^{1}H NMR ($CDCl_3$), δ: 1.30 (s, 6H, CH_3), 1.37 (s, 9H, CH_3, ^{t}Bu), 1.50 (s, 9H, CH_3, ^{t}Bu), 1.61 (s, 9H, CH_3, ^{t}Bu), 1.75 (s, 3H, CH_3), 1.81 (s, 3H, CH_3), 2.04 (m, 6H, CH_2, COD), 2.25 (s, 3H, CH_3), 2.26 (s, 3H, CH_3), 2.4 (m, 2H, CH_2, COD), 3.25 (m, 1H, CH_2-S), 3.31 (m, 1H, CH_2-O), 3.65-3.70 (m, 1H, CH_2-S), 3.75-3.81 (m, 1H, CH_2-O), 3.98 (m, 1H, C*H*CH_2S), 4.08-4.11 (m, 2H, C*H*CH_2O, CH= COD), 4.43 (m, 1H, CH=, COD), 5.36 (m, 1H, CH=, COD), 6.09 (m, 1H, CH=, COD), 7.19-7.69 (m, 14H, CH=). ^{13}C NMR ($CDCl_3$), δ: 16.6 (CH_3), 16.8 (CH_3), 20.3 (CH_3), 20.5 (CH_3), 26.6 (CH_3), 26.7 (CH_3), 28.8 (CH_2, COD), 29.9 (CH_2,

COD), 31.1 (CH_3, ^{t}Bu), 31.4 (CH_3, ^{t}Bu), 32.2 (CH_3, ^{t}Bu), 33.8 (CH_2, COD), 34.8 (C, ^{t}Bu), 35.1 (C, ^{t}Bu), 35.1 (CH_2, COD), 36.8 (CH_2-S), 66.2 (CH_2-O), 69.8 (CH=, COD), 72.8 (CH=, COD), 76.1 (*C*HCH_2S), 77.5 (*C*HCH_2O), 99.4 (CH=, COD), 99.5 (CH=, COD), 110.5 (CMe_2), 117.6-144.5 (aromatic carbons), 161.6 (q, C-B, BAr_F, $^1J_{C-B}$= 49 Hz).

[Ir(cod)(**L4a**)]BAr_F: ^{31}P NMR (400 MHz, $CDCl_3$) δ: 101.5 (s). ^{1}H NMR ($CDCl_3$), δ: 1.22 (s, 3H, CH_3), 1.24 (s, 3H, CH_3), 1.33 (s, 18H, CH_3, ^{t}Bu), 1.54 (s, 9H, CH_3, ^{t}Bu), 1.62 (s, 9H, CH_3, ^{t}Bu), 1.78 (m, 2H, CH_2, COD), 1.96 (m, 2H, CH_2, COD), 2.11 (m, 2H, CH_2, COD), 2.22 (m, 2H, CH_2, COD), 2.60 (s, 3H, CH_3), 2.68 (s, 3H, CH_3), 3.43 (m, 1H, CH_2-S), 3.69-3.76 (m, 1H, CH_2-O), 3.95-4.06 (m, 4H, CH_2-S, CH= COD, C*H*CH_2S), 4.12-4.16 (m, 4H, CH COD, CH_2-O, C*H*CH_2O), 4.43 (m, 1H, CH=, COD), 4.57 (m, 1H, CH=, COD), 7.18-7.68 (m, 19H, CH=). ^{13}C NMR ($CDCl_3$), δ: 22.7 (CH_3), 23.0 (CH_3), 26.9 (CH_3), 30.7 (CH_2, COD), 30.9 (CH_2, COD), 31.4 (CH_3, ^{t}Bu), 31.5 (CH_3, ^{t}Bu), 31.9 (CH_3, ^{t}Bu), 34.6 (CH_2, COD), 35.0 (C, ^{t}Bu), 35.1 (C, ^{t}Bu), 35.5 (C, ^{t}Bu), 35.6 (C, ^{t}Bu), 47.3 (CH_2-S), 69.3 (CH_2-O), 77.4 (*C*HCH_2S), 80.2 (*C*HCH_2O), 103.7 (CH=, COD), 110.9 (CMe_2), 117.6-149.9 (aromatic carbons), 161.5 (q, C-B, BAr_F, $^1J_{C-B}$= 49 Hz).

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

[Ir(cod)(**L4e**)]BAr_F: ^{31}P NMR (400 MHz, $CDCl_3$) δ: 97.0 (s). ^{1}H NMR ($CDCl_3$), δ: 0.85 (s, 3H, CH_3), 0.90 (s, 3H, CH_3), 0.90 (m, 2H, CH_2, COD),1.07 (s, 9H, CH_3, ^{t}Bu), 1.26 (s, 9H, CH_3, ^{t}Bu), 1.36 (m, 2H, CH_2, COD),1.39 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 1.57 (m, 2H, CH_2, COD), 1.73 (m, 2H, CH_2, COD), 1.74 (s, 3H, CH_3), 1.87 (s, 3H, CH_3), 2.20 (s, 3H, CH_3), 2.21 (s, 3H, CH_3), 3.15 (m, 1H, CH_2-S), 3.18 (m, 1H, CH=, COD), 3.22 (m, 2H, CH_2-O), 3.47-3.52 (m, 1H, CH_2-S), 3.66 (m, 1H, CH=, COD), 3.68 (m, 1H, C*H*CH_2S), 3.76-3.78 (m, 1H, C*H*CH_2O), 4.00 (m, 1H, CH=, COD), 4.18 (m, 1H, CH=, COD), 6.78-7.30 (m, 17H, CH=). ^{13}C NMR ($CDCl_3$), δ: 16.4 (CH_3), 16.6 (CH_3), 20.3

(CH_3), 20.4 (CH_3), 22.4 (CH_3), 22.5 (CH_3), 26.4 (CH_3), 26.8 (CH_2, COD), 29.6 (CH_2, COD), 30.7 (CH_2, COD), 31.5 (CH_3, ^{t}Bu), 32.6 (CH_3, ^{t}Bu), 34.4 (CH_2, COD), 34.7 (C, ^{t}Bu), 48.0 (CH_2-S), 67.9 (CH=, COD), 68.6 (CH_2-O), 74.7 (CH=, COD), 77.5 (*C*HCH_2S), 80.4 (*C*HCH_2O), 101.8 (CH=, COD), 103.3 (CH=, COD), 110.3 (CMe_2), 117.4-140.7 (aromatic carbons), 161.6 (q, C-B, BAr_F, $^1J_{C\text{-}B}$= 49 Hz).

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

[Ir(cod)(**L5e**)]BAr_F: ^{31}P NMR (400 MHz, $CDCl_3$) δ: 98.5 (s). ^{1}H NMR ($CDCl_3$), δ: 1.25 (s, 3H, CH_3), 1.32 (s, 3H, CH_3), 1.38 (s, 9H, CH_3, ^{t}Bu), 1.45 (m, 2H, CH_2, COD), 1.63 (s, 9H, CH_3, ^{t}Bu), 1.71 (s, 3H, CH_3), 1.76 (m, 3H, CH_2, Ad), 1.82 (s, 3H, CH_3), 1.93 (m, 2H, CH_2, COD), 2.04 (m, 3H, CH_2, Ad), 2.14 (m, 2H, CH_2, COD), 2.21 (m, 3H, CH, Ad), 2.26 (s, 6H, CH_3), 2.34 (m, 2H, CH_2, COD), 3.29 (m, 2H, CH_2-S, CH_2-O), 3.60 (m, 1H, CH_2-S), 3.82 (m, 1H, CH_2-O), 4.02-4.11 (m, 3H, C*H*CH_2O, C*H*CH_2S, CH=, COD), 4.43 (m, 1H, CH=, COD), 5.58 (m, 1H, CH=, COD), 6.16 (m, 1H, CH=, COD), 7.24-7.71 (m, 14H, CH=). ^{13}C NMR ($CDCl_3$), δ: 16.4 (CH_3), 16.6 (CH_3), 20.3 (CH_3), 26.4 (CH_3), 26.5 (CH_3), 26.7 (CH_2, COD), 28.7 (CH_2, COD), 29.6 (CH_2, COD), 30.3 (3CH, Ad), 31.1 (CH_3, ^{t}Bu), 32.1 (CH_3, ^{t}Bu), 33.5 (CH_2, COD), 33.9 (CH_2-S), 34.6 (C, ^{t}Bu), 34.9 (C, ^{t}Bu), 35.3 (CH_2, Ad), 43.2 (CH_2, Ad), 58.5 (C, Ad), 66.0 (CH_2-O, $J_{C\text{-}P}$= 15 Hz), 69.1 (CH=, COD), 72.5 (CH=, COD), 76.0 (*C*HCH_2S), 77.1 (*C*HCH_2O), 99.0 (CH=, COD), 99.1 (CH=, COD), 110.2 (CMe_3), 117.3-144.4 (aromatic carbons), 161.6 (q, C-B, BAr_F, $^1J_{C\text{-}B}$= 49 Hz).

[Ir(cod)(**L6d**)]BAr_F: ^{31}P NMR (400 MHz, $CDCl_3$) δ: 94.2 (s). ^{1}H NMR ($CDCl_3$), δ: 1.15 (s, 3H, CH_3), 1.21 (s, 3H, CH_3), 1.31 (m, 2H, CH_2, COD),1.45 (s, 9H, CH_3, ^{t}Bu), 1.67 (s, 9H, CH_3, ^{t}Bu), 1.72 (s, 3H, CH_3), 1.74 (s, 3H, CH_3), 1.87-2.13 (m, 6H, CH_2,

COD), 2.20 (s, 6H, CH_3), 3.34-3.51 (m, 3H, CH_2-S, CH_2-O, CH=, COD), 3.85 (m, 1H, C*H*CH_2S), 4.06 (m, 2H, CH_2-O, CH=, COD), 4.16 (m, 1H, C*H*CH_2O), 4.57 (m, 2H, CH_2-O, CH=, COD), 5.17 (m, 1H, CH=, COD), 7.05-8.42 (m, 21H, CH=). ^{13}C NMR ($CDCl_3$), δ: 16.3 (CH_3), 16.6 (CH_3), 20.3 (CH_3), 20.4 (CH_3), 26.5 (CH_3), 29.3 (CH_2, COD), 29.5 (CH_2, COD), 29.7 (CH_2, COD), 31.4 (CH_3, ^{t}Bu), 34.0 (CH_2, COD), 34.7 (C, ^{t}Bu), 35.1 (C, ^{t}Bu), 45.1 (CH_2-S), 66.2 (CH=, COD), 69.0 (CH_2-O), 75.7 (CH=, COD), 77.2 (*C*HCH_2S), 79.0 (*C*HCH_2O), 105.7 (CH=, COD), 111.9 (CMe_2), 117.4-144.9 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^1J_{C\text{-}B}$= 49 Hz).

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

[Ir(cod)(**L7d**)]BAr_F: ^{31}P NMR (400 MHz, $CDCl_3$) δ: 94.1 (s). ^{1}H NMR ($CDCl_3$), δ: 1.49 (s, 6H, CH_3), 1.66 (s, 9H, CH_3, ^{t}Bu), 1.83 (m, 2H, CH_2, COD), 1.96 (s, 9H, CH_3, ^{t}Bu), 2.00 (s, 3H, CH_3), 2.04 (s, 3H, CH_3), 2.20 (m, 4H, CH_2, COD), 2.35 (m, 2H, CH_2, COD), 2.49 (s, 6H, CH_3), 3.78 (m, 1H, CH_2-O), 3.90 (m, 2H, CH_2-S, CH=, COD), 4.16 (m, 1H, C*H*CH_2S), 4.25 (m, 1H, CH_2-O), 4.40-4.34 (m, 1H, CH_2-S), 4.53 (m, 1H, C*H*CH_2O), 4.78 (m, 1H, CH=, COD), 4.86 (m, 2H, CH=, COD), 7.47-8.23 (m, 21H, CH=). ^{13}C NMR ($CDCl_3$), δ: 16.3 (CH_3), 16.6 (CH_3), 20.3 ($2CH_3$), 26.5 ($2CH_3$), 28.2 (CH_2, COD), 28.8 (CH_2, COD), 29.7 (CH_2, COD), 31.3 (CH_3, ^{t}Bu), 32.3 (CH_3, ^{t}Bu), 32.9 (CH_2, COD), 34.7 (C, ^{t}Bu), 35.1 (C, ^{t}Bu), 46.5 (CH_2-S), 67.9 (CH=, COD), 68.3 (CH_2-O, $J_{C\text{-}P}$= 14.4 Hz), 75.0 (CH=, COD), 77.2 (*C*HCH_2S), 79.9 (*C*HCH_2O), 101.5 (CH=, COD), 104.4 (CH=, COD), 111.4 (CMe_2), 117.4-144.7 (aromatic carbons), 161.6 (q, C-B, BAr_F, $^1J_{C\text{-}B}$= 49 Hz).

[Ir(cod)(**L7e**)]BAr_F: ^{31}P NMR (400 MHz, $CDCl_3$) δ: 96.9 (s). ^{1}H NMR ($CDCl_3$), δ: 1.28 (s, 6H, CH_3), 1.48 (s, 9H, CH_3, ^{t}Bu), 1.60 (m, 2H, CH_2, COD), 1.76 (s, 9H, CH_3, ^{t}Bu), 1.81 (s, 3H, CH_3), 1.84 (s, 3H, CH_3), 1.93 (m, 2H, CH_2, COD), 2.14 (m, 4H, CH_2, COD), 2.3 (s, 6H, CH_3), 3.45 (m, 1H, CH=, COD), 3.64 (m, 2H, CH_2-O), 3.87 (m, 1H, CH_2-S) 4.18 (m, 2H, CH_2-S, C*H*CH_2S), 4.31 (m, 1H, C*H*CH_2O), 4.40 (m, 1H, CH=, COD),

4.58 (m, 1H, CH=, COD), 4.74 (m, 1H, CH=, COD), 7.26-8.06 (m, 21H, CH=). ^{13}C NMR ($CDCl_3$), δ: 16.4 (CH_3), 16.6 (CH_3), 20.3 (CH_3), 20.4 (CH_3), 26.4 (CH_3), 27.0 (CH_2, COD), 29.6 (CH_2, COD), 30.0 (CH_2, COD), 31.0 (CH_2, COD), 31.4 (CH_3, ^{t}Bu), 32.1 (CH_3, ^{t}Bu), 34.3 (C, ^{t}Bu), 34.7 (C, ^{t}Bu), 48.3 (CH_2-S), 67.8 (CH=, COD), 69.1 (CH_2-O, $J_{C\text{-}P}$= 14.4 Hz), 75.0 (CH=, COD), 77.6 (*C*HCH_2S), 79.6 (*C*HCH_2O), 102.9 (CH=, COD), 103.1 (CH=, COD), 110.3 (CMe_2), 117.4-143.9 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^1J_{C\text{-}B}$= 49 Hz).

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

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

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

3H, CH_3), 3.26 (m, 1H, CH=, COD), 3.33 (m, 1H, CH_2-S), 4.13-4.20 (m, 2H, C*H*CMe_2O, CH_2-S), 4.29-4.37 (m, 2H, C*H*CH_2S, CH=, COD), 4.45 (m, 1H, CH=, COD), 4.61 (m, 1H, CH=, COD), 7.26-7.71 (m, 19H, CH=). ^{13}C NMR ($CDCl_3$), δ: 16.1 (CH_3), 16.4 (CH_3), 20.2 (CH_3), 20.3 (CH_3), 22.7 (CH_3), 22.8 (CH_3), 26.4 (CH_3), 26.5 (CH_3), 27.0 (CH_2, COD), 29.8 (CH_2, COD), 30.1 (CH_2, COD), 30.7 (CH_2, COD), 31.6 (CH_3, ^{t}Bu), 32.2 (CH_3, ^{t}Bu), 34.3(C, ^{t}Bu), 34.7 (C, ^{t}Bu), 48.3 (CH_2-S), 69.1 (CH=, COD), 75.8 (*C*HCH_2S), 76.0 (CH=, COD), 83.9 (*C*HCMe_2O), 91.2 (d, *C*Me_2O, $J_{C\text{-}P}$= 20.5 Hz), 99.9 (CH=, COD), 100.5 (CH=, COD), 109.2 (CMe_2), 117.4-145.2 (aromatic carbons), 161.6 (q, C-B, BAr_F, $^1J_{C\text{-}B}$= 49 Hz).

3.4.4.3 Typical procedure for the hydrogenation of olefins

The alkene (0.5 mmol) and Ir complex (2 mol %) were dissolved in CH_2Cl_2 (2 mL) an placed in a high-pressure autoclave. The autoclave was purged 4 times with hydrogen. Then, it was pressurized at the desired pressure. After the desired reaction time, the autoclave was depressurized and the solvent evaporated off. The residue was dissolved in Et_2O (1.5 ml) and filtered through a short plug of celite. The conversions were determined by ^1H NMR and GC and enantiomeric excesses were determined by chiral GC. The enantiomeric excesses of hydrogenated products from **S1-S3** were determined using the conditions previously described.[8e]

3.4.4.4 Typical Procedure for Catalyst Recycling

After each catalytic run, the autoclave was depressurized. The colorless propylene carbonate solution was then extracted with dry/deoxygenated hexane under an argon atmosphere in order to remove the substrate and the hydrogenated product. After the extractions, the corresponding amount of substrate was then added for starting a new run.

3.4.5. Acknowledgements

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Chapter 4

Asymmetric Pd catalyzed allylic substitution

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4. Asymmetric Pd-catalyzed allylic substitution

4.1 Background

As we discussed in the introduction most of the successful ligands reported to date for Pd-catalyzed allylic substitution reactions have been designed using two main strategies. The first one was to increase the ligand's bite angle in order to create a chiral cavity in which the allyl system is perfectly embedded. This idea allowed the successful application of ligands with large bite angles for the allylic substitution of sterically undemanding substrates. The second strategy was the use of heterodonor ligands that result in an electronic discrimination of the two allylic terminal carbon atoms due to the different *trans* influences of the donor groups. This made it possible to successfully use a wide range of heterodonor ligands in allylic substitution reactions. More recently, we found that the use of biaryl phosphite-containing heterodonor ligands is highly advantageous by overcoming the most common limitations of this process, such as low reaction rates and high substrate specificity. Introducing a biaryl phosphite in the ligand design was beneficial because of its larger π-acceptor ability, which increases reaction rates, and because of its flexibility that allows the catalyst chiral pocket to adapt to both hindered and unhindered substrates. In addition, the presence of a biaryl phosphite moiety was also beneficial in the allylic substitution of more challenging monosubstituted substrates.

Until now, mixed phosphorus-nitrogen ligands have played a dominant role among the heterodonor ligands. Less attention has been paid to catalysts containing heterodonor thioether-phosphorus ligands in asymmetric allylic substitution. However, thioether-phosphine and thioether-phosphinite ligands have also demonstrated their potential utility in this process. Only one family of thioether-phosphite ligands, with a furanoside backbone, has been applied in this process but with moderate results (Figure 1.3.18, Chapter 1). This encourages further research into thioether-phosphite ligands to study the scope of this type of compounds as a new class of ligands for this process.

Less attention has been paid to catalysts containing monodentated ligands in asymmetric allylic substitution reactions. However, the groups of RajanBabu and Zhang obtained an enantioselectivity of 94% with catalysts precursors containing monophospholane ligands (Figure 1.3.6, Chapter 1). This encourages further research into monophosphorus ligands.

In this chapter, we therefore report the application of the thioether-phosphite (**L1-L8a-e**) and furanoside monophosphite (**L9**-**L19a**-**c**,**f**-**g**) ligand libraries previously reported in Chapter 3 in the Pd-catalyzed asymmetric allylic substitution of several substrates. More specifically, in section 4.2 we report the application of the thioether-phosphite (**L1-L8a-e**) ligand library, derived from L-(+)-tartaric acid. Systematic variation of the thioether moiety, substituent at the alkyl backbone chain next to the phosphite moiety and the substituents/configurations in the biaryl phosphite group provide useful information about the ligand parameters that control the enantiodiscrimination. By carefully selecting the ligand parameters, full conversions and good enantioselectivities were obtained for several linear substrates (ee's up to 83 %). In section 4.3 we report the application of the modular sugar-based monophosphite ligand library (**L9**-**L19a**-**c**,**f**-**g**) for this process. These ligands are derived from D-(+)-glucose, D-(+)-galactose and D-(+)-fructose, which lead to a wide range of sugar backbones, and contain several substituents in the C-3 of the furanoside backbone and several substituents/configuration in the biaryl moiety, with different steric and electronic properties. Systematic variation of the ligand parameters indicates that the catalytic performance (activities and enantioselectivities) is highly affected by sugar backbone, the substituents and configuration of C-3 and C-4 of the ligand backbone and the type of substituents/configuration in the biaryl phosphite moiety. Unfortunately, low-to-moderate enantioselectivities were obtained (ee's up to 76%).

4.2 Asymmetric Pd-catalyzed allylic substitution using a thioether-phosphite ligand library.

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

Abstract. A series of readily available thioether-phosphite ligands have been tested in the Pd-catalyzed allylic substitution reactions of several linear substrates with different steric properties. Systematic variation of the thioether moiety, substituent at the alkyl backbone chain next to the phosphite moiety and the substituents/configurations in the biaryl phosphite group provide useful information about the ligand parameters that control the enantiodiscrimination. By carefully selecting the ligand parameters, full conversions and good enantioselectivities were obtained for several linear substrates (ee's up to 83 %).

4.2.1 Introduction

The development of methods for enantioselective formation of carbon-carbon and carbon-heteroatom bonds is one of the key issues in organic synthesis. A versatile method for achieving this is asymmetric palladium-catalyzed allylic substitution with several stabilized nucleophiles.[1] Most of the successful ligands reported to date for this process have been designed using three main strategies. The first, developed by Hayashi and coworkers, involves a secondary interaction of the nucleophile with a side chain of the ligand to direct the approach of the nucleophile to one of the allylic terminal carbon atoms.[1,2] The second strategy, developed by Trost and coworkers, increases the ligand's bite angle to create a chiral cavity in which the allyl system is embedded.[1,3] This idea made it possible for ligands with large bite angles to be successfully applied to the allylic substitution of sterically undemanding substrates. The third strategy, developed by groups led by Helmchen, Pfaltz and Williams, uses heterodonor ligands to electronically discriminate between the two allylic terminal carbon atoms because of the different *trans* influences of the donor groups.[1, 4] This made it possible to successfully use a wide range of heterodonor ligands in allylic substitution reactions. Mixed phosphorus-nitrogen ligands have played a dominant role among the heterodonor ligands.[1] To a lesser extent, thioether-phosphorus ligands have also demonstrated their potential utility in Pd-catalyzed asymmetric allylic substitution reactions.[1h] In this context, several combinations of P-S ligands mainly

thioether-phosphine[5] and thioether-phosphinite[6] have been studied and have proved to be effective.

Less attention has been paid to catalysts containing thioether-phosphite ligands[7] despite that the presence of biaryl-phosphite moieties in ligand design has shown to be highly advantageous by overcoming the most common limitations of this process, such as low reaction rates and high substrate specificity.[1j,8] There is only one report on the use of thioether-phosphite ligands in this process but with moderate success (Figure 4.2.1).

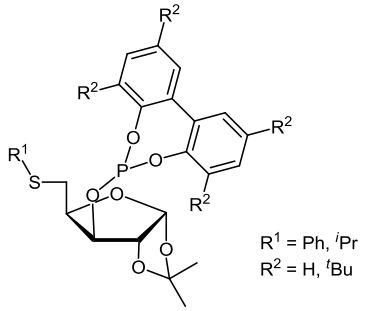


Figure 4.2.1. Previously applied thioether-phosphite ligands.

Therefore, a study of the possibilities offered by thioether-phosphite as new ligands for this process is still needed. For this purpose, in this chapter we have applied the previously reported thioether-phosphite ligands (**L1**-**L8a**-**e**; Figure 4.2.2) in the asymmetric Pd-catalyzed allylic substitution reactions. These ligands combine the advantages of the thioether and phosphite moieties (such as high resistance to oxidation and straightforward modular constructions)[9,10] with the availability at low price of the backbone derived from L-(+)-tartaric acid.[11] With this library we have been able to investigate the effect of systematically varying the electronic and steric properties of the thioether group (ligands **L1**-**L7**), the substituents in the alkyl backbone chain next to the phosphite moiety (ligands **L1** and **L8**) and the substituents/configurations in the biaryl phosphite moiety (**a**-**e**). By carefully selecting the ligand parameters, full conversions and good enantioselectivities were obtained for several linear substrates (ee's up to 83 %).

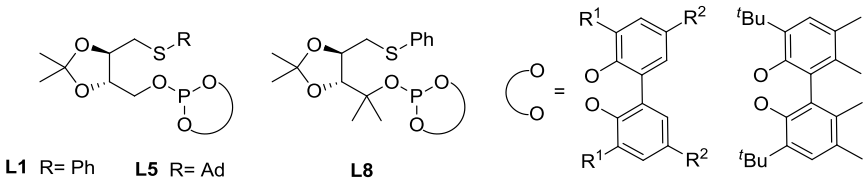
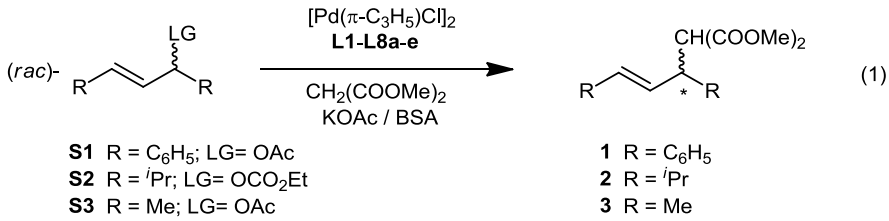


Figure 4.2.2. Thioether-phosphite ligands **L1**-**L8a**-**e**.

4.2.2 Results and discussion

4.2.2.1 Allylic substitution of disubstituted linear substrates

In this section, we report the use of the chiral thioether-phosphite ligand library (**L1-L8a**-**e**) in the Pd-catalyzed allylic substitution of linear disubstituted substrates with different steric properties (Eq. 1): *rac*-1,3-diphenyl-3-acetoxyprop-1-ene (**S1**) (widely used as a model substrate); *rac*-(*E*)-ethyl-2,5-dimethyl-3-hex-4-enylcarbonate (**S2**) and *rac*-1,3-dimethyl-3-acetoxyprop-1-ene (**S3**). In all the cases, the catalysts were generated *in situ* from the π-allyl-palladium chloride dimer $[PdCl(\eta^3\text{-}C_3H_5)]_2$ and the corresponding ligand. The nucleophile was generated from dimethyl malonate in the presence of *N,O*-bis(trimethylsilyl)-acetamide (BSA).[1]



Allylic substitution of rac-1,3-diphenyl-3-acetoxyprop-1-ene S1

For an initial evaluation of the thioether-phosphite ligand library (**L1-L8a**-**e**), we chose the Pd-catalyzed allylic substitution of **S1** (Eq 1, R= Ph), which is widely used as a model substrate. Initially, we determined the optimal reaction conditions by conducting a first set of experiments in which the solvent and the 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= 0.75, L/Pd= 1.1 and

L/Pd= 2) with ligand **L1a**. The results show that the efficiency of the process depended on the nature of the solvent and ligand-to-palladium ratio (Table 4.2.1). The optimum trade-off between activities and enantioselectivities was obtained by using dichloromethane as the solvent. Enantioselectivities dropped when an excess of ligand were used (entries 1-3). The use of DMF as a solvent has also a negative effect on enantioselectivity (entry 6). This can be explained by the formation of a less selective PdL_2 species,[12] due to the presence of excess of ligand or to DMF coordination to Pd. Interestingly, a clear kinetic resolution (KR) of the substrate was observed in all the solvents except DMF. However, the kinetic resolution in THF is advantageous, because it provides higher enantioselectivities in product **S1** than in dichloromethane or toluene (entry 4 vs 5 and 7).

Table 4.2.1 Pd-catalysed allylic substitution of **S1** using ligand **L1a**. Effect of the solvent and ligand-to-palladium ratio.[a]

Entry	L/Pd	Solvent	% Conv (h)[b]	% ee **1**[c]	% ee **S1**[c]	$k_{(R)\text{-}\mathbf{S1}}$ / $k_{(S)\text{-}\mathbf{S1}}$[d]
1	0.75	DCM	100 (3)	17 (*S*)	-	-
2	1.1	DCM	100 (3)	18 (*S*)	-	-
3	2	DCM	100 (3)	11 (*S*)	-	-
4	1.1	THF	90 (3)	17 (*S*)	95 (*R*)	3.2
5	1.1	Toluene	64 (3)	16 (*S*)	35 (*R*)	2.0
6	1.1	DMF	100 (3)	4 (*S*)	-	-
7	1.1	DCM	93 (1.5)	18 (*S*)	52 (*R*)	1.5

[a] All reactions were run at room temperature. 0.5 mol% $[PdCl(\eta^3\text{-}C_3H_5)]_2$. **S1** (1 mmol), solvent (2 mL), BSA (3 eq), dimethyl malonate (3 eq), KOAc (pinch). [b] Conversion percentage determined by ^{1}H-NMR. [c] Enantiomeric excesses determined by HPLC on a Chiralcel-OJ column. Absolute configuration drawn in parentheses. [d] Calculated from k_R/K_S= ln[(1-Conv/100)(1-ee/100)]/ ln[(1-Conv/100)(1+ee/100)].[13]

Under the optimized conditions (i.e. a ligand-to-palladium ratio of 1.1 and dichloromethane as the solvent) we tested the remaining ligands. Table 4.2.2 shows the results. They indicate that enantioselectivities are highly affected by the thioether substituent, the substituents in the alkyl backbone chain next to the phosphite moiety and the configuration of the biaryl phosphite moiety. However, the effect of the ligand parameters in activity is less pronounced. Full conversions and enantioselectivities up to 80% were obtained with ligand **L8d**.

We first investigated the effect of the substituents/configurations at the biaryl phosphite moiety with ligands **L1a**-**e**. The results indicated that the nature of the substituents at the biaryl phosphite moiety has no effect on enantioselectivities (Table 4.2.2, entries 1-3), while enantioselectivities are highly affected by the configuration of the biaryl phosphite moiety (Table 4.2.2, entries 4-

5 vs 1-3). Ligands containing an *R*-biaryl phosphite moiety (**d**) provide therefore higher enantioselectivities than ligands containing an *S*-biaryl group (**e**) (i.e. entry 4 vs 5).

Concerning the effect of the thioether substituent, the highest enantioselectivity of the series was achieved using a phenyl thioether substituent (i.e. Table 4.2.2; entry 4 vs 8, 11, 13, 15 and 17).

Interestingly the introduction of methyl substituents at the alkyl backbone chain next to the phosphite moiety (ligands **L8**) has extremely positive effect on enantioselectivity (i.e. entry 4 vs 20).

Table 4.2.2 Pd-catalysed allylic substitution of **S1** using ligands **L1**-**L8a**-**e**.[a]

Entry	Ligand	% Conv (h)	% ee
1	**L1a**	100 (3)	18 (*S*)
2	**L1b**	100 (3)	17 (*S*)
3	**L1c**	100 (3)	17 (*S*)
4	**L1d**	100 (3)	33 (*R*)
5	**L1e**	100 (3)	17 (*S*)
6	**L2a**	100 (3)	4 (*S*)
7	**L3a**	92 (3)	17 (*R*)
8	**L3d**	96 (3)	23 (*R*)
9	**L3e**	100 (3)	12 (*S*)
10	**L4a**	100 (3)	11 (*R*)
11	**L4d**	100 (3)	27 (*R*)
12	**L4e**	100 (3)	14 (*S*)
13	**L5d**	100 (3)	25 (*R*)
14	**L5e**	100 (3)	0
15	**L6d**	100 (3)	22 (*R*)
16	**L6e**	100 (3)	4 (*R*)
17	**L7d**	100 (3)	14 (*R*)
18	**L7e**	100 (3)	4 (*R*)
19	**L8a**	100 (3)	40 (*R*)
20	**L8d**	100 (3)	80 (*R*)
21	**L8e**	100 (3)	10 (*R*)

[a] 0.5 mol% $[PdCl(\eta^3\text{-}C_3H_5)]_2$, ligand (0.011 mmol), **S1** (1 mmol), CH_2Cl_2 (2 mL), BSA (3 eq), dimethyl malonate (3 eq), KOAc (pinch). [b] Conversion percentage determined by ^{1}H-NMR. [c] Enantiomeric excesses determined by HPLC on a Chiralcel-OJ column. Absolute configuration drawn in parentheses.

Allylic substitution of rac-(E)-ethyl-2,5-dimethyl-3-hex-4-enylcarbonate S2

We next screened the thioether-phosphite ligand library **L1**-**L8a**-**e** in the allylic substitution process of **S2** using dimethyl malonate as nucleophile (Eq 1, R= ^{i}Pr, LG= OCO_2Et). This substrate is more sterically demanding than substrate **S1**, which we used before.[1] If ee's are to be high, the ligand must create a bigger chiral pocket around the metal center to be able to accommodate the sterically demanding isopropyl substituents.[1] Due to the flexibility conferred by the biaryl phosphite moiety, we expect to obtain also good enantioselectivities for this substrate. The most interesting results are shown in Table 4.2.3. In general, the trends were the same as for the allylic substitution of **S1**.

Table 4.2.3 Pd-catalysed allylic substitution of **S2** using ligands **L1**-**L8a**-**e**.[a]

Entry	Ligand	% Conv (h)	% ee
1	**L1a**	100 (24)	21 (*R*)
2	**L1b**	100 (24)	22 (*R*)
3	**L1c**	100 (24)	20 (*R*)
4	**L1d**	100 (24)	38 (*S*)
5	**L1e**	100 (24)	20 (*R*)
6	**L2a**	100 (24)	7 (*R*)
7	**L3a**	99 (24)	19 (*S*)
8	**L3d**	100 (24)	26 (*S*)
9	**L3e**	100 (24)	17 (*R*)
10	**L4a**	100 (24)	15 (*S*)
11	**L4d**	100 (24)	34 (*S*)
12	**L4e**	100 (24)	19 (*R*)
13	**L5d**	100 (24)	31 (*S*)
14	**L5e**	100 (24)	4 (R)
15	**L6d**	100 (24)	29 (*S*)
16	**L6e**	100 (24)	9 (*S*)
17	**L7d**	100 (24)	19 (*S*)
18	**L7e**	100 (24)	7 (*S*)
19	**L8a**	100 (24)	42 (*S*)
20	**L8d**	100 (24)	83 (*S*)
21	**L8e**	100 (24)	12 (*S*)

[a] All reactions were run at room temperature. 1 mol% $[PdCl(\eta^3\text{-}C_3H_5)]_2$. L/Pd= 1.1. CH_2Cl_2 as solvent. [b] Conversion percentage determined by ^{1}H-NMR. [c] Enantiomeric excesses determined by ^{1}H-NMR using $Eu(hfc)_3$. Absolute configuration drawn in parentheses.

Again, the catalyst precursor containing thioether-phosphite ligand **L8d** provided the best enantioselectivity (ee's up to 83%; Table 4.2.3, entry 20). As expected, the activities were lower than in the alkylation reaction of **S1**.[1] The stereoselectivity of the alkylation of **S2** was the same as for the alkylation reaction of **S1**, though the CIP descriptor was inverted because of the change in the priority of the groups.

Allylic substitution of rac-1,3-dimethyl-3-acetoxyprop-1-ene S3

Finally, we also screened the thioether-phosphite ligand library **L1**-**L8a**-**e** in the allylic alkylation of the linear substrate **S3** (Eq 1, R= Me). This substrate is less sterically demanding than substrates **S1**-**S2**. The enantioselectivity for **S3** is therefore more difficult to control than with hindered substrates such as **S1**. If ee values are to be high, the ligand must create a small chiral pocket around the metal center, mainly because of the presence of less sterically demanding methyl *syn* substituents.[1] There are therefore fewer successful catalytic systems for the Pd-catalyzed allylic substitution of this substrate than for the allylic substitution of hindered substrate **S1**.[7b,14] Due to the presence of a bulky biaryl phosphite moiety in ligands **L1**-**L8a**-**e**, which are known to be flexible and to provide large bite angles, we expected to be able to tune the size of the chiral pocket appropriately.

Table 4.2.4 summarizes the results of using the thioether-phosphite ligand library. Again, enantioselectivities were affected by the substituents in both the thioether and alkyl backbone chain next to the phosphite moiety and by the configuration of the biaryl phosphite group. However, the effect of the thioether substituent on enantioselectivity was different from their effect on the alkylation of hindered substrates **S1-S2**. Thus, the presence of a 2-naphthyl thioether substituent increases the enantioselectivity from 29% ee (for a phenyl thioether substituent) to 40% ee (entries 4 vs 17). Nonetheless, the positive effect on enantioselectivity of introducing methyl substituents at the alkyl backbone chain is more pronounced than the effect of the thioether substituent (Table 4.2.4, entry 17 vs 20). Despite having a phenyl thioether substituent, the best enantioselectivity was therefore obtained with ligand **L8d**, which contains a methyl substituent at the alkyl backbone chain and an *R*-configuration at the biaryl phosphite moiety (ee's up to 64%, entry 20).

Table 4.2.4. Pd-catalysed allylic substitution of **S3** using ligands **L1**-**L8a**-**e**.[a]

Entry	Ligand	% Conv (h)	% ee
1	**L1a**	100 (6)	11 (*R*)
2	**L1b**	100 (6)	9 (*R*)
3	**L1c**	100 (6)	10 (*R*)
4	**L1d**	100 (6)	29 (*S*)
5	**L1e**	100 (6)	12 (*R*)
6	**L2a**	100 (6)	3 (*R*)
7	**L3a**	100 (6)	15 (*R*)
8	**L3d**	100 (6)	21 (*S*)
9	**L3e**	100 (6)	19 (*R*)
10	**L4a**	100 (6)	8 (*R*)
11	**L4d**	100 (6)	22 (*S*)
12	**L4e**	100 (6)	15 (*R*)
13	**L5d**	100 (6)	20 (*S*)
14	**L5e**	100 (6)	10 (*R*)
15	**L6d**	100 (6)	24 (*S*)
16	**L6e**	100 (6)	7 (*R*)
17	**L7d**	100 (6)	40 (*S*)
18	**L7e**	100 (6)	8 (*R*)
19	**L8a**	100 (6)	8 (*R*)
20	**L8d**	100 (6)	64 (*S*)
21	**L8e**	100 (6)	29 (*R*)

[a] 0.5 mol% $[PdCl(\eta^3\text{-}C_3H_5)]_2$, ligand (0.011 mmol), **S3** (1 mmol), CH_2Cl_2 (2 mL), BSA (3 eq), dimethyl malonate (3 eq), KOAc (pinch). [b] Conversion measured by GC. Reaction time shown in parentheses. [c] Enantiomeric excesses measured by GC. The absolute configuration appears in parentheses.

4.2.3 Conclusions

A library of thioether-phosphite ligands, derived from L-(+)-tartaric acid, has been evaluated in the Pd-catalyzed allylic substitution reactions of linear substrates with different steric properties. Systematic variation of the ligand parameters indicates that the introduction of a substituent at the alkyl backbone chain next to the phosphite moiety and the presence of an *R*-biaryl phosphite group have an extremely positive effect on enantioselectivity. By carefully selecting the ligand parameters, full conversions and good enantioselectivities were therefore obtained for several linear substrates (ee's up to 83 %).

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**-**L8a**-**e** has been previously described in Chapter 3.2. Racemic substrates **S1**-**S3** were prepared as previously reported.[15,16] All other reagents were used as commercially available**.** ^{1}H-NMR spectra were recorded using a 400 MHz spectrometer. Chemical shifts are relative to that of $SiMe_4$ as internal standard.

4.2.4.2 Typical procedure for the allylic alkylation of S1-S3

A degassed solution of $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (1.8 mg, 0.005 mmol) and the thioether-phosphite ligand (0.011 mmol) in dichloromethane (0.5 mL) was stirred for 30 min. Subsequently, a solution of substrate (1 mmol for **S1** and **S3,** and 0.5 mmol for **S2**) 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 the desired reaction time, the reaction mixture was diluted with Et_2O (5 mL) and a 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 compound **1**, 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 basic alumina using dichloromethane as the eluent.[7] For compound **2**, the conversion was measured by ^{1}H-NMR and the ee was determined by ^{1}H-NMR using $[Eu(hfc)_3]$.[6b] For compound **3** conversion and enantiomeric excess were determined by GC.[17]

4.2.5 Acknowledgements

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4.3 Asymmetric Pd-catalyzed allylic substitution using a furanoside monophosphite ligand library. Scope and limitations.

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Abstract. We have applied a modular sugar-based phosphite ligand library for the Pd-catalyzed allylic substitution reactions of several substrates. These ligands are derived from D-(+)-glucose, D-(+)-galactose and D-(+)-fructose, which lead to a wide range of sugar backbones, and contain several substituents at C-3 of the furanoside backbone and several substituents/configurations in the biaryl moiety, with different steric and electronic properties. Systematic variation of the ligand parameters indicates that the catalytic performance (activities and enantioselectivities) is highly affected by sugar backbone, the substituents at the C-3 of the furanoside backbone, the configurations at carbon C-3 and C-4 of the ligand backbone and the type of substituents/configurations in the biaryl phosphite moiety as well as the substrate type. While for disubstituted substrates moderate enantioselectivities (up to 76%) were therefore achieved using ligand **L14f**, the highest enantioselectivity (up to 40%) for monosubstituted substrate was obtained using ligand **L17a**.

4.3.1 Introduction

Palladium-catalyzed asymmetric allylic alkylation is a useful synthetic method for the enantioselective formation of C-C bonds.[1] The selection of chiral ligands for highly enantioselective allylic substitution has focussed on the use of bidentated nitrogen and phosphorus donors (both homo- and heterodonors).[1] Less attention has been paid to catalysts containing monodentated ligands in this process. However, in 2000, the groups of RajanBabu and Zhang obtained an enantioselectivity of 94% with catalysts precursors containing monophospholane ligands in the Pd-catalyzed allylic alkylation to *rac*-1,3-diphenyl-3acetoxyprop-1-ene.[2] Despite this success, few monophosphorus ligands have been applied in the Pd-catalyzed asymmetric allylic substitution.[3] This encourages further research into monophosphorus ligands to study their possibilities as a new class of ligands for this process. Recently, a group of less electron-rich phosphorus compounds – biaryl phosphite-based 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.[1i,4] Therefore, these ligand systems have provided excellent enantioselectivities and activities in different substrate types.[4]

Following our interest in modular π-acceptor ligands[4] and encouraged by the success of monophosphorus ligands, we report here the design of a library of chiral monophosphite ligands **L9**-**L19a**-**c**,**f**-**g** (Figure 4.3.1) and screen their use in the palladium allylic substitution reaction of several substrate types. These ligands are derived from natural D-(+)-glucose, D-(+)-galactose and D-(+)-fructose and have the advantage of carbohydrate and phosphite ligands, such as availability at low price from readily available alcohols and facile modular constructions.[5] In addition they are less sensitive to air than typical phosphines, widely used as ligands in asymmetric catalysis. All these favourable features enable series of chiral ligands to be synthesized and screened in the search for high activity and selectivity. Although carbohydrate-based bidentate ligands have been successfully used in some enantioselective reactions,[5] few good monodentated chiral ligands have been reported based on carbohydrates.[6,7]

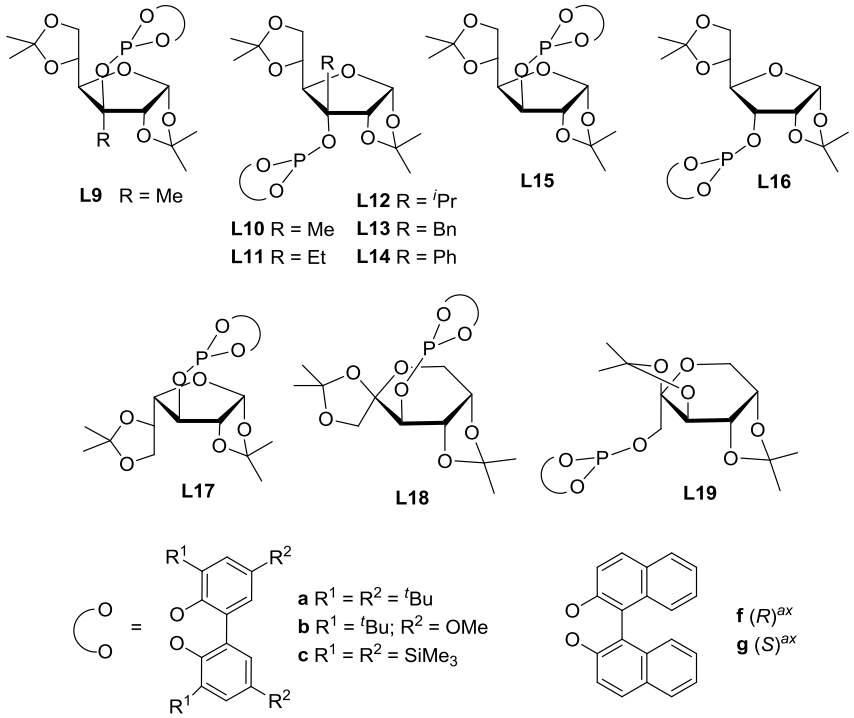


Figure 4.3.1. Furanoside monophosphite ligand library **L9**-**L19a**-**c**,**f**-**g**.

4.3.2 Results and discussion

4.3.2.1 Ligand design

The sugar-based monophosphite ligands are derived from D-(+)-glucose, D-(+)-galactose and D-(+)-fructose, which lead to a wide range of sugar backbones (**L15**-**L19**), and contain several substituents at C-3 of the furanoside backbone (**L9**-**L14**) and substituents/configurations in the biaryl moiety (**a**-**c**,**f**-**g**), with different steric and electronic properties, whose effect on the catalytic performance will be studied. Therefore, ligands **L9**-**L19a**-**c**,**f**-**g** consist of chiral di-*O*-protected either furanoside (ligands **L9**-**L17**) or pyranoside (ligands **L18** and **L19**) backbones, which determine their underlying structure, and one hydroxyl group. Several phosphoric acid biaryl esters (**a**-**c**,**f**-**g**) were attached to these basic frameworks (Figure 4.3.1).

The influence of the different groups attached to the *ortho*- and *para*-positions of the biphenyl moieties on enantioselectivity was investigated using ligands **L15a**-**c**, which have the same configuration on the carbon atom C-3. To determine whether there is a cooperative effect between the stereocenters of the ligand backbone and the configuration of the biaryl phosphite moieties, we prepared a series of enantiomerically pure binaphthol-based ligands **L9**-**L10f**-**g** and **L15**-**L16f**-**g**.

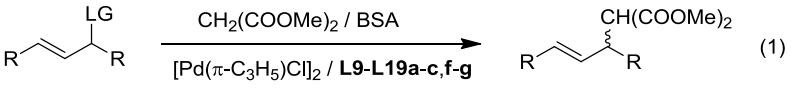
We studied the effects of the stereogenic carbon atom C-3 on enantioselectivity by comparing diastereomeric ligands **L9** and **L10** and **L15** and **L16**, respectively, which have opposite configuration at C-3. The influence of the configuration of carbon atom C-4 in the catalytic performance was studied using ligands **L15** and **L17** which only differ in the configuration at C-4.

We also studied the effect of a range of substituents at C-3 of the furanoside backbone with ligands **L9**-**L14**. These ligands contain substituents with different electronic and steric properties at C-3 of the sugar backbone.

The influence of the carbohydrate ring size in the catalytic performance of the Pd-catalysts was studied with ligands **L18**, which have a pyranoside backbone and the same configuration at C-3 than furanoside ligand **L15**. Finally, with ligands **L19** we studied how the flexibility of the ligand backbone may affect the catalytic performance. These ligands also have a pyranoside backbone as ligands **L18**, but differ from the rest of ligands in a phosphite moiety attached to a primary alcohol, providing a more flexible ligand.

4.3.2.2 Allylic substitution of disubstituted linear substrates

In this section, we report the use of the chiral phosphite ligand library (**L9**-**L19a**-**c**,**f**-**g**) in the Pd-catalyzed allylic alkylation (Eq 1) of three disubstituted linear substrates with different steric properties: *rac*-1,3-diphenyl-3-acetoxyprop-1-ene **S1**, *rac*-(*E*)-ethyl-2,5-dimethyl-3-hex-4-enylcarbonate **S2** and *rac*-1,3-dimethyl-3-acetoxyprop-1-ene **S3**. In all the cases, the catalysts were generated *in situ* from 0.5 mol % of π-allyl-palladium chloride dimer $[PdCl(\eta^3\text{-}C_3H_5)]_2$ and the corresponding ligand.[1]



(1)

S1 R= Ph; LG= OAc
S2 R= ^{i}Pr; LG= OCOOEt
S3 R= Me; LG= OAc

1 R= Ph
2 R= ^{i}Pr
3 R= Me

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. The effect of the solvent and the ligand-to-palladium ratio were investigated using the catalyst precursor containing ligand **L16b** (Table 4.3.1). The results indicated that solvent affected catalytic performance. The optimum trade-off between enantioselectivities and activities was obtained when dichloromethane was used as a solvent (Table 4.3.1, entry 4). We next studied the effect of the ligand-to-palladium ratio. As expected the catalytic performance were best with a ligand-to-palladium ratio of 2 (Table 4.3.1, entries 4 vs 5).

Table 4.3.1. Pd-catalyzed allylic alkylation of 1,3-diphenyl-3-acetoxyprop-1-ene **S1** using ligands **L16b**.[a]

Entry	Solvent	Ratio **L**/Pd	% Conv (h)[b]	% ee[c]
1	DMF	2	43 (4)	11 (*S*)
2	Toluene	2	9 (8)	19 (*S*)
3	THF	2	24 (4)	17 (*S*)
4	CH_2Cl_2	2	31 (4)	23 (*S*)
5	CH_2Cl_2	1	14 (4)	20 (*S*)

[a] 0.5 mol% $[Pd(\pi\text{-}C_3H_5)Cl]_2$, room temperature, 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 ^{1}H NMR. Reaction time shown in parentheses. [c] Determined by HPLC (Chiralcel OD).

Under the optimized conditions, we first evaluated the rest of phosphite ligands in the Pd-catalyzed allylic substitution of *rac*-1,3-diphenyl-3-acetoxyprop-1-ene **S1**. The results, which are summarized in Table 4.3.2, indicate that the catalytic performance (activities and enantioselectivities) is highly affected by the substituents at C-3 of the furanoside backbone, the substituents/configuration of the biaryl moiety, the configuration of carbon atoms C-3 and C-4 and the size of the ring of the sugar backbone.

The results using ligands **L9**-**L10a**,**f**-**g** and **L15-L16a**-**c**,**f**-**g** allow us to study the influence of the substituents/configuration of the biaryl moiety on the product outcome (Table 4.3.2, entries 1-6 and 11-20). We found that the presence of bulky substituents at the *ortho* positions of the biphenyl phosphite moiety has a negative effect on activity. Activities were therefore best when binaphthyl phosphite moieties (**f**,**g**) were present. The effect of the biaryl groups on enantioselectivity depends on the substituents attached to C-3 of the furanoside backbone. For ligands **L9**-**L10**, containing a methyl substituent at C-3, the highest enantioselectivities were achieved with an *R*-binaphthyl phosphite moiety (**f**; Table 4.3.2, entries 2 and 5). However, for ligands **L15** and **L16**, without the methyl substituent at C-3, the best enantioselectivities were achieved with ligands containing trimethylsilyl substituents at the *ortho* positions of the biphenyl phosphite moiety (**c**; Table 4.3.2, entries 13 and 18).

We next studied the effect of the substituents attached to C-3 of the furanoside backbone with ligands **L10**-**L14**. The results indicated that the highest enantioselectivities were obtained using ligand **L14f**, with a phenyl substituent at C-3 (Table 4.3.2, entry 10).

Comparing the results using ligands **L15** with **L16**, that only differ in the configuration at C-3, we observed that this configuration controls the sense of enantioselectivity. Accordingly, ligands **L15a**-**c**,**f**-**g** with an *S* configuration at the C-3 of the ligand backbone, gave the *R*-**1** product, while ligands **L16a**-**c**,**f**-**g** with an *R* configuration at C-3 gave *S*-**1** product (Table 4.3.2, entries 11-15 *vs* 16-20). Furthermore, comparing ligands **L15f**-**g** and **L16f**-**g**, we found a cooperative effect between the configuration of the binaphthyl phosphite moiety and the configuration at C-3, that results in a matched combination for ligand **L16f** (Table 4.3.2, entry 19). The results also showed that ligand **L17** with an *S* configuration at C-4 gave lower enantioselectivity than ligands **L15** with an opposite configuration at this position (Table 4.3.2, entry 21 *vs* 11). In addition, ligands **L18** which have a pyranoside backbone provided lower yields and enantioselectivities than their

relative furanoside ligands **L15** (Table 4.3.2, entries 22-23 *vs* 11-12). Finally, the most flexible ligand **L19**, which has the phosphite moiety attached to a primary carbon, provided the lowest enantioselectivity (Table 4.3.2, entry 24).

Table 4.3.2. Pd-catalyzed allylic alkylation of substrates **S1**-**S3** in CH_2Cl_2 using ligands **L9**-**L19a**-**c**,**f**-**g**.[a]

Entry	Substrate	Ligand	% Conv (h)[b]	% ee[c]
1	**S1**	**L9a**	48 (4)	6 (*R*)
2	**S1**	**L9f**	100 (4)	12 (*R*)
3	**S1**	**L9g**	100 (4)	10 (*R*)
4	**S1**	**L10a**	57 (4)	12 (*S*)
5	**S1**	**L10f**	100 (4)	37 (*S*)
6	**S1**	**L10g**	40 (4)	4 (*S*)
7	**S1**	**L11f**	100 (4)	36 (*S*)
8	**S1**	**L12f**	42(4)	12 (*S*)
9	**S1**	**L13f**	100 (4)	39 (*S*)
10	**S1**	**L14f**	100 (4)	65 (*S*)
11	**S1**	**L15a**	84 (4)	22 (*R*)
12	**S1**	**L15b**	35 (4)	31 (*R*)
13	**S1**	**L15c**	42 (4)	40 (*R*)
14	**S1**	**L15f**	100 (4)	18 (*R*)
15	**S1**	**L15g**	100 (4)	19 (*R*)
16	**S1**	**L16a**	81 (4)	20 (*S*)
17	**S1**	**L16b**	31 (4)	23 (*S*)
18	**S1**	**L16c**	53 (4)	41 (*S*)
19	**S1**	**L16f**	100 (4)	28 (*S*)
20	**S1**	**L16g**	100 (4)	16 (*S*)
21	**S1**	**L17a**	64 (4)	15 (*R*)
22	**S1**	**L18a**	8 (4)	14 (*R*)
23	**S1**	**L18b**	10 (4)	15 (*R*)
24	**S1**	**L19a**	82 (4)	11 (*S*)
25[d]	**S1**	**L14f**	29 (8)	72 (*S*)
26	**S2**	**L14f**	94 (24)	66 (*R*)[e]
27	**S3**	**L14f**	46 (24)	42 (*S*)[f]

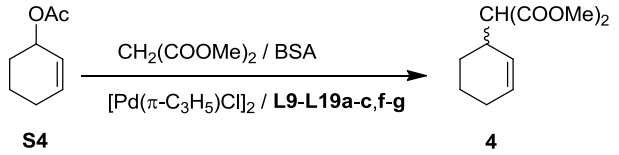
[a] 0.5 mol% $[Pd(\pi\text{-}C_3H_5)Cl]_2$, 2 mol% ligand, room temperature, 30 min; 3 equiv of $CH_2(COOMe)_2$ and *N*,*O*-bis(trimethylsilyl)acetamide (BSA), a pinch of KOAc, room temperature. [b] Measured by ^{1}H NMR. Reaction time shown in parentheses. [c] Determined by HPLC (Chiralcel OD).[d] T= 0 °C. [e] Measured by ^{1}H NMR using $Eu(hfc)_3$. [f] Measured by GC.

In addition to the effect of structural parameters on enantioselectivity, the reaction parameters can also be controlled to further improved selectivity. In this case, enantioselectivity was further improved (ee's up to 72%) with ligand **L14f** by lowering the reaction temperature to 0 °C (Table 4.3.2, entry 25).

We then tested ligand **L14f** (the one that provided the best result in the alkylation of **S1**) in the allylic alkylation of more hindered linear substrate **S2** and unhindered linear substrate **S3** (Eq 1). For hindered substrate **S2**, similar enantioselectivities (66% (*R*) ee) than **S1** were achieved (Table 4.3.2, entry 26). Substrate **S3** is less sterically demanding than substrates **S1** and **S2**. The enantioselectivity for **S3** is therefore more difficult to control than with hindered substrates such as **S1**.[1] Unfortunately, the Pd-**L14f** catalytic system provided moderate enantioselectivity (ee's up to 42%; Table 4.3.2, entry 27).

4.3.2.3 Allylic substitution of cyclic substrate

To further study the potential of ligands **L9**-**L19a**-**c**,**f**-**g**, we also tested the them in the allylic alkylation of cyclic substrate **S4**. As for unhindered linear substrate **S3**, enantioselectivity in cyclic substrates is difficult to control mainly because of the presence of less sterically *anti* substituents (Eq 2). These *anti* substituents are thought to play a crucial role in the enantioselection observed with cyclic substrates in the corresponding Pd-allyl intermediates.[1]



S4 **4** (2)

The results are summarized in Table 4.3.3. The results followed a similar trend to that observed for **S1**. Again, the best enantioselectivity was achieved using Pd/**L14f** catalytic system (ee's up to 44%). As observed for linear substrates, changing the solvent from dichloromethane to other solvents did not increase enantioselectivity (Table 4.3.3, entries 5 vs 13-15).

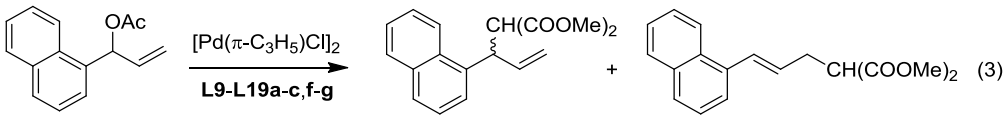
Table 4.3.3. Selected results for the Pd-catalyzed allylic alkylation of *rac*-3-acetoxy-cyclohexene **S4** using ligands **L9**-**L19a**-**c**,**f**-**g**.[a]

Entry	Solvent	Ligand	% Conv (h)[b]	% ee[c]
1	CH_2Cl_2	**L9f**	52 (24)	7 (*R*)
2	CH_2Cl_2	**L9g**	48 (24)	9 (*R*)
3	CH_2Cl_2	**L10f**	54 (24)	29 (*S*)
4	CH_2Cl_2	**L10g**	62 (24)	7 (*S*)
5	CH_2Cl_2	**L14f**	49 (24)	44 (*S*)
6	CH_2Cl_2	**L15a**	19 (24)	11 (*R*)
7	CH_2Cl_2	**L15f**	39 (24)	9 (*R*)
8	CH_2Cl_2	**L15g**	47 (24)	6 (*R*)
9	CH_2Cl_2	**L16a**	11 (24)	9 (*S*)
10	CH_2Cl_2	**L16f**	100 (24)	8 (*S*)
11	CH_2Cl_2	**L16g**	100 (24)	2 (*S*)
12	CH_2Cl_2	**L17a**	100 (24)	2 (*R*)
13	DMF	**L14f**	84 (24)	8 (*S*)
14	THF	**L14f**	27 (24)	37 (*S*)
15	Toluene	**L14f**	12 (24)	32 (*S*)

[a] 0.5 mol% $[Pd(\pi\text{-}C_3H_5)Cl]_2$, 2 mol% ligand, room temperature, 30 min; 3 equiv of $CH_2(COOMe)_2$ and *N*,*O*-bis(trimethylsilyl)acetamide (BSA), a pinch of the corresponding base, room temperature. [b] Measured by GC. Reaction time shown in parentheses. [c] Determined by GC.

4.3.2.4 Allylic substitution of monosubstituted linear substrates

Finally, we also examined the regio- and stereoselective allylic alkylation of 1-(1-naphthyl)allyl acetate **S5** with dimethyl malonate (Eq 3). It is not only the enantioselectivity of the process that needs to be controlled for this substrate; the regioselectivity is also a problem, because a mixture of regioisomers may be obtained. Most Pd-catalysts developed to date favor the formation of achiral linear product **6** rather than the desired branched isomer **5**. Therefore, the development of highly regio- and enantioselective Pd-catalysts is still a challenge.[4d,8]



S5 **5** **6** (3)

The results obtained with the phosphite ligands are summarized in Table 4.3.4. Unfortunately, the enantioselectivities (ee's up to 40%) were not high. However, good regioselectivities (regio's up to 80%) have been obtained.[9]

Table 4.3.4. Pd-catalyzed allylic alkylation of **S5** in CH_2Cl_2 using ligands **L19a**-**c**,**f**-**g**.[a]

Entry	Ligand	% Conv (h)[b]	**5**/**6**[b]	% ee[c]
1	**L9a**	100 (6)	80/20	9 (*R*)
2	**L9f**	100 (6)	40/60	15 (*R*)
3	**L9g**	100 (6)	25/75	0
4	**L10a**	100 (6)	75/25	6 (*R*)
5	**L10f**	100 (6)	20/80	12 (*R*)
6	**L10g**	100 (6)	30/70	8 (*R*)
7	**L11f**	100 (6)	25/75	14 (*R*)
8	**L12f**	64 (6)	30/70	6 (*R*)
9	**L13f**	97 (6)	25/75	18 (*R*)
10	**L14f**	85 (6)	25/75	24 (*R*)
11	**L15a**	100 (6)	75/25	9(*R*)
12	**L15b**	100 (6)	80/20	7 (*R*)
13	**L15c**	100 (6)	80/20	18 (*R*)
14	**L15f**	100 (6)	35/65	17 (*S*)
15	**L15g**	100 (6)	20/80	0
16	**L16a**	100 (6)	70/30	21 (*R*)
17	**L16b**	100 (6)	75/25	10 (*R*)
18	**L16c**	100 (6)	60/40	<5 (*R*)
19	**L16f**	100 (6)	20/80	18 (*R*)
20	**L16g**	100 (6)	25/75	3 (*S*)
21	**L17a**	100 (6)	45/55	40 (*R*)
22	**L18a**	100 (6)	30/70	<5 (*R*)
23	**L18b**	100 (6)	35/65	<5 (*S*)
24	**L19a**	100 (6)	70/30	25 (*R*)

[a] 0.5 mol% $[Pd(\pi\text{-}C_3H_5)Cl]_2$, 2.2 mol% ligand, room temperature, 30 min; 3 equiv of $CH_2(COOMe)_2$ and *N*,*O*-bis(trimethylsilyl)acetamide (BSA), a pinch of the corresponding base, room temperature. [b] Measured by ^{1}H NMR. Reaction time shown in parentheses. [c] Determined by HPLC (Chiralcel OJ).

The results indicated that if regioselectivity is to be high, bulky substituents at the *ortho* positions of the biaryl phosphite moiety and a furanoside backbone with an *R* configuration at C-4 (ligands **L15**-**L16a**-**c**) are necessary (entries 11-13 and 16-18). However, enantioselectivities were best for furanoside ligand

L17a with *S* configurations at both C-3 and C-4 of the furanoside backbone (entry 21).

4.3.3 Conclusions

A library of readily available monophosphite ligands has been screened in the asymmetric Pd-catalyzed allylic alkylation of several substrates with different electronic and steric properties. By carefully designing this library we were able to systematically investigate the effect of varying the sugar backbone, the substituents at C-3 of the furanoside backbone, the configurations at carbon C-3 and C-4 of the ligand backbone and the type of substituents/configurations in the biaryl phosphite moiety. In general, the catalytic performance (activities and enantioselectivities) is highly affected by these ligand parameters as well as the substrate. For disubstituted substrates **S1**-**S4** enantioselectivities were best with ligand **L14f** (ee's up to 76%) while for monosubstituted substrate **S5** ligand **L17a** provided the best ee's (up to 40%).

4.3.4 Experimental Section

4.3.4.1 General Considerations

All syntheses were performed by using standard Schlenk techniques under argon atmosphere. Solvents were purified by standard procedures. Ligands **L15-L19a-c**,**f-g** have been prepared as previously described.[10] Ligands **L9**-**L14a**,**f**-**g** has been previously described in Chapter 3. Racemic substrates **S1**-**S5** were prepared as previously reported.[11,12,13] All other reagents were used as commercially available.

4.3.4.2 Typical procedure of allylic alkylation of substrates S1-S4

A degassed solution of $[Pd(\pi\text{-}C_3H_5)Cl]_2$ (1.8 mg, 0.005 mmol) and the corresponding monophosphite (0.022 mmol) in dichloromethane (1 mL) was stirred for 30 min. Subsequently, a solution of corresponding substrate (1 mmol) in dichloromethane (1.5 mL), dimethyl malonate (342 μL, 3 mmol), *N*,*O*-bis(trimethylsilyl)-acetamide (740 μL, 3 mmol) and a pinch of KOAc were added. The reaction mixture was stirred at room temperature. After the desired reaction time, the reaction mixture was diluted with Et_2O (5 mL) and a 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**, conversion was measured by ^{1}H-NMR and enantiomeric excess was determined by HPLC (Chiralcel-OD, 0.5% 2-propanol/hexane, flow 0.5 mL/min).[14] For substrate **S2**, the conversion was measured by ^{1}H-NMR and the ee was determined by ^{1}H-NMR using [Eu(hfc)$_3$].[15] For substrates **S3** and **S4**, conversion and enantiomeric excess were determined by GC using a FS-Cyclodex β-I/P 25 m column.[16]

4.3.4.3 Typical procedure of allylic alkylation of monosubstituted linear substrate S5

A degassed solution of $[Pd(\pi\text{-}C_3H_5)Cl]_2$ (1.8 mg, 0.005 mmol) and the corresponding monophosphite ligand (0.022 mmol) in dichloromethane (0.5 mL) was stirred for 30 min. 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. The reaction mixture was stirred at room temperature. After the desired reaction time, the reaction mixture was diluted with Et_2O (5 mL) and a 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, 3% 2-propanol/hexane, flow 0.7 mL/min), a sample was filtered over basic alumina using dichloromethane as the eluent.[17]

4.3.5 Acknowledgements

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UNIVERSITAT ROVIRA I VIRGILI
SCREENING OF MODULAR SUGAR DERIVED PHOSPHITE-BASED LIGAND LIBRARIES FOR M-CATALYZED REACTIONS. A GREEN APPROACH TO CATALYSTS DISCOVERY
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Chapter 5

Asymmetric Ni catalyzed 1,2 addition

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5. Asymmetric Ni-catalyzed 1,2-addition

5.1 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 group, few successful ligands have been developed. Most of them use chiral monodentated phosphoroamidite and phosphite ligands. Nevertheless, our group has demonstrated that bidentated phosphite-phosphoroamidite ligands are also able to induce high enantioselectivities.

With the aim to expand the range of successful ligands for this process, in this chapter, we report the application of the two sugar-based ligand libraries described in Chapter 3 (thioether-phosphite (**L1**-**L8a**-**e**) and monophosphite (**L9**-**L14a**,**f**-**g**) in the asymmetric Ni-catalyzed 1,2-addition of trialkylaluminum reagents to aldehydes. More specifically, in section 5.2 we report the application of thioether-phosphite ligand library (**L1**-**L8a**-**e**), derived from L-(+)-tartaric acid. Our results indicated that selectivity depended strongly on the thioether substituent, the substituents in the alkyl backbone chain next to the phosphite moiety and the configuration at the biaryl phosphite moiety. The best enantioselectivities (ee's up to 71%) were obtained using the catalysts precursor containing the thioether-phosphite ligand **L5a** in the 1,2-addition of several aryl aldehydes. In section 5.3, we report the application of the modular sugar-based monophosphite ligand library **L9**-**L14a**,**f**-**g** for the Ni-catalyzed 1,2-addition of trialkylaluminum reagents to aldehydes. These ligands are based on previously developed successful furanoside monophosphite ligands, in which new substituents have been attached to C-3 of the furanoside backbone. We found that the introduction of a methyl substituent at C-3 of the sugar backbone in allofuranoside ligands is highly advantageous in terms of enantioselectivity (ee's increased from 44% to 84%).

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5.2 Thioether-phosphite ligands derived from L-(+)-tartaric acid for the Ni-catalyzed trialkylaluminum addition to aldehydes

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

Abstract. We have described the first application of bidentated P,S-ligands in the asymmetric Ni-catalyzed trialkylaluminum addition to several aldehydes. The ligands are prepared from inexpensive L-(+)-tartaric acid and combine the advantages of a sugar core and the presence of both thioether and phosphite moieties (i.e. modular design at a low price and high stability towards oxygen and other oxidizing reagents). Good yields and moderate enantioselectivities have been achieved for a range of aryl aldehydes using several organoaluminum sources.

5.2.1 Introduction

The catalytic asymmetric carbon-carbon bond formation is one of the most actively pursued areas of research in the field of asymmetric catalysis. In this context, the catalytic addition of organometallic 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.[1] For alkylation reagents, dialkylzinc compounds have played a dominant role;[2] although trialkylaluminum compounds are more interesting than other organometallic reagents because they are economically obtained in industrial scale from aluminum hydride and olefins.[3] Despite this advantage their use is rare.[4,5] In this respect, the few most successful catalysts for the enantioselective addition of trialkylaluminum to aldehydes have been titanium complexes bearing chiral diols or N-sulfonylated amino alcohols as ligands.[4] However, the high catalyst loadings needed and the slow turnover rate hamper the potential utility of these catalytic systems. This limitation has been overcome by using Ni-catalyst modified with chiral monodentated phosphoroamidite[5a,b,f] and phosphite[5c] ligands. More recently, our group found that the use of bidentated phosphite-phosphoroamidite[5e] can also led to excellent enantioselectivities with low catalyst loadings.

To further expand the range of ligands and performance of this asymmetric nickel-catalyzed addition of organoaluminum reagents to aldehydes process, we report in this chapter the application of bidentated thioether-

phosphite ligand library **L1**-**L8a**-**e** (Figure 5.2.1), described in Chapter 3.2. These ligands, which are derived from natural L-(+)-tartaric acid, have the advantage of sugar and phosphite ligands, such as availability at low price from readily available alcohols, high resistance to oxidation, and facile modular constructions.[6] In addition, the introduction of a thioether moiety in the ligand design may be beneficial, because the S atom becomes a stereogenic center when coordinated to metal, which moves the chirality closer to the metal.[7] The highly modular construction of these ligands makes it easy for us to study the effect of: (a) systematically varying the electronic and steric properties of the thioether group (ligands **L1**-**L7**), (b) varying the substituents in the alkyl backbone chain next to the phosphite moiety (ligands **L1** and **L8**); and (c) the effect of the substituents and configurations in the biaryl phosphite moiety (**a**-**e**). To the best of our knowledge this is the first example of bidentated P-S ligands applied to this process.

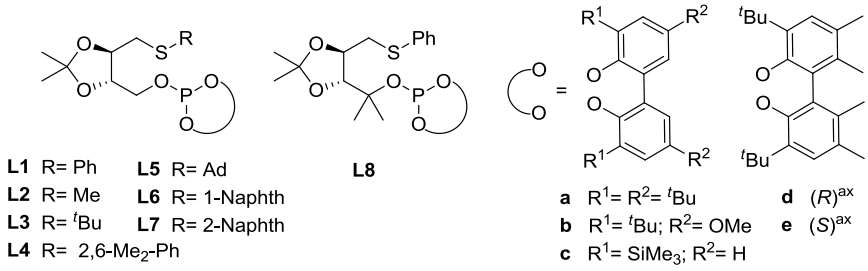


Figure 5.2.1. Thioether-phosphite ligands **L1**-**L8a**-**e**.

5.2.2 Results and discussion

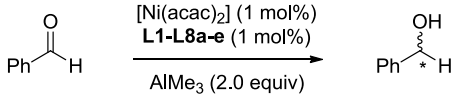
5.2.2.1 Asymmetric addition of trimethylaluminum to benzaldehyde S1

To make an initial evaluation of this new type of ligands (**L1**-**L8a**-**e**), we chose the nickel-catalyzed asymmetric addition of trimethylaluminum to benzaldehyde **S1**, which was used as the model substrate (Table 5.2.1).[4,5] The catalytic system was generated *in situ* by adding the corresponding ligand to a suspension of the catalyst precursor [Ni(acac)$_2$] (acac = acetylacetonate).

The results indicate that enantioselectivities are highly affected by the thioether substituent, the substituents in the alkyl backbone chain next to the phosphite moiety and the configuration of the biaryl phosphite moieties. In all cases excellent isolated yields (>88%) of the desired 2-phenylethanol have been obtained without excess of ligand needed. The best enantioselectivity (ee's up to

61%, Table 5.2.1, entry 15) were obtained using ligand **L5a**, which has the appropriate combination of ligand parameters.

Table 5.2.1. Ni-catalyzed asymmetric addition of $AlMe_3$ to benzaldehyde using thioether-phosphite ligand library **L1**-**L8a**-**e**



Entry	Ligand	L/Ni	% Conv[b]	% Yield[c]	% ee[d]
1	**L1a**	1	100	96	42 (*R*)
2	**L1a**	0.5	98	95	41 (*R*)
3	**L1a**	2	100	94	42 (*R*)
4	**L1b**	1	100	93	41 (*R*)
5	**L1c**	1	100	91	40 (*R*)
6	**L1d**	1	100	96	12 (*R*)
7	**L1e**	1	100	97	31 (*R*)
8	**L2a**	1	100	92	28 (*R*)
9	**L3a**	1	100	96	52 (*R*)
10	**L3d**	1	100	95	12 (*R*)
11	**L3e**	1	100	97	17 (*R*)
12	**L4a**	1	100	96	45 (*R*)
13	**L4d**	1	100	96	20 (*R*)
14	**L4e**	1	100	96	31 (*R*)
15	**L5a**	1	100	91	61 (*R*)
16	**L5d**	1	100	96	29 (*R*)
17	**L5e**	1	100	96	39 (*R*)
18	**L6a**	1	100	89	41 (*R*)
19	**L6d**	1	100	91	11 (*R*)
20	**L6e**	1	100	93	29 (*R*)
21	**L7a**	1	100	90	41 (*R*)
22	**L7d**	1	100	89	10 (*R*)
23	**L7e**	1	100	95	29 (*R*)
24	**L8a**	1	100	92	5 (*R*)
25	**L8d**	1	100	88	28 (*R*)
26	**L8e**	1	100	89	20 (*S*)

[a] Reaction conditions: T= -20 °C, $[Ni(acac)_2]$ (1 mol%), $AlMe_3$ (2 equiv.), substrate (1 mmol), THF (8 mL). [b] % Conversion determined by GC after 3 hours. [c] Isolated yield. [d] Enantiomeric excess measured by GC using Cyclodex-B column.

The effect of the thioether substituent was studied with ligands **L1**-**L7a** (Table 5.2.1, entries 1, 8, 9, 12, 15, 18 and 21). We found that these substituents mainly affected the enantioselectivity. Our results showed that the enantioselectivity depended upon the steric properties of these substituents. Enantioselectivities were therefore higher when more sterically demanding substituents were present (i.e., Ad > ^{t}Bu > Ph > Me).

With ligands **L1**-**L7a**-**e**, we next studied the effect of the biaryl phosphite moiety on the product outcome. The results using **L1a**-**c** indicated that the substituents at both *ortho* and *para*-positions of the biphenyl moiety had no effect on the enantioselectivity (i.e. Table 5.2.1, entries 1 vs 4 and 5). However, the results using ligands **L1**-**L7d**-**e**, which contain enantiopure biphenyl moieties, show a clear cooperative effect between the configuration of the biaryl phosphite moiety and the ligand backbone. This resulted in a matched combination for ligands **L1**-**L7e**, which contains an enantiopure (*S*)-biphenyl phosphite moiety (i.e. entry 7 vs 6). Nevertheless, it should be pointed that the highest enantioselectivities were achieved using ligands containing tropoisomeric biphenyl moieties (i.e. entries 1 vs 6 and 7).

With ligands **L1** and **L8**, we studied how the substituents at the alkyl backbone chain next to the phosphite moiety affected the product outcome. The results indicate that replacing the methylenic group (ligands **L1**) by a CMe_2 group (ligands **L8**) led to lower enantioselectivities (i.e. entry 1 vs 24).

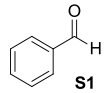
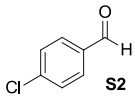
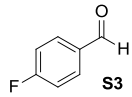
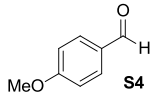
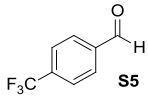
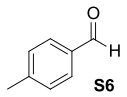
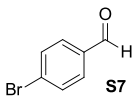
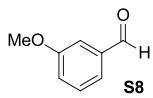
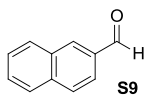
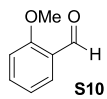
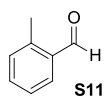
5.2.2.2 Asymmetric addition of several aluminum reagents to a range of aldehydes

To further assess the catalytic efficiency of the Ni/**L5a** catalytic system, we next tested it in the nickel-catalyzed addition of several trialkylaluminum sources (AlR'_3, R' = Me or Et; and DABAL-Me_3) to other benchmark aldehydes with different steric and electronic properties. The results are summarized in Table 5.2.2.

The results using trimethylaluminum as alkylating reagent indicated that catalytic performance (activity and enantioselectivity) were hardly affected by the presence of either electron-donating or electron-withdrawing groups at the *para* or *meta*-position of the phenyl group of the substrate (Table 5.2.2, entries 1-3, 5-9). However, while the presence of a methoxy group at the *para* position had a slightly negative effect on the enantioselectivity (Table 5.2.2, entry 1 vs 4), the highest enantioselectivity was achieved using 2-naphthaldehyde as substrate. In contrast to the most successful sugar-based phosphite ligands,[5c,e] conversions and

enantiomeric excesses did not decreased when 2-substituted benzaldehydes were used (entries 10 and 11).

Table 5.2.2 Ni-catalyzed asymmetric addition of aluminum reagents to aldehydes with **L5a**[a]

		$AlMe_3$		$AlEt_3$		DABAL-Me_3[b]	
Entry	Substrate	% Conv[c]	% ee[d]	% Conv[c]	% ee[d]	% Conv[c]	% ee[d]
1	 **S1**	100 (98)	61 (*R*)	100 (96)	60 (*R*)	94 (81)	54 (*R*)
2	 **S2**	100 (95)	60 (*R*)	100 (91)	59 (*R*)	89 (83)	53 (*R*)
3	 **S3**	100 (93)	62 (*R*)	100 (92)	63 (*R*)	84 (72)	59 (*R*)
4	 **S4**	99 (94)	49 (*R*)	100 (95)	47 (*R*)	86 (76)	43 (*R*)
5	 **S5**	100 (92)	64 (*R*)	100 (87)	61 (*R*)	78 (64)	58 (*R*)
6	 **S6**	100 (97)	61 (*R*)	100 (92)	61 (*R*)	91 (77)	54 (*R*)
7	 **S7**	100 (93)	59 (*R*)	100 (91)	60 (*R*)	87 (73)	55 (*R*)
8	 **S8**	100 (92)	60 (*R*)	100 (94)	58 (*R*)	91 (79)	54 (*R*)
9	 **S9**	100 (92)	71 (*R*)	100 (93)	69 (*R*)	83 (71)	63 (*R*)
10	 **S10**	100 (94)	64 (*R*)	100 (90)	65 (*R*)	88 (76)	61 (*R*)
11	 **S11**	100 (91)	66 (*R*)	100 (92)	64 (*R*)	79 (68)	60 (*R*)

[a] Reaction conditions: T= -20 °C, [Ni(acac)$_2$] (1 mol%), AlR'$_3$ (2 equiv.), substrate (1 mmol), THF (8 mL). [b] Reaction conditions: T= 5 °C, [Ni(acac)$_2$] (1 mol%), DABAL-Me_3 (1.2 equiv.), substrate (1 mmol), THF (8 mL). [c] % Conversion determined by GC after 3 hour. In brackets are shown the yields determined by GC using dodecane as internal standard. [d] Enantiomeric excess measured by GC using Cyclodex-B column.

The results of using triethylaluminum and air-stable methylating reagent DABAL-Me_3 indicated that the catalytic performance follows the same trend as for the trimethylaluminum addition. However, yields and enantioselectivities were somewhat lower using DABAL-Me_3, probably because of the higher temperature required to achieve full conversions.

5.2.3 Conclusions

A library of bidentated P,S-ligands have been applied for the first time in the Ni-catalyzed trialkylaluminum addition to several aldehydes. The ligands are prepared from L-(+)-tartaric acid and combine the advantages of a sugar core and the presence of both thioether and phosphite moieties (i.e. modular design at a low price and high stability towards oxygen and other oxidizing reagents). We were able to systematically investigate the effect of varying the thioether substituent, the substituents in the alkyl backbone chain next to the phosphite moiety and the substituents/configurations in the biaryl phosphite moiety. By judicious choice of the ligand components we obtained good yields and moderate enantioselectivities (ee values up to 71%) with several aryl aldehydes, with low catalyst loadings (1 mol %) and no excess of ligand.

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**-**L8a**-**e** has been previously described in Chapter 3.2. All other reagents were used as commercially available.

5.2.4.3 Typical procedure for the Ni-catalyzed enantioselective 1,2- addition of trialkylaluminum reagents to aldehydes

[$Ni(acac)_2$] (2.4 mg, 9.32 μmol, 1 mol %) and the corresponding ligand (9.32 μmol, 1 mol %) were stirred in dry THF (8 mL) under an argon atmosphere at -20 ^oC for 10 min. Neat aldehyde (1 mmol) was then added and trialkylaluminum (2 mmol) was added dropwise over 10 min. After the desired reaction time, the reaction was quenched with 2 M HCl (8 mL). Then, dodecane (80 μL) was added and the mixture was extracted with Et_2O (10 mL). The organic layer was dried over $MgSO_4$ and analyzed by GC.[5a]

5.2.4.4 Typical procedure for the Ni-catalyzed enantioselective 1,2-addition of DABAL-Me_3 to aldehydes

[$Ni(acac)_2$] (2.4 mg, 9.32 μmol, 1 mol %) and the corresponding ligand (9.32 μmol, 1 mol %) were stirred in dry THF (8 mL) under an argon atmosphere at 5°C for 10 min. Neat aldehyde (1 mmol) was then added and DABAL-Me_3 (336 mg, 1.3 mmol, 1.3 equiv) was added over 10 min. After the desired reaction time, the reaction was quenched with 2 M HCl (8 mL). Then, dodecane (80 μL) was added and the mixture was extracted with Et_2O (10 mL). The organic layer was dried over $MgSO_4$ and analyzed by GC.[5a]

5.2.5. Acknowledgements

We would like to thank the Spanish Government for providing grant CTQ2010-15835, the Catalan Government for grant 2009SGR116, and the ICREA Foundation for providing M. Diéguez and O. Pàmies with financial support through the ICREA Academia awards.

5.2.6 References

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[5] For examples of Ni-catalysts, see: a) Biswas, K.; Prieto, O.; Goldsmith, P. J.; Woodward, S. *Angew. Chem., Int. Ed.* **2005**, 44, 2232; b) Biswas, K.; Chapron, A.; Cooper, T.; Fraser, P. K.; Novak, A.; Prieto, O.; Woodward, S. *Pure Appl. Chem.* **2006**, 78, 511; c) Mata, Y.; Diéguez, M.; Pàmies, O.; Woodward, S. *J. Org. Chem.* **2006**, 71, 8159; d) Mata, Y.; Diéguez, M.; Pàmies, O.; Woodward, S. *Inorg. Chim. Acta* **2008**, 361, 1381; e) Raluy, E.; Diéguez, M.; Pàmies, O. *Tetrahedron Lett.* **2009**,

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5.3 Sugar-monophosphite ligands applied to the asymmetric Ni-catalyzed trialkylaluminum addition to aldehydes

Sabina Alegre, Montserrat Diéguez, Oscar Pàmies in *Tetrahedron: Asymmetry* **2011**, *22*, 834.

Abstract. A series of readily available sugar-based phosphite ligands were applied to the Ni-catalyzed asymmetric trialkylaluminum additions to aldehydes. The ability of the catalysts to transfer chiral information to the product could be tuned by choosing suitable ligand components (configuration at C-3 of the furanoside backbone; the steric hindrance of the substituent at C-3 and the substituents/configuration of the biaryl phosphite moiety). Good enantioselectivities (ee's up to 84%) were obtained for several aryl aldehydes using several organoaluminum sources.

5.3.1 Introduction

The value of enantiopure alcohols lies mainly in their use as valuable building blocks for the synthesis of natural, pharmaceutical and agricultural products.[1] The asymmetric catalytic addition of organoaluminum reagents to aldehydes can provide a potential synthetic tool for preparing these compounds. Although organoaluminum reagents can be economically obtained on an industrial scale,[2] they are rarely used.[3–5] Recently, Woodward et al. discovered that nickel-based catalysts can allow high enantioselectivities at low catalyst loadings (0.05–1 mol %),[4,5a] thus overcoming the previously used Ti-catalysts' main drawback of requiring high catalyst loadings (10–20 mol %).[3] Despite this advance, there have been relatively few publications describing the highly enantioselective Ni-catalyzed 1,2-addition of trialkylaluminum to aldehydes. Consequently, we herein aim to expand the range of ligands for this process, to which only three types of ligands have been successfully applied to date. The first successful application reported the use of binol-based monophosphoroamidite ligands as the chiral source.[4] The second successful application used a series of sugar-based phosphite-phosphoroamidite ligands.[5c] The third successful application reported the use of a sugar-based monophosphite ligand library containing several ligand backbones.[5a] For these latter ligands, the best results were obtained using glucofuranoside ligand **1**, while the allofuranoside ligand **2**, with an opposite configuration at C-3, provided much lower enantioselectivities (Figure 5.3.1). Despite this success, the use of other phosphite ligands has not yet been reported and a study of the

possibilities offered by phosphites as new ligands for this process is still required. For this purpose, we have herein made further modifications to the previous ligands **1** and **2** by introducing new substituents with different electronic and steric properties at C-3 of the sugar backbone (Figure 5.3.2).

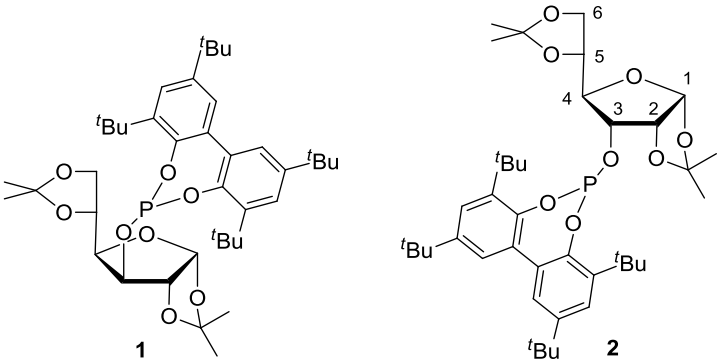


Figure 5.3.1. Monophosphite ligands **1** and **2** previously applied in this process.

Herein, we report the application of 18 potential chiral monophosphite ligands **L9**-**L14a**,**f**-**g** (Figure 5.3.2) in the asymmetric Ni-catalyzed 1,2-addition of trialkylaluminum to several aldehydes. These ligands also have the advantages of carbohydrate and phosphite ligands; that is, they are available at low cost from readily available feedstocks; have high resistance to oxidation, and have straightforward modular constructions.[6,7] With this library we therefore fully investigated the effects of systematically varying the configuration of the C-3 carbon atom of the sugar backbone (**L9**-**L10**), the electronic and steric hindrance of the new substituent at C-3 (**L10-L14**) and the substituents/configuration of the biaryl phosphite moieties **a**,**f**-**g**. By carefully selecting these elements, we achieved good enantioselectivities and activities with different substrate types.

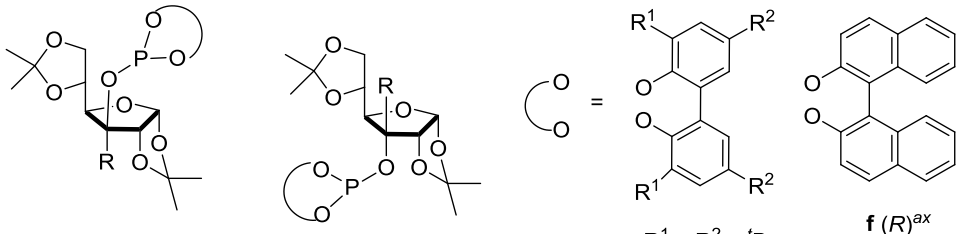
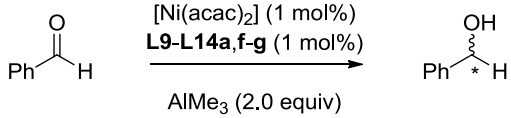


Figure 5.3.2. Carbohydrate-based monophosphite ligands **L9**-**L14a**,**f**-**g**.

5.3.2 Results and discussion

5.3.2.1 Asymmetric addition of AlR_3 to aldehydes

Initially, we evaluated phosphite ligands **L9**-**L14a**,**f**-**g** (Figure 5.3.2) in the nickel-catalyzed asymmetric addition of trimethylaluminum to benzaldehyde, which was used as the model substrate (Scheme 5.3.1). The catalytic system was generated in situ by adding the corresponding ligand to a suspension of the catalyst precursor [Ni(acac)$_2$] (acac = acetylacetonate).



Scheme 5.3.1. Nickel-catalyzed asymmetric addition of $AlMe_3$ to benzaldehyde using phosphite ligands **L9**-**L14a**,**f**-**g**.

The results, which are summarized in Table 5.3.1, indicate that enantioselectivities are highly affected by the configuration at the C-3 carbon atom of the sugar backbone, the steric hindrance of the new substituent at C-3 and the substituents/configuration of the biaryl phosphite moieties. In all cases excellent isolated yields (>95%) of the desired 2-phenylethanol have been obtained. The best enantioselectivity (ee's up to 75%, Table 5.3.1, entry 4) were obtained using ligand **L10a**, which has the appropriate combination of ligand parameters.

With ligands **L9** and **L10**, we studied how the configuration of C-3 of the sugar backbone affected the product outcome. The results indicate that this configuration affects the enantioselectivity (Table 5.3.1, entries 1–6). Therefore,

allofuranoside ligands **L10** with an (*R*)-configuration at C-3 generally provided higher enantioselectivities than when glucofuranoside ligands **L9** were used.

The effect of the substituent at C-3 of the sugar backbone was studied with ligands **L10**-**L14f** (Table 5.3.1, entries 5, 7–10). We found that these substituents mainly affected the enantioselectivity. Our results showed that the enantioselectivity depended upon the steric properties of these substituents. Enantioselectivities were therefore higher when less sterically demanding substituents were present (i.e., Me ≈Ph > Et ≈ Bn >> ^{i}Pr).

With ligands **L9a**,**f**-**g** and **L10a**,**f**-**g**, we next studied the effect of the biaryl phosphite moiety on the product outcome. Our results indicated that the presence of bulky *tert*-butyl groups at the *ortho*- and *para*-positions of the biphenyl moiety had a positive effect on the enantioselectivity (e.g., Table 5.3.1, entries 4 vs 5 and 6). In contrast to the results observed for related ligands **1** and **2**,[5a] the results using ligands **L9f**-**g** and **L10f**-**g**, which contain enantiopure binaphthyl moieties, show a clear cooperative effect between the configuration of the biaryl phosphite moiety and the C-3 configuration of the sugar backbone. This resulted in a matched combination for ligand **L10f** (Table 5.3.1, entry 5). Moreover, when comparing the results of using ligands **L9a**,**f**-**g** and **L10a**,**f**-**g** are compared (Table 5.3.1, entries 1–3 vs 4–6) we can conclude that whereas the biphenyl phosphite moiety in ligand **L9a** adopts an (*S*)-configuration, in ligand **L10a** it adopts an (*R*)-configuration upon complexation to the nickel.

After comparing these results with those previously reported for related ligands **1** and **2** (Figure 5.3.1),[5a] we found that replacing the hydrogen group with a methyl substituent at C-3 of the sugar backbone had an extremely positive effect on the enantioselectivity for ligand **2** (from 44% (*R*) to 75% (*S*)), while it has a negative effect for ligand **1**.

Next, we used ligand **L10a** which provided the best results to study the effect of the ligand-to-nickel ratio on the product outcome. Our results showed that no excess of ligand was needed for yields and enantioselectivities to be high (Table 5.3.1, entries 4, 11 and 12).

To further investigate the catalytic efficiency of the Ni/**L10a** catalytic system, we next tested it in the nickel-catalyzed addition of several trialkylaluminum sources (AlR'_3, R' = Me or Et; and DABAL-Me_3) to other benchmark aldehydes with different steric and electronic properties. The results are summarized in Table 5.3.2.

Table 5.3.1. Selected results for the nickel-catalyzed asymmetric addition $AlMe_3$ to benzaldehyde using phosphite ligands **L9**-**L14a**,**f**-**g**[a]

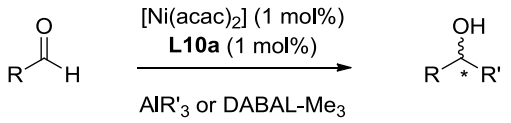
Entry	Ligand	L/Ni	% Conv[b]	% Yield[c]	% ee[d]
1	**L9a**	1	100	96	56 (*R*)
2	**L9f**	1	100	95	13 (*S*)
3	**L9g**	1	100	94	45 (*R*)
4	**L10a**	1	100	98	75 (*S*)
5	**L10f**	1	100	95	68 (*S*)
6	**L10g**	1	100	98	29 (*R*)
7	**L11f**	1	100	95	53 (*S*)
8	**L12f**	1	100	97	9 (*S*)
9	**L13f**	1	100	96	53 (*S*)
10	**L14f**	1	100	95	65 (*S*)
11	**L10a**	0.5	100	97	67 (*R*)
12	**L10a**	2	100	96	65 (*R*)

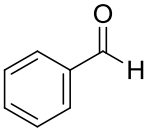
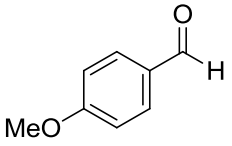
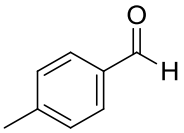
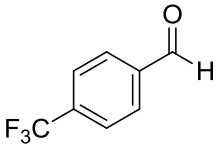
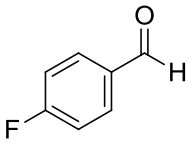
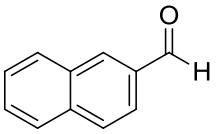
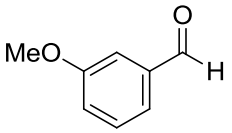
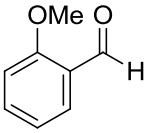
[a] Reaction conditions: T = -20 °C, $[Ni(acac)_2]$ (1 mol %), $AlMe_3$ (2 equiv), substrate (1 mmol) THF (8 mL). [b] % Conversion determined by GC after 3 h. [c] Isolated yield. [d] Enantiomeric excess measured by GC using a Cyclodex-B column.

We found that the conversion and enantioselectivity for the $AlMe_3$ addition were hardly affected by the presence of either electron-donating and electron-withdrawing groups at the *para* or *meta*-position of the phenyl group (Table 5.3.2, entries 1, 7, 10, 13 and 19). However, the presence of a methoxy group at the *para* position had a slightly negative effect on the enantioselectivity (Table 5.3.2, entry 1 vs 4). The trimethylaluminum addition to 2-naphthaldehyde provided the highest enantioselectivity (ee's up to 82%, Table 5.3.2, entry 16). Finally, the catalytic performance of the reaction was also significantly influenced by the steric factors in the substrate (Table 5.3.2, entry 22). Thus, both the conversion and enantioselectivity considerably decreased when 2-methoxybenzaldehyde was used.

The results of using triethylaluminum as an alkylating reagent indicated that the catalytic performance follows the same trend as for the trimethylaluminum addition, providing similar levels of enantioselectivity (Table 5.3.2, entries 3, 6, 9, 12, 15, 18, 21 and 24).

Table 5.3.2. Selected results for the nickel-catalyzed asymmetric addition AlR'_3 (R' = Me or Et) and DABAL-Me_3 to aldehydes using ligand **L10a**[a]



Entry	Aldehyde	Organoaluminum source	% Conv[b]	% ee[c]
1		$AlMe_3$	100 (98)	75 (*S*)
2[d]		DABAL-Me_3	98 (95)	76 (*S*)
3		$AlEt_3$	100 (99)	72 (*S*)
4		$AlMe_3$	99 (94)	66 (*S*)
5[d]		DABAL-Me_3	76 (73)	65 (*S*)
6		$AlEt_3$	92 (90)	64 (*S*)
7		$AlMe_3$	100 (97)	76 (*S*)
8[d]		DABAL-Me_3	93 (91)	77 (*S*)
9		$AlEt_3$	100 (95)	75 (*S*)
10		$AlMe_3$	100 (92)	77 (*S*)
11[d]		DABAL-Me_3	99 (93)	76 (*S*)
12		$AlEt_3$	100 (91)	77 (*S*)
13		$AlMe_3$	100 (94)	74 (*S*)
14[d]		DABAL-Me_3	97 (91)	73 (*S*)
15		$AlEt_3$	100 (94)	71 (*S*)
16		$AlMe_3$	100 (91)	82 (*S*)
17[d]		DABAL-Me_3	192 (88)	84 (*S*)
18		$AlEt_3$	100 (94)	81 (*S*)
19		$AlMe_3$	100 (93)	78 (*S*)
20[d]		DABAL-Me_3	87 (82)	76 (*S*)
21		$AlEt_3$	100 (95)	75 (*S*)
22		$AlMe_3$	35 (33)	45 (*R*)
23[d]		DABAL-Me_3	19 (11)	46 (*R*)
24		$AlEt_3$	33 (31)	45 (*R*)

[a] Reaction conditions: T = -20 ºC, $[Ni(acac)_2]$ (1 mol %), **L10a** (1 mol%), AlR'_3 (2 equiv), substrate (1 mmol), THF (8 mL). [b] % Conversion determined by GC after 3 h. Isolated yields in brackets. [c] Enantiomeric excess measured by GC using a Cyclodex-B column. [d] DABAL-Me_3 (1.3 equiv), T = 5 ºC.

Woodward et al. discovered the advantages of using DABAL-Me_3 as an air-stable methylating reagent in nickel-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 slightly lower than in the trimethylaluminum addition (Table 5.3.2, entries 2, 5, 8, 11, 14, 17, 20 and 23).

5.3.3 Conclusions

A series of sugar-based monophosphite ligands have been synthesized and applied in the Ni-catalyzed trialkylaluminum addition to several aldehydes. By carefully designing these ligands we were able to systematically investigate the effect of varying the configuration of the C-3 carbon atom of the furanoside backbone, the introduction of several alkyl and aryl groups at C-3 and the type of substituents/configurations in the biaryl phosphite moiety. By judicious choice of the ligand components we obtained good enantioselectivities (ee values up to 84%) and high activities with several aryl aldehydes, with low catalyst loadings (1 mol %) and no excess of ligand. We also demonstrated that the introduction of a methyl substituent at C-3 of the sugar backbone in allofuranoside ligands **2** is highly advantageous in terms of enantioselectivity.

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 **L9**-**L14a**,**f**-**g** has been previously described in Chapter 3. All other reagents were used as commercially available.

5.3.4.3 Typical procedure for the Ni-catalyzed enantioselective 1,2- addition of trialkylaluminum reagents to aldehydes

At first, [$Ni(acac)_2$] (2.4 mg, 9.32 μmol, 1 mol %) and ligand (9.32 μmol, 1 mol %) were stirred in dry THF (8 mL) under an argon atmosphere at -20 ^oC for 10 min. Neat aldehyde (1 mmol) was then added and trialkylaluminum (2 mmol) was added dropwise over 10 min. After the desired reaction time, the reaction was

quenched with 2 M HCl (8 mL). The mixture was extracted with Et_2O (10 mL). The organic layer was dried over $MgSO_4$ and analyzed by GC.[5a]

5.3.4.4 Typical procedure for the Ni-catalyzed enantioselective 1,2-addition of DABAL-Me_3 to aldehydes

At first, [Ni(acac)$_2$] (2.4 mg, 9.32 µmol, 1 mol %) and ligand (9.32 µmol, 1 mol %) were stirred in dry THF (8 mL) under an argon atmosphere at 5^{o}C for 10 min. Neat aldehyde (1 mmol) was then added and DABAL-Me_3 (336 mg, 1.3 mmol, 1.3 equiv) was added over 10 min. After the desired reaction time, the reaction was quenched with 2 M HCl (8 mL). The mixture was extracted with Et_2O (10 mL). The organic layer was dried over $MgSO_4$ and analyzed by GC.[5a]

5.3.5. Acknowledgements

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5.3.6 References

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Chapter 6

Conclusions

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6. Conclusions

1. Chapter 3. *Asymmetric hydrogenation reactions.* The conclusions of this chapter can be summarized as follows:

- In the Rh-catalyzed asymmetric hydrogenation of functionalized olefins (α,β-unsaturated carboxylic acid derivatives and enamides) using a modular thioether-phosphite ligand library, the results indicate that the catalytic performance is mainly affected by the substituents in both the thioether group and at the alkyl backbone chain next to the phosphite moiety, and the configuration of the biaryl phosphite moiety. By carefully selecting the ligand components, full conversions and high enantioselectivities have been achieved in the reduction of several α-dehydroamino acid esters (up to 96% ee), dimethyl itaconate (up to 75% ee), and a range of enamides (up to 85% ee).

- In the Rh-catalyzed asymmetric hydrogenation of functionalized olefins (α,β-unsaturated carboxylic acid derivatives and enamides) using a new furanoside monophosphite ligand library, we observed an effect of the configuration at C-3 of the furanoside backbone and at the binaphthyl moiety as well as the substrate. Thus, for α,β-unsaturated carboxylic acids, enantioselectivities improved when introducing a methyl substituent at C-3 in glucofuranoside ligand containing an *S*-binaphthyl group, achieving enantioselectivities >99.9% and 85% in the asymmetric reduction of dimethyl itaconate and dehydroamino acid derivatives, respectively. However, in the reduction of enamides, the introduction of substituents at C-3 of the furanoside backbone has a negative effect on enantioselectivity. Only moderate enantioselectivities could be therefore achieved for this substrate class (ee's up to 67%).

- In the Ir-catalyzed asymmetric hydrogenation of minimally functionalized alkenes using a modular thioether-phosphite ligand library, we found that catalytic performance depended strongly on the ligand parameters (the thioether substituent, the substituents/configuration in the biaryl phosphite moiety and the substituent at the alkyl chain next to the phosphite moiety) as well as the substrate. While for trisubstituted olefins only moderate enantioselectivities were achieved (ee's up to 70%), the hydrogenation of more challenging disubstituted substrate 3,3-dimethyl-2-phenyl-1-butene let to excellent enantioselectivities (ee's up to 98%). For the latter substrate, the presence of atropoisomeric chiral biaryl moieties is crucial for the high enantioselectivities achieved. Moreover, the sense of enantioselectivity is controlled by the configuration of the biaryl phosphite

group which gives access to both enantiomers of the hydrogenation product in excellent enantiocontrol.

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

- In the asymmetric Pd-catalyzed allylic substitution reactions using a modular thioether-phosphite ligand library, we observed that the introduction of a substituent at the alkyl backbone chain next to the phosphite moiety and the presence of an *R*-biaryl phosphite group have an extremely positive effect on enantioselectivity. By carefully selecting the ligand parameters, full conversions and good enantioselectivities were therefore obtained for several linear substrates (ee's up to 83 %).

- In the asymmetric Pd-catalyzed allylic substitution reactions using a furanoside monophosphite ligand library, the results indicated that the catalytic performance highly affected by the effect of varying the sugar backbone, the substituents at C-3 of the furanoside backbone, the configurations at carbon C-3 and C-4 of the ligand backbone and the type of substituents/configurations in the biaryl phosphite moiety, as well as the substrate. By carefully selecting the ligand parameters, for disubstituted substrates enantioselectivities up to 76% were achieved, while for monosubstituted substrate ee's up to 40% were obtained.

3. Chapter 5. *Asymmetric Ni-catalyzed 1,2-addition.* The conclusions of this chapter can be summarized as follows:

- In the asymmetric Ni-catalyzed trialkylaluminum addition to several aldehydes using a modular thioether-phosphite ligand library, we found important effects of varying the thioether substituent, the substituents in the alkyl backbone chain next to the phosphite moiety and the substituents/configurations in the biaryl phosphite moiety. By judicious choice of the ligand components we obtained good yields and moderate enantioselectivities (ee values up to 71%) with several aryl aldehydes, with low catalyst loadings (1 mol %) and no excess of ligand.

- In the asymmetric Ni-catalyzed trialkylaluminum addition to several aldehydes using a furanoside monophosphite ligand library, we observed important effects on the catalytic performance of varying the configuration of the C-3 carbon atom of the furanoside backbone, the introduction of several alkyl and aryl groups at C-3 and the type of substituents/configurations in the biaryl phosphite moiety. By judicious choice of the ligand components we obtained good enantioselectivities (ee values up to 84%) and high activities with several aryl

aldehydes, with low catalyst loadings (1 mol %) and no excess of ligand. We also demonstrated that the introduction of a methyl substituent at C-3 of the sugar backbone is highly advantageous in terms of enantioselectivity.

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Chapter 7

Resum

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7. Resum

Actualment la preparació de productes enantiomèricament purs esta creixent en importants àrees com fàrmacs, productes agroquímics, química fina i productes naturals. Això es perquè en moltes aplicacions només es necessari un dels enantiòmers, ja que només un és el que té les propietats desitjades mentres que l'altre es inactiu o te efectes secundaris indesitjats. Per tant el descobriment de rutes sintètiques per la preparació de compostos enantiomèricament purs es un dels reptes mes importants pels químics orgànics moderns. En aquest context, les reaccions asimètriques catalitzades per metalls de transició s'han mostrat com una de les principals eines per l'obtenció d'aquests compostos. La major part de la recerca feta es centra en el desenvolupament de nous catalitzadors organometàl·lics modificats per lligands quirals. La síntesi de nous lligands quirals és essencial per descobrir bons sistemes catalítics en catàlisi asimètrica. Els sucres són una font important de lligands per l'elevada disponibilitat i baix preu. A més, són compostos altament funcionalitzats amb centres estereogènics. Això permet la síntesi de sèries sistemàtiques de lligands amb l'objectiu d'obtenir altes activitats i selectivitats per cada reacció en particular.

Els objectius d'aquesta tesi son el desenvolupament de dues noves llibreries de lligands derivats de sucre. Concretament tioèter-fosfit i furanòsid monofosfit, per la seva aplicació en diverses reaccions asimètriques catalitzades per metall de transició, tals com la hidrogenació d'olefines funcionalitzades catalitzades per rodi, la hidrogenació d'olefines mínimament funcionalitzades catalitzada per iridi, les reacció de substitució al·lílica catalitzades per pal·ladi i les adicions 1,2 a aldehids catalitzades per níquel.

Després de la introducció **capítol 1** i els objectius **capítol 2**, al **capítol 3** es discuteix les reaccions d'hidrogenació. Aquest capítol es composa de tres parts on s'estudia la síntesi i aplicació de les dues noves llibreries de lligands. La primera part inclou el manuscrit, *Asymmetric Rh-catalyzed hydrogenation using a thioether-phosphite ligand library*, on es descriu la síntesis i l'aplicació de lligands tioèter-fosfit en la reacció d'hidrogenació asimètrica, catalitzada per rodi, de diverses olefines funcionalitzades. S'ha observat un important efecte dels substituents del grup tioèter i dels de la cadena alquílica al costat del grup fosfit i la configuració del grup biaril. S'han obtingut elevades enantioselectivitats en la reducció de α-dehidroamino àcid esters (>96% ee), dimetil itaconat (>75% ee) i enamides (>85% ee). La segona part està composada pel treball, *Asymmetric Rh-*

catalyzed hydrogenation using a furanoside monophosphite ligand library, on es descriu la síntesis i l'aplicació de lligands furanòsid monofosfit en la reacció d'hidrogenació asimètrica, catalitzada per rodi, de diverses olefines funcionalitzades. Els resultats catalítics indiquen un important efecte de la introducció de substituents al carboni-3, de la configuració del carboni-3 de l'esquelet furanòsid i del grup binaftil i del substrat. L' introducció d'un grup metil al carboni-3 de l'esquelet furanòsid i la presencia d'un grup *S*-binaftil té un efecte positiu en la reducció del dimetil itaconat i derivats dehidroamino àcids (>99% ee i >85% ee, respectivament), però negatiu en la reducció d' enamides. La tercera part està composada pel treball, *Asymmetric Ir-catalyzed hydrogenation using a thioether-phosphite ligand library*, descriu l'aplicació dels compostos tioèter-fosfit com a lligands en la hidrogenació asimètrica d'olefines no funcionalitzades catalitzada per iridi. Els resultats mostren que els millors excessos enantiomèrics (> 98% ee) s'obtenen en la hidrogenació de substrats terminals.

En el **capítol 4**, s'han aplicat les lligandteques, prèviament descrites al capítol 3, en la reacció de substitució al·lílica catalitzada per pal·ladi. Aquest capítol es divideix en dues parts. La primera part està composada pel treball, *Asymmetric Pd-catalyzed allylic substitution using a thioether-phosphite ligand library*, descriu l'ús dels lligands tioèter-fosfit prèviament descrits en la substitució al·lílica de substrats lineals catalitzada per pal·ladi. Els resultats indiquen que la introducció d'un substituent a la cadena alquílica al costat del grup fosfit i la presencia d'un grup *R*-biaril tenen un efecte extremadament positiu en l'enantioselectivitat; obtenint bones enantioselectivitats (>83% ee). La segona part esta composada pel treball, *Asymmetric Pd-catalyzed allylic substitution using a furanoside monophosphite ligand library*, descriu l'aplicació dels lligands furanòsid monofosfit prèviament descrits en la substitució al·lílica catalitzada per pal·ladi. S'ha observat un important efecte del tipus d'esquelet de sucre, els substituents del carboni-3 de l'esquelet furanòsid, la configuració del carboni-3 i del carboni-4 de l'esquelet del lligand i dels substituents/configuració del grup biaril, i del substrat. Així, per substrats disubstituïts s'aconsegueixen ee's per sobre del 76% mentres que per monosubstituïts ee's per sobre del 40%.

Per últim en el **capítol 5**, s'han aplicat les lligandteques, prèviament descrites al capítol 3, en l'adició 1,2 asimètrica catalitzada per níquel. Aquest capítol es divideix en dues parts. La primera part està composada pel treball, *Thioether-phosphite ligands applied to the asymmetric Ni-catalyzed trialkylaluminum addition to aldehydes*, descriu l'ús dels lligands tioèter-fosfit

prèviament descrits en l'adició 1,2 de trialquilalumini a aldehids catalitzada per níquel. Els resultats indiquen que l'enantioselectivitat està afectada pels substituents del grup tioèter i de la cadena alquílica al costat del grup fosfit, i dels substituents/configuració del grup biaril. S'obtenen bons rendiments i enantioselectivitats moderades (>71% ee) amb baixes carregues de catalitzador (1 mol %) i sense excés de lligand. La segona part, esta composada per el article, *Sugar-monophosphite ligands applied to the asymmetric Ni-catalyzed trialkylaluminum addition to aldehydes*, on es descriu l'aplicació dels lligands furanòsid monofosfits en l'adició 1,2 de trialquilalumini a aldehids catalitzada per níquel. S'ha observat un important efecte de la configuració del carboni-3 de l'esquelet furanòsid, la introducció de substituents alquils i arils al carboni-3 i dels substituents/configuració del grup biaril. S'obtenen bons rendiments i enantioselectivitats (>84% ee) amb baixes carregues de catalitzador (1 mol %) i sense excés de lligand. També demostrem que l' introducció d'un grup metil al carboni-3 de l'esquelet furanòsid es altament avantatjós en termes d'enantioselectivitat.

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Chapter 8

Appendix

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8. List of papers and meeting contributions

8.1. List of papers

1. Alegre, S.; Diéguez, M.; Pàmies, O. "*Sugar-monophosphite ligands applied to the asymmetric Ni-catalyzed trialkylaluminum addition to aldehydes*" *Tetrahedron: Asymmetry* **2011***, 22, 834.* (Chapter 5).

2. Alegre, S.; Alberico, E.; Diéguez, M.; Pàmies, O. "*Rh-catalyzed asymmetric hydrogenation using a furanoside monophosphite second-generation ligand library. Scope and limitations*" submitted to *Tetrahedron: Asymmetry* (Chapter 3).

3. Alegre, S.; Borràs, C.; Alberico, E.; Diéguez, M.; Pàmies, O. "*Asymmetric Rh-catalyzed hydrogenation using a thioether-phosphite ligand library*" in preparation (Chapter 3).

4. Alegre, S.; Borràs, C.; Diéguez, M.; Pàmies, O. *"Asymmetric Ir-catalyzed hydrogenation of minimally functionalized olefins using a thioether-phosphite ligand library derived from L-(+)-tartaric acid"* in preparation (Chapter 3).

5. Alegre, S.; Borràs, C.; Diéguez, M.; Pàmies, O. *"Asymmetric Pd-catalyzed allylic substitution using a thioether-phosphite ligand library"* in preparation (Chapter 4).

6. Alegre, S.; Diéguez, M.; Pàmies, O. *"Asymmetric Pd-catalyzed allylic substitution using a furanoside monophosphite ligand library. Scope and limitations"* in preparation (Chapter 4).

7. Alegre, S.; Borràs, C.; Diéguez, M.; Pàmies, O. *"Thioether-phosphite ligands derived from L-(+)-tartaric acid for the Ni-catalyzed trialkylaluminum addition to aldehydes"* in preparation (Chapter 5).

8.2. Meeting contributions

1. Pàmies, O.; Alegre, S.; Diéguez, M. "*Furanoside phosphite ligands for the asymmetric Ni-catalyzed trialkylaluminum to aldehydes*". 18th

International Symposium on Homogeneous Catalysis. Toulouse. France. July 2012. Poster communication.

2. Alegre, S.; Diéguez, M.; Pàmies, O. "*P-S ligands derived from tartaric acid for asymmetric hydrogenation*". XXXIV Reunión Bienal de la Real Sociedad Española de Química. Santander. Spain. September 2013. Poster communication.