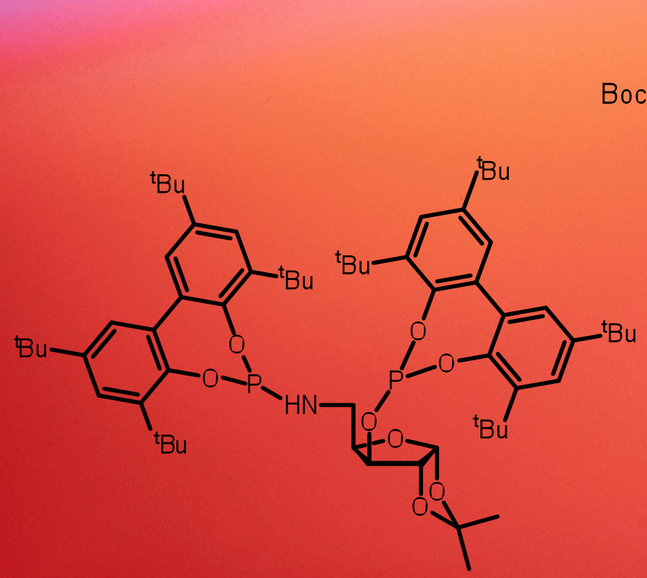
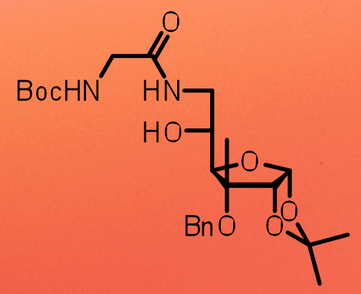
SUGAR-BASED LIGAND LIBRARIES FOR ASYMMETRIC REDUCTIONS AND C-C BOND FORMING REACTIONS

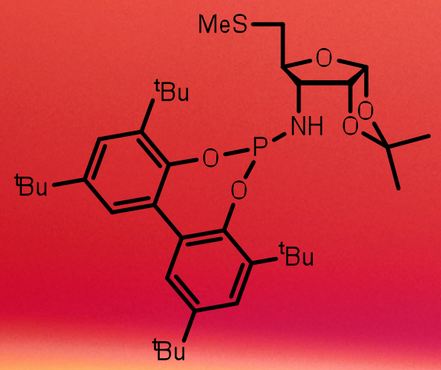
Mª Mercè Coll Serrahima

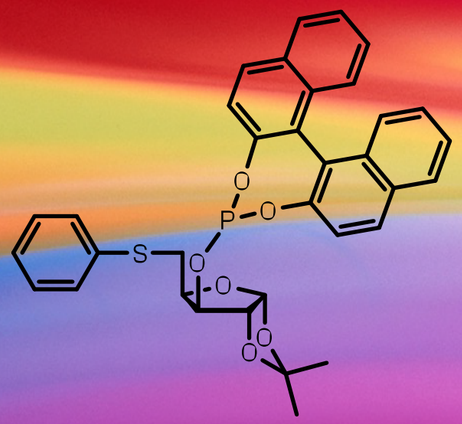
Dipòsit Legal: T. 150-2012

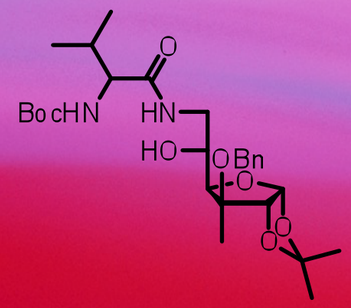
UNIVERSITAT ROVIRA I VIRGILI
SUGAR-BASED LIGAND LIBRARIES FOR ASYMMETRIC REDUCTIONS AND C-C BOND FORMING REACTIONS
M. Mercè Coll Serrahima
DL:T. 150-2012









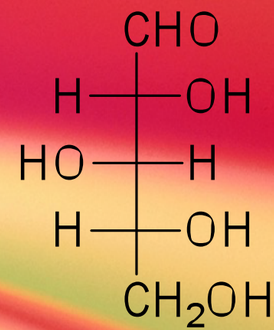


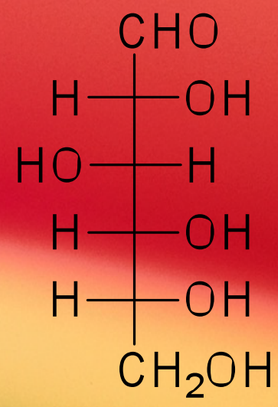
UNIVERSITAT ROVIRA I VIRGILI

Sugar-based ligand libraries for asymmetric reductions and C-C bond forming reactions

Mª Mercè Coll Serrahima 2011

Sugar-based ligand libraries for asymmetric reductions and C-C bond forming reactions





Mª Mercè Coll Serrahima

Mª Mercè Coll Serrahima

SUGAR-BASED LIGAND LIBRARIES FOR ASYMMETRIC REDUCTIONS AND C-C BOND FORMING REACTIONS.

PhD-Thesis

Supervised by Prof. Montserrat Diéguez

and Dr. Oscar Pàmies

Departament de Química Física i Inorgànica

UNIVERSITAT ROVIRA I VIRGILI

TARRAGONA

December 2011

UNIVERSITAT ROVIRA I VIRGILI
SUGAR-BASED LIGAND LIBRARIES FOR ASYMMETRIC REDUCTIONS AND C-C BOND FORMING REACTIONS
M. Mercè Coll Serrahima
DL:T. 150-2012

UNIVERSITAT ROVIRA I VIRGILI
Departament de Química Física i Inorgànica

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 "**SUGAR-BASED LIGAND LIBRARIES FOR ASYMMETRIC REDUCTIONS AND C-C BOND FORMING REACTIONS**", que presenta Mª MERCÈ COLL SERRAHIMA 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 2011

Prof. Montserrat Diéguez Fernández Dr. Oscar Pàmies Ollé

UNIVERSITAT ROVIRA I VIRGILI
SUGAR-BASED LIGAND LIBRARIES FOR ASYMMETRIC REDUCTIONS AND C-C BOND FORMING REACTIONS
M. Mercè Coll Serrahima
DL:T. 150-2012

Agraïments / Acknowledgements

Tot i haver acabat de redactar la tesi encara em queda un últim repte, el d'agrair a tothom que m'he trobat durant aquest camí l'ajut rebut, la paciència, la comprensió, els bons moments, els no tant bons,....

Per començar aquesta difícil tasca he escollit a les persones sense les quals aquesta tesi no hagués estat possible, els meus directors de tesi, la Prof. Montserrat Diéguez i el Dr. Òscar Pàmies. Gràcies als dos per confiar en mi, introduir-me en el món de la recerca donant-me l'oportunitat de treballar en el vostre grup i ajudar-me a créixer com a científica (he après molta química amb vosaltres) i com a persona (les dificultats sempre es poden superar).

Continuaré agraint a la resta de professores del departament: a Carmen por sus siempre esperadas cenas y su disposición a ayudar en todo lo posible; a l'Anna i la Mar per les neteges de nevera i reunions diverses; a l'Elena, l'Aurora, la Núria, la Yolanda i la Pilar. Ha estat un plaer compartit aquests anys amb vosaltres.

No puc deixar de donar les gràcies a aquells que no es fan notar gaire però que sense ells el dia a dia seria molt més complicat: a l'Arantxa que sempre estarà present entre nosaltres, a la Mª José por pedir y pedir disolventes y otras cosas necesarias; al Jordi per les llaminadures, les xerrades, la seva disposició a ajudar-nos,...; a les secretaries del departament per l'ajut amb els papers; a la gent de recursos científics: al Miguel per la seva ajuda en algun moment de desesperació amb els aparells de RMN i, en especial, al Ramón per la seva paciència amb mi, per ajudar-me sempre amb els experiments de baixa temperatura, overnight,..., per escoltar les meves queixes i tranquil·litzar-me sempre, sense tu, part d'aquesta tesi no hagués estat possible.

En els inicis de la tesis, en concret en l'any de màster, vaig tenir la sort de tenir com a companys a persones molt agradables i amb les que he passat bons moments, a ells també vull agrair la seva petita aportació. Núria, Carlo, Moira, Isidoro i Miriam, muchas gracias por las clases compartidas i las inolvidables cenas de Navidad con amigos invisibles incluidos.

Ara és el torn d'agrair als experimentats doctors, passats i presents, el seu ajut i indicacions per seguir el camí més adequat: a Ali por darme buenos consejos y ser como un compañero mas; a l'Aitor per compartir els seus coneixements químics sense cap mena d'objecció; a la Marta, que tot i estar poc temps amb nosaltres, has deixat la

teva petjada; a l'Isa per les converses al seminari; a Carolina por compartir conmigo los madrugones y esos ratos de la mañana en que solo nosotras estábamos trabajando; a la Verònica, la "filla" que sempre m'ha portat més feina, per tots els moments que hem viscut juntes dins i fora de la universitat i pels teus consells, sobretots els relatius als tiols; al Cyril, a l'Henrik, al Bernabé i al Jamin per estar sempre disposats ha donar un cop de mà.

Al llarg d'aquest temps ha passat molta gent pels diferents laboratoris realitzant estades, màsters, post-doctorats,...: Gawaine, Kara, Vanessa, Lina, Franchesca, Benjamin, Norbert, Audre, Bill, Mike, Amo, Sheila, Sarah, Takahiro, Dagoberto, Nasjla... gràcies a tots. Vull agrair de manera especial a l'Olivier (cacaolat man) pels bons moments viscuts; al Nicolas , entre altres coses, per les creps tan bones que de tant en tant ens feia per esmorçar; a Lourdes porque además de ser compañera de máster hemos compartido muchas otras cosas; a Tatiana por todas las comida, cenas,... que hemos disfrutado juntas; y a Doris, que es una persona muy especial, por haberme transmitido tranquilidad, alegría y otra manera de ver las cosas.

Un cop recordats tots els que han estat de passada toca dirigir-me als amics i companys de laboratori, part molt important de la tesi ja que han compartit amb mi totes o algunes de les etapes del doctorat. En primer lloc estan els meus petitons, els que fa poc que estan per aquí però que ja formen part de la meva segona família: Laia, Gerard, Xavi, Marc i Jèssica M., gràcies per compartir aquest breu temps amb mi, espero que la cosa no quedi aquí ja que us vull veure créixer. Ah!!! per cert, molta sort en aquesta aventura que inicieu. Als que han arribat fa poc i marxaran aviat; Matteo, suerte con tu trabajo y gracias por quedarte hasta mi tesis (bueno, hasta la celebración de las tesis). Als que ja porten més temps; Sabina, Jèssica C., Helena, Siham i Jorge; molta sort i ànims, quan se n'adoneu ja estareu redactant la tesi. Aix!!!!! hem sembla que m'he deixat a dues personetes, les meves petites Eli i Jèssica; Eli, que puc dir-te, moltes gràcies per les xerrades al labo, pels ànims que sempre m'has donat i per ser com ets, un solet; i Jèssica, la que sempre esta al corrent de totes les noticies importants, moltes gràcies pels dinars, les excursions, les interessants converses sobre mil temes diferents, les rialles,..., ets una noia única (en el bon sentit) i per molt que et diguin no canviïs. Sort a les dues amb els vostres treballs, segur que traureu unes tesis magnífiques.

Ara és el moment dels quasi pretesics Javi, Oriol i Amadeu (ja pretesic total), que dir-vos nois, a part de que teniu més perill que una caixa de bombes, gràcies per tots els bons moments compartits en congressos, dinars, sopars, calçotades,..., per ajudar-me

a resoldre els meus dubtes químics i no químics, per tenir paciència amb mi, i per ser més que uns companys de laboratori, uns bons companys (jajajajaja). Molta sort als tres en l'etapa final, espero poder estar en el moment que feu el pas de doctorands a doctors.

Tatiana, Manuel y Angélica, suerte en vuestras defensas, seguro que pronto seremos nosotros los que diremos a los que vienen detrás que esto solo es un trámite. Tati, gracias por ser siempre tan alegre y por tener siempre una buena palabra que decir; Manuel, empezamos juntos en el máster y leeremos casi al mismo tiempo, ha sido un placer compartir esta experiencia contigo; Angélica, mi compañera de laboratorio durante todo este tiempo con la que he compartido, sobretodo, muchas risas, gracias por estar siempre ahí y acordarte de mí para desayunos y comidas, por ayudarme con mis problemillas químicos y por caminar conmigo en este último tramo del camino, me ha dado la sensación que hacerlo juntas lo ha hecho menos cuesta arriba.

I que puc dir a les meves nenes, les persones amb les que he compartit més moments en aquest temps, les que espero i desitjo que sempre estiguin presents en la meva vida. Eva, gràcies per tot, m'has ajudat més del que et penses no tan sols en la química sinó també en lo personal, ets una gran persona que espero sempre tenir com a amiga ;). Ariadna, l'amiga que m'ha fet molts cops de confident i que ha sigut de gran ajuda en moments difícils, gràcies per estar sempre en el lloc adequat en el moment adequat, per ajudar incondicionalment i per aguantar els meus rotllos (quina paciència que has hagut de tenir). Dolores, gràcies per ser tan bona companya de taula i per compartir tants moments juntes fora i dins de la universitat (a veure si de tant en tant ho repetim eh!!!). Raquel, que et pensaves que m'havia oblidat de tu ???? doncs no, gràcies per ser tan pacient, per saber escoltar i per sempre intentar buscar una solució als problemes, ets una gran persona i et mereixes lo millor. Cris Solé, la meva nena més boja, la que sempre intenta treure't un somriure, gràcies per ser com ets, per dir els bons dies amb tanta energia i ser tant activa. Cris Pubill, per mi la més especial, la meva nena preferida (no us poseu geloses la resta eh!!!), gràcies per compartir tantíssimes coses amb mi, per ser amiga a més de companya, per escoltar-me en tot moment i ser tal com ets, no canviïs mai i sempre fes de les teves brometes, a vegades resulten divertides ;). Merci a totes per tot, que sapigueu que heu deixat la vostra petjada en mi.

Eiiiii organics!!!!!!!! Moltes gràcies a tots per tot, sempre m'heu tractat molt bé quan he pujat a visitar-vos. Irene, sort amb la tesi, ja et queda poc.

I would like to thank Prof. Dr. Hans Adolfsson to accept me in his group. I'm so sorry to not have you in the defence board, it would have been a pleasure. I also want to

thank Dr. Katrin Ahlford for introducing me in the asymmetric transfer hydrogenation. I would like to thank as well to all the other people of the Hans's group for their help; Helena Lundberg, Elina Buitrago, Fredrik Tinnis and Hans Andersson. I also want to thank to Dr. Belen Martin-Matute. Belen, gracias por ayudarme con el inglés y por darme a conocer un poco mejor Estocolmo, me alegro mucho de haberte conocido y espero sigamos en contacto.

Als meus amics Laura, Antonio, Nuria, Rafa, Jose David, Edu, Jose, Gabriel i Luis, a tots vosaltres moltes gràcies per donar-me el vostre suport en tot moment, per mi es molt important saber que esteu al meu costat. Montse, que ja se que faltes tu!!!, gràcies per estar al meu costat en tot moment, per ajudar-me en tot el que has pogut i per compartir amb mi mil coses i mil moments, et considero la meva millor amiga i espero que sigui així per molt de temps.

I per últim la família. Rosalia, Baldomero, Montse, Carles, Marina i Berta, moltes gràcies a tots per tractar-me com una més de la vostra família, per compartir amb mi aquests moment igual que n'heu compartit d'altres, i per alegrar-vos tant per mi.

Als meus germans, Feliu, Esther, Juan Pera i Núria, gràcies per estar sempre al meu costat, per ensenyar-me tantes coses i obrir-me tantes portes (lo de ser la petita te les seves avantatges). Esther, gràcies també per fer-me sempre de segona mama. A tots el meus nebots, petit inclosos. Especialment a la Mireia i el Genis gràcies per haver passat amb mi els primers anys de doctorat mentre els donava repàs; i a l'Esther, gràcies per ajudar-me sempre en allò que et demano, ets la millor. I com no, als meus pares, Mª Dolors i Pau, que gràcies a ells estic on estic i sóc el que sóc. Moltes gràcies per estar sempre al meu costat i ajudar-me en tot el que heu pogut sense esperar res a canvi, se que per més que faci mai us ho podré compensar.

Tan sols hem queda una persona, la que comparteix amb mi la seva vida. Gerard, que et puc dir que tu no sàpigues llegir als meus ulls?? Moltíssimes gràcies per tot, per la teva paciència, per la teva comprensió, pels teus ànims i suport incondicional, per confiar en mi des del primer moment i per fer les coses més fàcils. Amb tot aquest temps, i sobretot en els últims mesos, m'he adonat que ets la millor persona que he pogut triar per tenir al meu costat.

Moltes gràcies a tots. Muchas gracias a todos. Thank you very much everybody. Tack så mycket för allt.

UNIVERSITAT ROVIRA I VIRGILI
SUGAR-BASED LIGAND LIBRARIES FOR ASYMMETRIC REDUCTIONS AND C-C BOND FORMING REACTIONS
M. Mercè Coll Serrahima
DL:T. 150-2012

"Todos somos muy ignorantes. Lo que ocurre es que no todos ignoramos las mismas cosas"

Albert Einstein

UNIVERSITAT ROVIRA I VIRGILI
SUGAR-BASED LIGAND LIBRARIES FOR ASYMMETRIC REDUCTIONS AND C-C BOND FORMING REACTIONS
M. Mercè Coll Serrahima
DL:T. 150-2012

Table of contents

Structure of the thesis

The thesis is divided into eight chapters.

- Chapter 1. *Introduction*. This chapter first presents the importance of metal asymmetric catalysis in the synthesis of enantiomerically pure compounds. An important step in this synthesis is the design and preparation of chiral ligands. Among them, new chiral ligands derived from carbohydrate are presented. These ligands are applied to 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 carbohydrate ligands. The state-of-the-art and current needs in this field justify the objectives of the thesis.

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

- Chapter 3. *Asymmetric hydrogenation reactions*. This chapter contains three sections on the development and application of several carbohydrate ligand libraries in the asymmetric hydrogenation reactions. The first section, *Asymmetric Rh-catalyzed hydrogenation using a furanoside phosphite-phosphoroamidite and diphosphoroamidite ligand library*, describes the application of a furanoside phosphite-phosphoroamidite and diphosphoroamidite ligand library in the asymmetric Rh-catalyzed hydrogenation of several α,β-unsaturated esters and enamides. This section also includes kinetic and NMR studies to provide greater insight into the origin of the enantioselectivity. The second section, *A modular furanoside thioether-phosphite/phosphinite ligand library for asymmetric Ir-catalyzed hydrogenation of minimally functionalized olefins*, includes the design and application of a new thioether-phosphite/phosphinite ligand library in the asymmetric Ir-catalyzed hydrogenation of a broad range of minimally functionalized olefins. This chapter also discusses the characterization of the dihydridoiridium (III) complexes. The third section, *Asymmetric hydrogenation of alkenes lacking coordinating groups with a furanoside thioether-phosphoroamidite ligand library*, describes the synthesis and application of a furanoside thioether-phosphoroamidite ligand library in the asymmetric Ir-catalyzed hydrogenation of several minimally functionalized olefins. These thioether-phosphoroamidite ligands are based on previous

furanoside thioether-phosphite/phosphinite ligands, in which a biaryl phosphoroamidite moiety was used instead of a phosphite/phosphinite motif.

- Chapter 4. *Asymmetric transfer hydrogenation of ketones.* This chapter contains two sections, on the development and application of three carbohydrate ligand libraries in the asymmetric transfer hydrogenation of several ketones. The first section, *Carbohydrate-based pseudo-dipeptides: New ligands for the highly enantioselective Ru-catalyzed transfer hydrogenation reaction*, describes the successful evaluation of a new pseudo-dipeptide ligand library in the Ru-catalyzed asymmetric transfer hydrogenation of a broad range of ketones. The ligand library is based on the combination of various *N*-Boc-protected α-amino acids and a sugar amino alcohol unit. The second section, *Modular furanoside pseudo-dipeptides and thioamides, readily available ligand libraries for metal-catalyzed transfer hydrogenation reactions. Scope and limitations*, includes the design of two new carbohydrate-based libraries of 36 potential pseudo-dipeptides and 36 potential thioamide ligands. The first set is based on the previous sugar-based pseudo-dipeptide ligands, in which a 1,3-amino alcohol sugar core was used instead of a classical 1,2-amino alcohol motif. In the second set (carbohydrate-thioamide ligands), the peptide bond in the previous ligands was converted to a thioamide group. We also report their use in the asymmetric Rh- and Ru-catalyzed transfer hydrogenation of a broad range of ketones.

- Chapter 5. *Asymmetric Pd-catalyzed allylic substitution.* This chapter contains one section, *Novel P,S ligands for Pd-catalyzed asymmetric allylic substitution reactions*, which discusses the application of previously developed thioether-phosphite, thioether-phosphinite and thioether-phosphoroamidite ligand libraries (see Chapter 3) in the Pd-catalyzed allylic substitution reactions of acyclic and cyclic allylic substrates.

- 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. This chapter also includes the reprints of two papers not discussed in this thesis, in which I have participated during the first year of my PhD. In the first paper, "*Rh-catalyzed asymmetric hydroformylation of heterocyclic olefins using chiral diphosphite ligands. Scope and limitations*", I have been involved in the synthesis and evaluation of

substrate: *N*-acetyl-3-pyrroline. In the second paper, "*Iridium phosphite-oxazoline catalysts for the highly enantioselective hydrogenation of terminal alkenes*", I have been involved in the synthesis and evaluation of some terminal substrates.

UNIVERSITAT ROVIRA I VIRGILI
SUGAR-BASED LIGAND LIBRARIES FOR ASYMMETRIC REDUCTIONS AND C-C BOND FORMING REACTIONS
M. Mercè Coll Serrahima
DL:T. 150-2012

UNIVERSITAT ROVIRA I VIRGILI
SUGAR-BASED LIGAND LIBRARIES FOR ASYMMETRIC REDUCTIONS AND C-C BOND FORMING REACTIONS
M. Mercè Coll Serrahima
DL:T. 150-2012

CHAPTER 1

Introduction

UNIVERSITAT ROVIRA I VIRGILI
SUGAR-BASED LIGAND LIBRARIES FOR ASYMMETRIC REDUCTIONS AND C-C BOND FORMING REACTIONS
M. Mercè Coll Serrahima
DL:T. 150-2012

1. Introduction

Nowadays the preparation of enantiomerically pure compounds plays a vital role in such important areas as pharmaceuticals, agrochemicals, fine chemicals and natural product chemistry.[1] Enantioselective homogeneous metal catalysis is an attractive method for producing enantiopure compounds.[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 attain the highest levels of reactivity and selectivity in catalytic enantioselective reactions, several parameters must be optimized. Of these, the selection and design of the chiral ligand is perhaps the most crucial step. One of the simplest ways of obtaining chiral ligands is to transform or derivatize natural chiral compounds. Carbohydrates are highly functionalized compounds with several stereogenic centers. Their modular nature offers a wide variety of opportunities for the derivatization and tailoring of synthetic tools in the search for the best ligand for each particular reaction.[2] One limitation of using natural compounds as precursors for ligands is that generally only one enantiomer is easily accessible and, indeed, the L-enantiomer of most naturally occurring D-carbohydrates are either expensive or unavailable. However, this problem can be solved by the use of pseudo-enantiomers that can be prepared from the D-series.[2]

The most widely used chiral ligands in asymmetric catalysis are phosphorus donors.[3] In general, transition-metal complexes with chiral sulfur ligands have been less investigated than complexes with other donor atoms,[4] although in recent decades the number of studies on sulphur-containing catalytic systems has increased notably.[4] Compared to phosphorus, sulfur has a less donor and acceptor character. In addition to these electronic considerations, the sulfur atom in thioether ligands has only two substituents, which can create a less hindered environment than trivalent phosphorus. The formation of mixtures of diastereomeric thioether complexes (because the S atom becomes a stereogenic center when coordinated to the metal) and the difficulty to control their interconversion in solution have also been regarded as a problem for asymmetric induction in catalytic reactions. Nevertheless, in recent years, S-containing

ligands have proven to be as useful as other classical asymmetric ligands, specially when combined with other donor atoms.[4] Thioethers have been combined with several donor atoms in heterodonor ligands. S,X-Donor ligands have several advantages over homodonors. They can provide different electronic environments because of the different *trans* influence of the sulfur and X atom.

This thesis focused on the development of new ligand libraries derived from carbohydrates and their application in several asymmetric catalytic transformations. In this respect, we have designed new carbohydrate-based phosphorus-thioether ligand libraries and evaluated them in the Ir-catalyzed asymmetric hydrogenation of minimally funcionalized olefins and Pd-catalyzed asymmetric allylic substitution reactions. We have also evaluated a furanoside phosphite-phosphoramidite and diphosphoroamidite ligand library in the enantioselective Ir-catalyzed hydrogenation of funcionalized olefins. Finally, we have also successfully developed and evaluated new carbohydrate-based pseudo-dipeptide and thioamide ligand libraries in the Ru- and Rh-catalyzed asymmetric transfer hydrogenation of several ketones. In next section, we collect the most important phosphorus-thioether ligand families developed for asymmetric metal-catalyzed reactions. In the following sections we describe the background of each asymmetric catalytic reaction studied in this thesis.

1.1. Phosphorus-thioether ligands

Several combinations of phosphorus-thioether ligands (e.g. phosphine-thioether, phosphinite-thioether and, to a lesser extent phosphite-thioether) have been developed and applied in asymmetric catalytic reactions.[4] In this section, we collect the most relevant phosphorus-thioether ligand families.

1.1.1. Phosphine-thioether ligands

A review of the research into phosphine-thioether ligands highlighted eight ligand families that differ in the backbone linker between the phosphine and the thioether groups.

- The family of ferrocenyl-based ligands **1**-**4** (Figure 1.1.1). Several research groups have developed this type of ligand mainly for the asymmetric Pd-catalyzed allylic substitution reaction.[5] In 1996, Pregosin and coworkers developed ligand **1**, with

multiple stereogenic units, which afforded an ee of 88% in the palladium allylic alkylation of 1,3-diphenylprop-2-enyl acetate.[5a] Subsequently, other groups developed new modifications by synthesizing ligands **2**-**4**, which improved enantioselectivities (ee's up to 97%).[5b-g,i-k] Ligands **2** have also been succesfully applied in the asymmetric hydrogenation of aryl-alkyl ketones (ee's up to 99%).[5h]

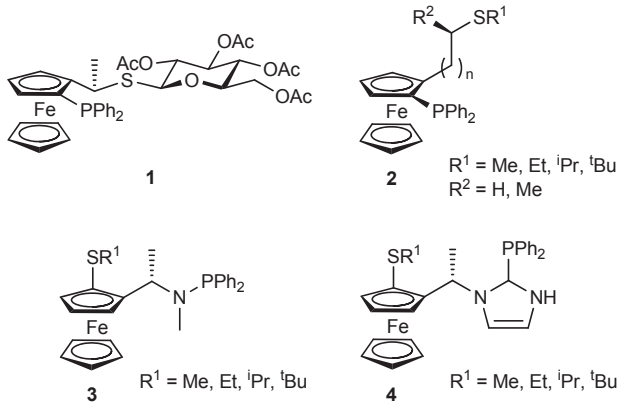


Figure 1.1.1. Ferrocenyl-based phosphine-thioether ligands **1**-**4**.

- The family of phosphine-thioether ligands derived from (*S*)-proline developed by Hiroi and coworkers (Figure 1.1.2).[6] These ligands have been applied in the Pd-allylic alkylation of 1,3-diphenylprop-2-enyl acetate with enantioselectivities up to 88% (*S*) for ligand **5g** and up to 87% (*R*) for ligand **6b**.

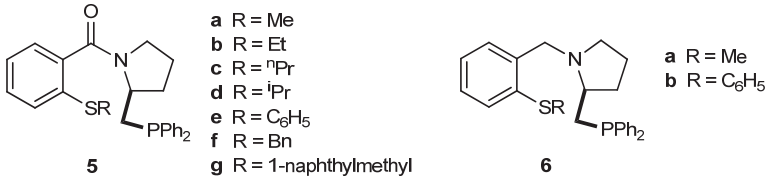


Figure 1.1.2. Phosphine-thioether ligands derived from (*S*)-proline.

- The family of carbohydrate-derivate phospholane-thioether ligands **7-9** (Figure 1.1.3) developed by RajanBabu and coworkers. These ligands were successfully applied in palladium-catalyzed allylic alkylation (ee's up to 99%).[7]

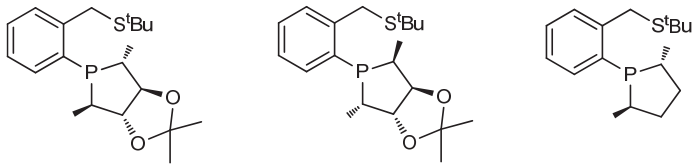


Figure 1.1.3. Phospholane-thioether ligands **7-9**.

- The family of phosphine-oxathiane ligands **10-12** (Figure 1.1.4). Initially ligands **10** and **11** were developed and applied in palladium-catalyzed allylic alkylation and amination reactions.[8] The best enantioselectivities were obtained with ligand **10** (ee's up to 94% in the alkylation and up to 86% in the amination reaction).[8a] Subsequently, in 2003, Nakano and coworkers developed xylofuranose phosphine-oxathiane ligand **12**. This ligand was successfully applied in the enantioselective palladium-catalyzed asymmetric allylic substitution reactions (ee's up to 91% in alkylation and 94% in amination).[8b-c] Interestingly, ee's increased to 99% by using a polymer-supported version of this latter ligand.[8d]

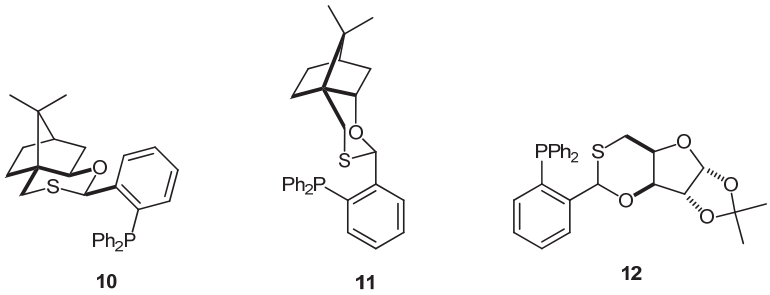


Figure 1.1.4. Phosphine-oxathiane ligands **10-12**.

- The family of binaphtyl-based ligands **13** (Figure 1.1.5). Ligand **13a** has been succesfully applied in the Pd-allylic alkylation of 1,3-diphenylprop-2-enyl acetate (ee's up to 96%).[9]

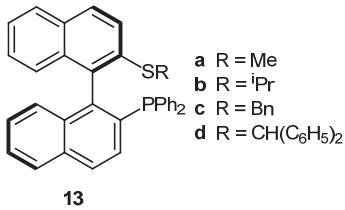
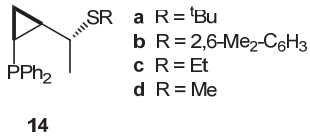


Figure 1.1.5. Binapthyl-based phosphine-thioether ligands **13**.

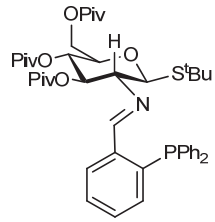
- The family of phosphine-thioeter ligands with a cyclopropane backbone developed by Molander and coworkers (Figure 1.1.6). The best enantioselectivity (ee's up to 93%) was obtained with ligand **14d** in the Pd-allylic alkylation of 1,3-diphenylprop-2-enyl acetate.[10]



14

Figure 1.1.6. Cyclopropane-based phosphine-thioether ligands **14**.

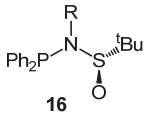
- The carbohydrate-derived phosphine-thioglycoside ligand **15** (Figure 1.1.7). This ligand was applied in the Pd-allylic alkylation of 1,3-diphenylprop-2-enyl acetate using dimethyl malonate with enantioselectivity up to 90%.[11]



15

Figure 1.1.7. Phosphine imine thioglycoside ligand **15**.

- The last phosphine-thioether ligands successfully applied in asymmetric catalysis are the *N*-phosphino *tert*-butylsulfinamides **16** (Figure 1.1.8). The best enantioselectivity (ee's up to 99%) was obtained with ligand **16b** in the Co-catalyzed asymmetric intermolecular Pausond-Khand reaction with norbornadiene.[12]



16

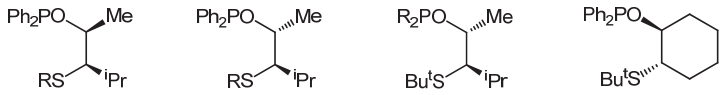
a R = Bn
b R = 4-OMe-$C_6H_4CH_2$
c R = 4-F-$C_6H_4CH_2$

Figure 1.1.8. *N*-phosphino *tert*-butylsulfinamides **16**.

1.1.2. Phosphinite-thioether ligands

A review of the research into phosphinite-thioether ligands highlighted four ligand families that differ in the backbone linker between the phosphinite and the thioether groups.

- The first successful family of phosphinite-thioether ligands was developed by Evans and coworkers (Figure 1.1.9). This large ligand family was succesfully applied in the Pd-catalyzed allylic substitution of several substrates.[13] The best results (ee's up to 98%) in the allylic alkylation reation were obtained with ligand **17a** and **20**. On the other hand, in the allylic amination reactions, enantioselectivities were best with ligand **18a** and **20** (ee's up to 99%). These ligands have also been succesfully applied in the Rh-catalyzed asymmetric hydrogenation of dehydroamino acid derivatives (ee's up to 97%) and in the Rh-catalyzed hydrosilylation of ketones (ee's up to 99%).[14]



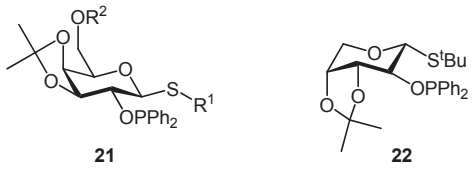
a R = ^{t}Bu
b R = 4-^{t}Bu-C_6H_4
c R = 3,5-Me_2-C_6H_3
d R = 1-naphthyl
e R = 2-naphthyl
f R = Bn
g R = Cy

a R = ^{t}Bu
b R = C_6H_5
c R = 4-^{t}Bu-C_6H_4
d R = 3,5-Me_2-C_6H_3
e R = 1-naphthyl
f R = 2-naphthyl
g R = Bn
h R = Cy

a R = 1-naphthyl
b R = 4-(MeO)-C_6H_4
c R = 2-(MeO)-C_6H_4
d R = 4-F-C_6H_4
e R = 3,5-$(CF_3)_2$-C_6H_3
f R = 3,5-Me_2-C_6H_3
g R = Cy

Figure 1.1.9. Phosphinite-thioether ligands **17**-**20** developed by Evans and coworkers.

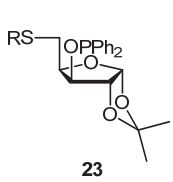
- The family of pyranoside phosphinite-thioglycosides **21**-**22** developed by Khiar and coworkers (Figure 1.1.10).[15] These ligands were applied in the palladium-catalyzed allylic substitution (ee's up to 96%) and in the rhodium hydrogenation of functionalized olefins (ee's up to 97%). Bulkier alkyl thioglycosides improve the enantioselectivities in both processes.



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 1.1.10. Phosphinite-thioglycoside ligands **21** and **22**.

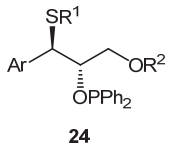
- The family of furanoside phosphinite-thioether ligands **23** derived from D-(+)-xylose (Figure 1.1.11). These ligands were applied in allylic alkylation (ee's up to 95%),[16] in the hydrogenation of prochiral olefins (ee's up to 96%)[17] and in the 1,4-addition of organometallic compounds to cyclohexenone (ee's up to 72%).[18]



a R = C_6H_5
b R = Me
c R = ^{i}Pr
d R = ^{t}Bu
e R = 4-Me-C_6H_4
f R = 4-CF_3-C_6H_4
g R = 2,6-Me_2-C_6H_4

Figure 1.1.11. Furanoside phosphinite-thioether ligands **23**.

- The family of phosphinite-thioether ligands **24** derived from (*S*)-glycidol (Figure 1.1.12).[19] These ligands were applied in the Pd-catalyzed allylic substitution of 1,3-diphenylprop-2-enyl acetate using dimethyl malonate (ee's up to 99%), benzylamine (ee's up to 95%) and benzyl alcohol (ee's up to 94%). Enantioselectivities were best with ligand **24g** containing bulky substituents at the sulfur, at the skeletal aryl group and at the protecting group of the glycidol.



a Ar = C_6H_5; R^1 = C_6H_5; R^2 = Me
b Ar = C_6H_5; R^1 = C_6H_5; R^2 = Bn
c Ar = C_6H_5; R^1 = C_6H_5; R^2 = CPh_3
d Ar = C_6H_5; R^1 = Cy; R^2 = CPh_3
e Ar = C_6H_5; R^1 = ^{t}Bu; R^2 = CPh_3
f Ar = C_6H_5; R^1 = Ad; R^2 = CPh_3
g Ar = Mesityl; R^1 = Ad; R^2 = CPh_3

Figure 1.1.12. Selected modifications of phosphinite-thioether ligands **24** developed by Pericàs and coworkers.

1.1.3. Phosphite-thioether ligands

Despite the advantages of phosphite ligands in asymmetric catalysis, only two families of phosphite-thioether ligands have been applied.

The first family is the furanoside phosphite-thioether ligands **25** derived from D-(+)-xylose (Figure 1.1.13). These ligands were applied with little success in the palladium-catalyzed allylic substitution (ee's up to 67%),[20a] iridium-catalyzed hydrogenation of functionalized olefins (ee's up to 51%)[20b] and copper-catalyzed 1,4-addition (ee's up to 41%)[20c].

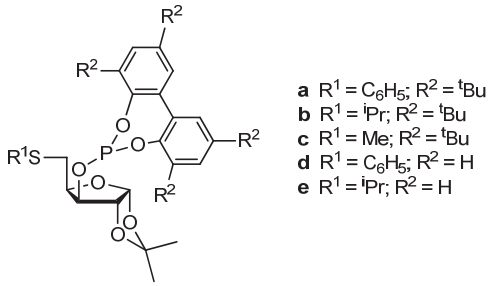


Figure 1.1.13. Furanoside phosphite-thioether ligands **25**.

In 2003, Takemoto and coworkers reported the successful aplication of a binol-based phosphite-thioether ligand **26** (Figure 1.1.14). This ligand provided high regio (up to 89%) and enantioselectivities (up to 97%) in the Ir-catalyzed allylic substitution of cinnamyl-phosphonate type substrates with diphenyliminoglycinate.[21]

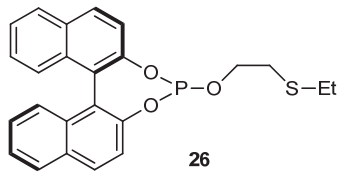
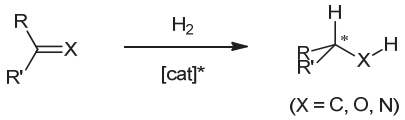


Figure 1.1.14. Phosphite-thioether ligand **26** developed by Takemoto and coworkers.

1.2. Hydrogenation reactions

Because of its high efficiency, atom economy and operational simplicity, the metal-catalyzed asymmetric hydrogenation using molecular hydrogen to reduce

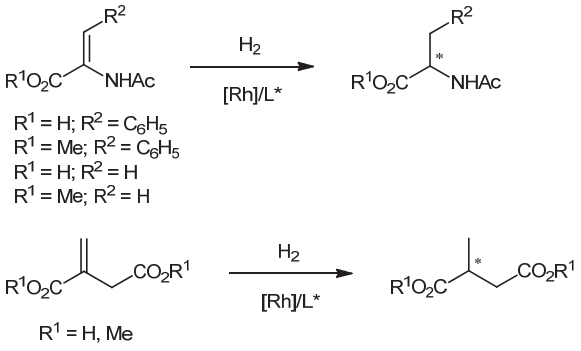
prochiral olefins, ketones and imines is one of the most suitable and direct synthetic tools for preparing chiral compounds (Scheme 1.2.1).[1,22] Both academic and industrial research groups have studied and developed this reaction for decades. Many intermediates and building blocks which are key to organic synthesis are obtained through this reaction.[1,22]



Scheme 1.2.1. Asymmetric hydrogenation of prochiral substances.

1.2.1. Asymmetric 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 1.2.2). The hydrogenation of dehydroamino acid derivatives and esters provides access to unnatural amino acids and amines that are useful intermediates for the pharmaceutical and agrochemical industries.[1,22] 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 centres have proven to be the best catalyst for the asymmetric hydrogenation of this type of substrate. Excellent activities and enantioselectivities have been achieved lasting recent decades for the asymmetric hydrogenation of dehydroamino acids and other functionalized substrates.[1,22]



Scheme 1.2.2. Hydrogenation of dehydroamino acids and itaconates.

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

The enantioselective hydrogenation of carbon-nitrogen double bonds is a simple and convenient way to synthesize chiral amines. However, their hydrogenation has some serious drawbacks: coordination can take place through the nitrogen atom and the double bond, and both the substrate and catalyst intermediates are unstable under catalytic conditions. Homogeneous catalysts can complex both the imine substrate and the amine product. In consequence, catalytic activity is often low. Unlike the asymmetric hydrogenation of functionalized substrates, iridium complexes are the best catalysts for imines.[1]

1.2.1.1. Mechanism

Figure 1.2.1 shows the mechanism for the asymmetric hydrogenation of dehydroamino acids and their esters with cationic precursors with diphosphines.[23] In the last decade, this mechanism has proved to be valid for other phosphorus-based ligands (i.e. diphosphinites, diphosphites, etc.).[24] 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 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.

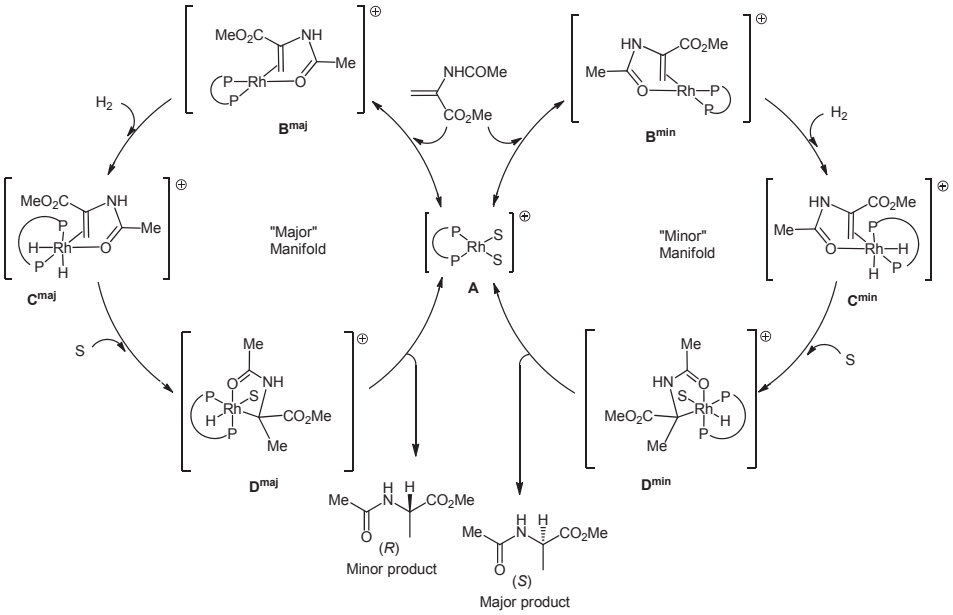


Figure 1.2.1. Mechanistic scheme for the Rh-catalyzed asymmetric hydrogenation of methyl (*Z*)-α-acetamidoacrylate.

1.2.1.2. Ligands

The development of homogeneous asymmetric hydrogenation was initiated by Knowles[25] and Horner[26] in the late 1960s after the discovery of Wilkinson's hydrogenation catalyst $[RhCl(PPh_3)_3]$.[27] 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 1.2.2).[28] Knowles made his significant discovery of the C_2-symmetric chelating diphosphine ligand, **DIPAMP** (Figure 1.2.2).[29] Because of its high catalytic efficiency, **DIPAMP** was used in the industrial production

of L-Dopa, a drug used to treat Parkinson's disease.[30] For this work Knowles was awarded the Nobel Prize in 2001.[31]

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**, Achiwas's **BPPM**, Rhode Poulenc's **CBD** and Giongo's bis(aminophosphine) ligand **PNNP** (Figure 1.2.2).[32] However, development in the early 1980s focused mainly on the chiral Rh-catalyst, and the substrate scope was limited to α-dehydroamino acids. Noyori's research on the **BINAP**-Ru catalyst opened up opportunities for the efficient hydrogenation of various substrates (Figure 1.2.2). Several prochiral olefins and ketones were hydrogenated with excellent enantioselectivity.[33] For this work Noyori was awarded the Nobel Prize in 2001. In the 1990s, the introduction of some efficient chiral diphosphorus ligands, such as **DUPHOS** and **BPE** developed by Burk and coworkers (Figure 1.2.2) for the hydrogenation of various functionalized olefins, significantly expanded the scope of asymmetric hydrogenation.[34]

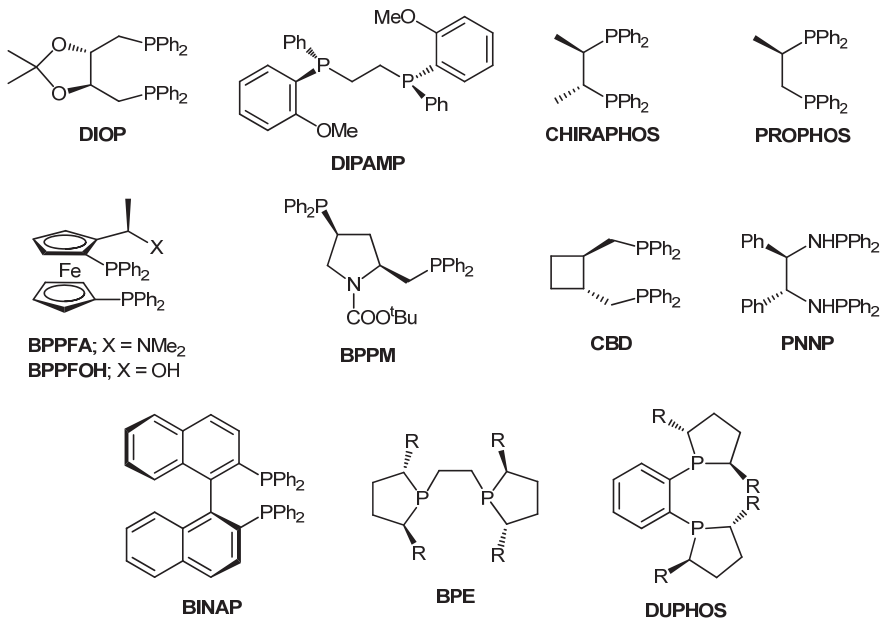


Figure 1.2.2. Successful diphosphine ligands in asymmetric hydrogenation.

Nowadays, many chiral ligands, mainly phosphorus donor ligands with either C_2- or C_1-symmetry, have been successfully applied. Catalysts containing diphosphine and diphosphinite have played a dominant role among the P-ligands.[1,22,32] 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,22,32,35] 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%).[4] Mixed P-S[4] and P-P'[35,36] (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.[37]

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. 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.

1.2.1.2.1. 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 **27** and **28**,[38] and then a conformationally rigid 1,4-dioxane backbone, which led to ligands **29** and **30** (Figure 1.2.3).[39] These ligands have provided excellent enantioselectivities (ee's up to 99%) in the Rh-catalyzed hydrogenation of aryl enamides.[38,39]

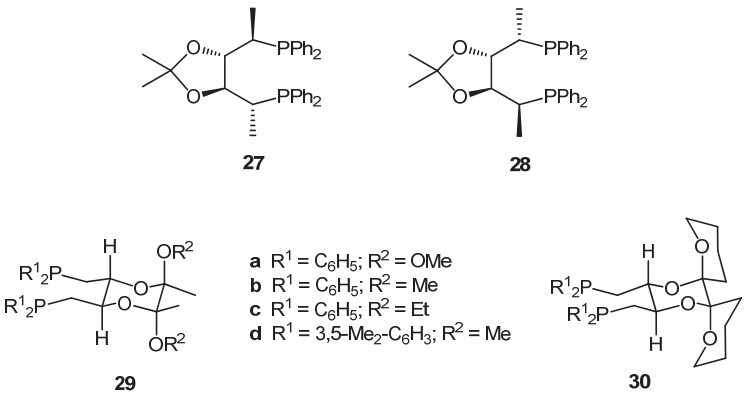


Figure 1.2.3. C_2-modified **DIOP** diphosphine ligands **27-30**.

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 **31**, **32a-c** and **33,** which have chiral information at both the α- and β-positions of the phosphorus atom (Figure 1.2.4). These ligands provided high enantioselectivities (from 93% to 99%).[40] Subsequently, Rieger and coworkers studied how the substituents in the α-position (R^2 groups) affect enantiodiscrimination with ligands **32b-f**. Their results indicated that the optimal substituents are generally Me and Et (Figure 1.2.4).[41]

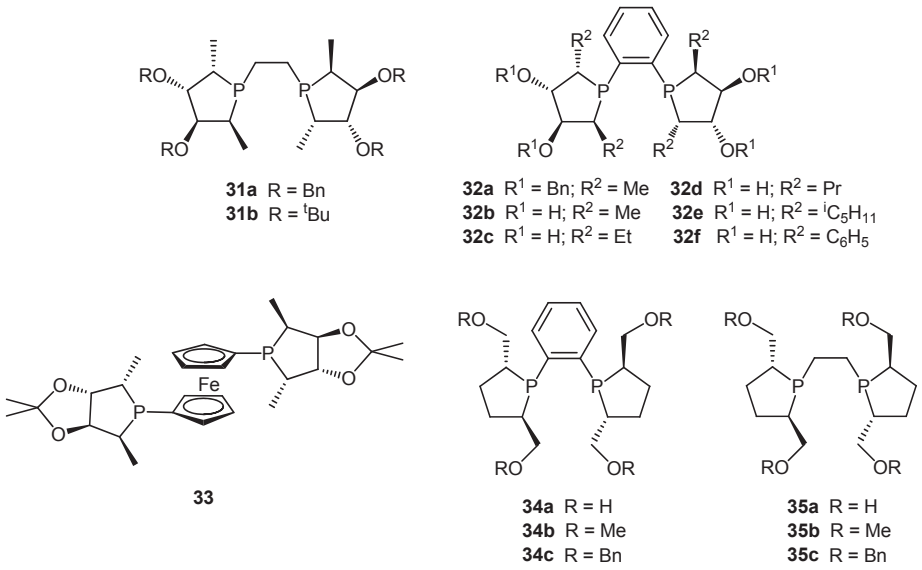
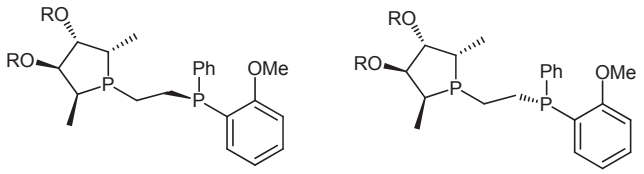


Figure 1.2.4. Diphospholane ligands **31-35**.

Another series of diphospholane ligands **34** and **35** (Figure 1.2.4) 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%).[42]

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 1.2.5). These ligands were applied in the Rh-catalyzed hydrogenation of several itaconates with ee's ranging from 80 to 95%.[43]

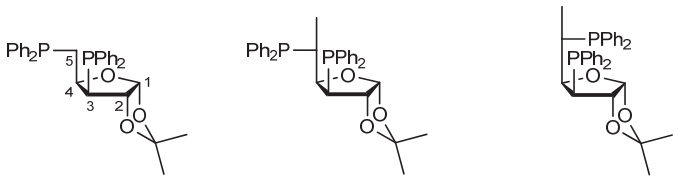


36a R = H
36b R = Me

37a R = H
37b R = Me

Figure 1.2.5. Phosphine-phospholane ligands developed by Brown and coworkers.

Another important series of compounds are the furanoside ligands **38**-**40** derived from D-(+)-xylose and D-(+)-glucose (Figure 1.2.6). These ligands were developed for the Rh asymmetric hydrogenation of dehydroamino acid and itaconic acid derivatives.[44] Ligands **39** and **40** differ from ligand **38** 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 **39** and **40**). Moreover, the configuration of C-5 strongly influenced enantioselectivity. The best results (activity and enantioselectivity) were therefore obtained with ligand **39** with (*R*)-configuration at C-5.



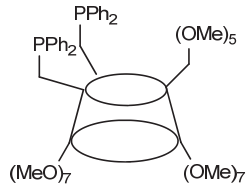
38
ee's up to 98%

39
ee's up to 98%

40
ee's up to 54%

Figure 1.2.6. Diphosphines **38**-**40** 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 cyclodextrines (ligand **41**, Figure 1.2.7) to take advantage of the properties of cyclodextrins as water-soluble chiral support. Ligand **41** contains phosphine at two of the positions six of a β-cyclodextrin. The Rh/**41** 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.[45]



41

Figure 1.2.7. Cyclodextrine containing diphosphine **41**.

Phosphinite ligands

The first examples of diphosphinite ligands being used with a carbohydrate backbone in asymmetric catalysis were reported by Cullen,[46] Thompson,[47] Selke,[48] Descotes[49] 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 **42**, mainly developed by Selke and coworkers (Figure 1.2.8, R^2 = Me, Ph, Bn and naphthyl; R^1 = Ph).[47,48,50] 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 **42** (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 **42** (Figure 1.2.8).[51]

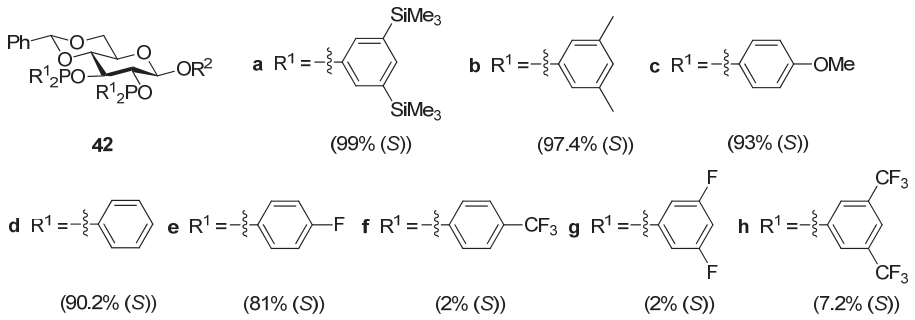


Figure 1.2.8. Diphosphinite ligand **42**. Enantioselectivities obtained in the hydrogenation of methyl α-acetamidocinnamate are shown as examples.

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 **42a** and **42b** (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 **42** from the expensive L-glucose, RajanBabu and coworkers developed pseudo-enantiomeric diphosphinite ligands to **42** with the corresponding 3,4-diphosphinite ligands **43** and **44** (Figure 1.2.9).[51] These ligands provided high enantioselectivities in favor of the (*R*)-enantiomer (ee's up to 98%) (Figure 1.2.9). 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.

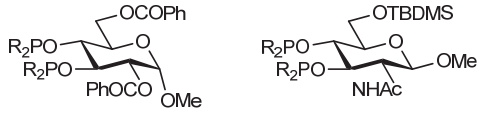


Figure 1.2.9. 3,4-Diarylphosphinite ligands **43** and **44**.

Diphosphinite derivatives with a furanoside backbone **45** and **46** (Figure 1.2.10) 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/**46** catalytic system and 78% (*R*) with the Ir/**45** catalytic system.[52] The phosphinite xylose derivatives **45** and **46** were also used as ligands in the Ir-catalyzed hydrogenation of imines although they provide only moderate enantioselectivities (ee's up to 57%) .[53]

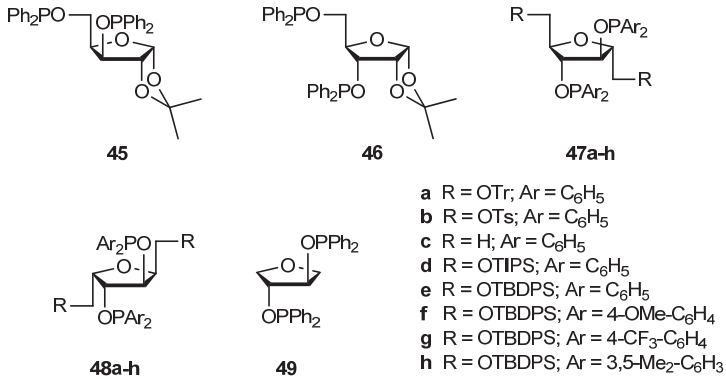


Figure 1.2.10. Diphosphinites ligands **45**-**49**.

Castillón and coworkers developed C_2-symmetric diphosphinites **47a-h** and **48a-d** derived from D-glucosamine and D-glucitol.[54] Ligands **47a-d** were used in the Rh-catalyzed hydrogenation of dehydroamino acids and itaconates. The best results were obtained with the catalytic system containing ligand **47c** (93% ee). Ligand **49**, 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 **47** and **48** 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.[55] Diphosphinites **48e-h** (Figure 1.2.10), 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 **48h**.

Phosphite ligands

A review of the research into carbohydrate phosphite ligands reveals two main trends: bidentate ligands and monodentate ligands.[35]

The first successful phosphite ligand for asymmetric hydrogenation came with the work of Reetz and coworkers. They developed a series of C_2-derivative ligands from D-mannitol **50** with different phosphite substituents (**a-e**) (Figure 1.2.11).[56] 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 **50e**.

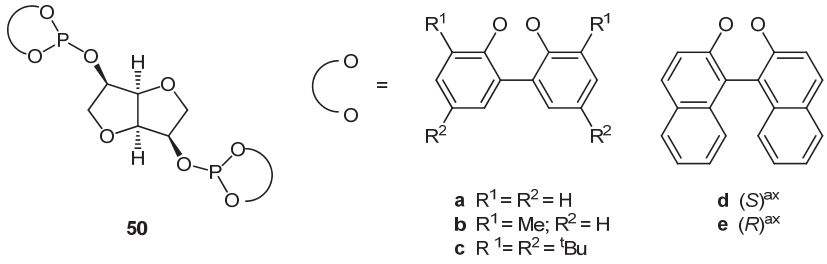


Figure 1.2.11. D-mannitol diphosphinite ligand developed by Reetz et al.

Our group developed a series of highly efficient modular C_1- diphosphite ligands **51-56** (Figure 1.2.12) with a furanoside backbone for the Rh-catalyzed hydrogenation.[57] 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 **54** with (*R*)-configuration on both C-3 and C-5 stereocenters. Bulky sustituents at the *ortho*-positions of the biaryl diphosphite moieties have a positive effect on enantioselectivity. Enantiomeric excess was highest for allofuranoside ligand **54d**, 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.

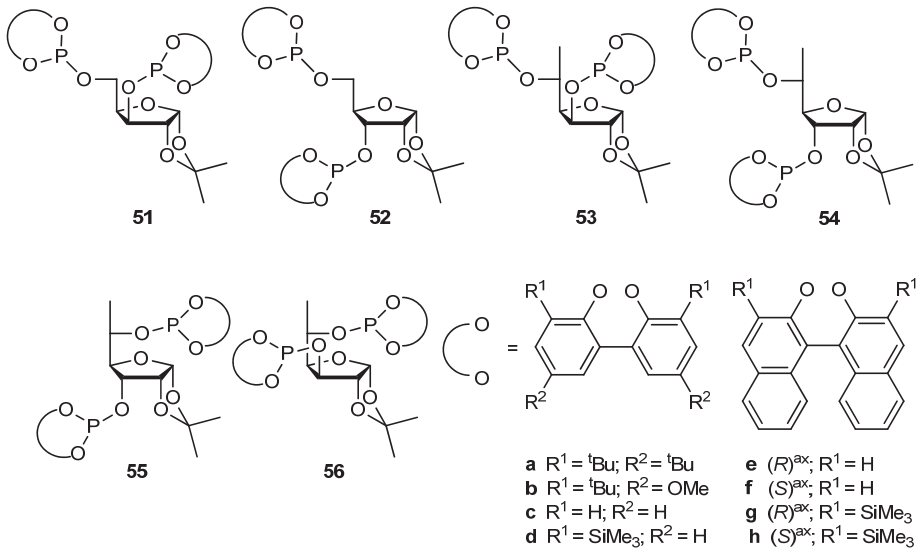


Figure 1.2.12. Diphosphite modular ligands **51-56**.

Diphosphite ligands **57-60** with C_2-symmetry and a tetrahydrofuran backbone have been synthesized starting from D-glucosamine and D-glucitol (Figure 1.2.13). These ligands have been used in the Rh-catalyzed asymmetric hydrogenation of methyl α-acetamidoacrylate with enantioselectivities up to 57%.[58]

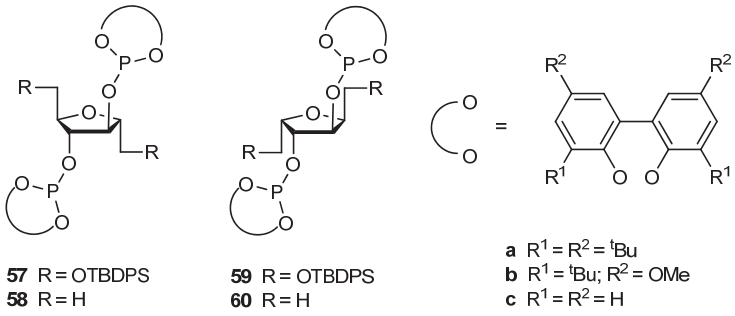
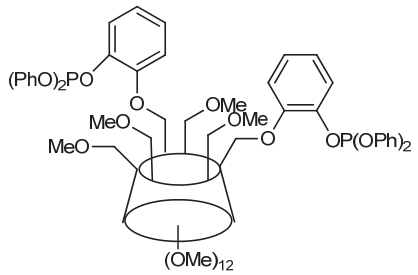


Figure 1.2.13. C_2-symmetric diphosphite ligands **57-60**.

Matt and coworkers successfully applied diphosphite ligand **61** (Figure 1.2.14), built on a cyclodextrin scaffold, in the Rh-catalyzed asymmetric hydrogenation of dimethyl itaconate with ee's up to 83%.[59]



61

Figure 1.2.14. Cyclodextrin-based diphosphite ligand **61** 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.[37] Research in this area was initiated by Reetz and coworkers. They found that the monophosphite ligands **62a-b** related to the previously described diphosphite ligands derived from D-mannitol **50** provided similar enantioselectivities in both enantiomers of the product (ee's up to 97%) (Figure 1.2.15).[60]

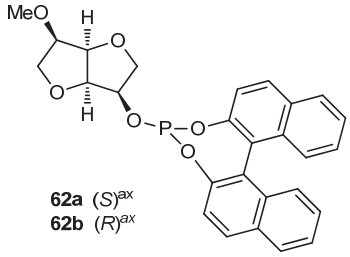


Figure 1.2.15. Monophosphite ligands **62**.

Other monophosphite ligands **63-70** (Figure 1.2.16), often containing a binaphthol moiety, were used for the Rh-catalyzed asymmetric hydrogenation of vinyl carboxylates, dehydroamino acids, and enamides.[61] The results of the vinyl carboxylate hydrogenation reported by Reetz and coworkers using ligands **63-65** 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 **63b**, prepared from (*R*)-Binol and a D-(+)-glucose derivative (ee's up to 94%).[61a]

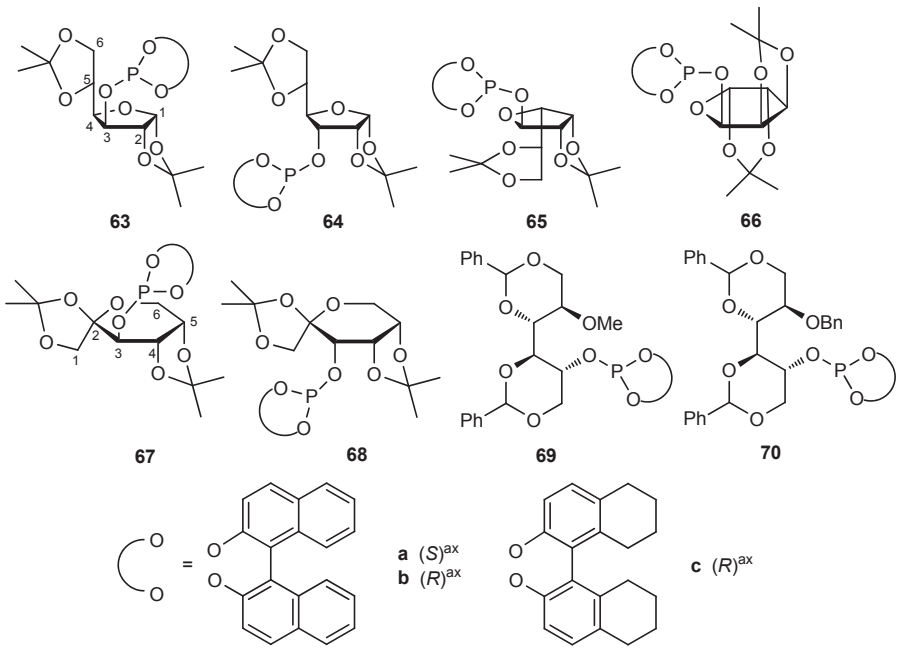


Figure 1.2.16. Monophosphite ligands **63**-**70**.

Chen and coworkers have also successfully used ligands **63**-**64** and **67**-**68** in the Rh-catalyzed hydrogenation of dehydroamino acids (ee's up to 98%) and enamides (ee's up to 99.9%).[61b-e] Their results indicate that the enantiomer excess depends strongly on the configuration of carbon atom C-3. In general, ligands **64** and **68** with an (*R*)-configuration produced a much higher enantioselectivity than ligands **63** and **65** 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 **68b**. Ligands **69** and **70** were also highly efficient in the hydrogenation of dehydroamino acids and enamides, providing high enantioselectivities (ee's up to 99.9%) and activities (TON up to 5000).[61d]

Phosphoroamidite ligands

In the last decade, several monophosphoroamidites derived from carbohydrates have been used for Rh-catalyzed asymmetric hydrogenation. However, only ligands **71** and **72** (Figure 1.2.17) derived from D-mannitol provided high enantioselectivity 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 **72e**.[62]

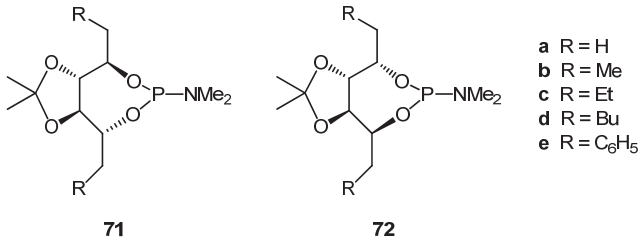


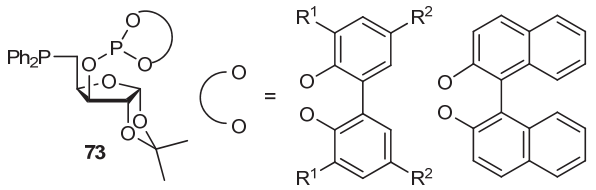
Figure 1.2.17. Phosphoroamidite ligands **71**-**72**.

1.2.1.2.2. 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.[35,36]

Furanoside phosphine-phosphite ligands **73** 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 1.2.18).[63,24c] The best enantioselectivity was obtained using ligand **73b**, 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.



73		% 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 1.2.18. Phosphine-phosphite ligands **73**. This figure also shows the enantioselectivities obtained in the hydrogenation of α,β-unsaturated carboxylic acid derivates.

Phosphinite-phosphite ligands **74** modified with different substituents (Figure 1.2.19) have shown not only considerable activity and selectivity but also higher enantioselectivities than the related diphosphite ligands **57**. These ligands have provided moderate enantioselectivities (ee's up to 76%) in the Ir-catalyzed hydrogenation of amines.[55] The best enantioselectivity was obtained with ligand **74a**.

Of the various mixed ligands, phosphite-phosphoroamidite ligands, **75** and **76** with a furanoside backbone were also efficiently used in Rh-catalyzed asymmetric hydrogenation (Figure 1.2.19). Enantioselectivities and activities were best (ee's up to >99%) when ligand **75a** was used with a *tert*-butyl group in the *ortho* and *para* positions of the biphenyl moieties and an (*R*)-configuration of C-3.[64]

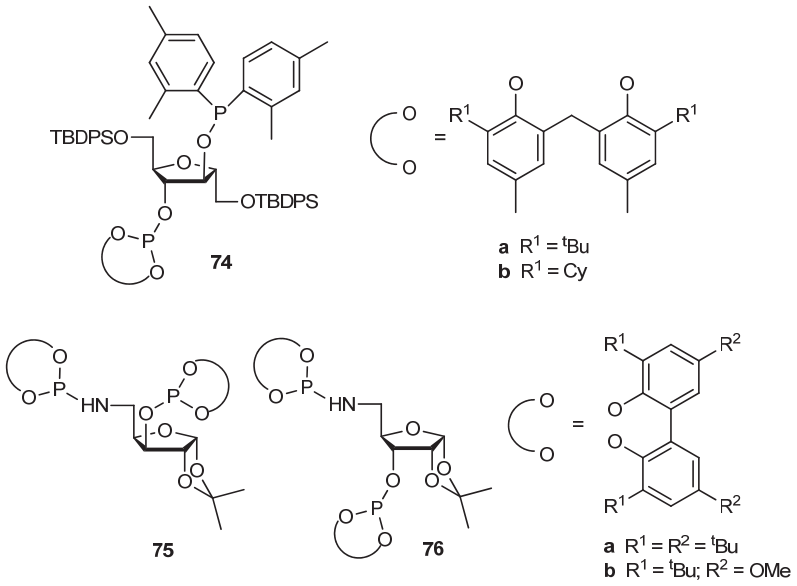


Figure 1.2.19. Phosphinite-phosphite **74** and phosphite-phosphoroamidite **75-76**.

P,S ligands

The furanoside phosphinite-thioether ligands **23** mentioned above (Figure 1.1.11) were successfully applied in the Rh- and Ir-catalyzed asymmetric hydrogenation of α-acylaminoacrylates and itaconic acid derivatives (ee's up to 96%). 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.[17]

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 **25** mentioned above (Figure 1.1.13).[20b] These ligands have been applied in the Rh- and Ir-catalyzed asymmetric hydrogenation of itaconic acid with enantioselectivities up to 51%.

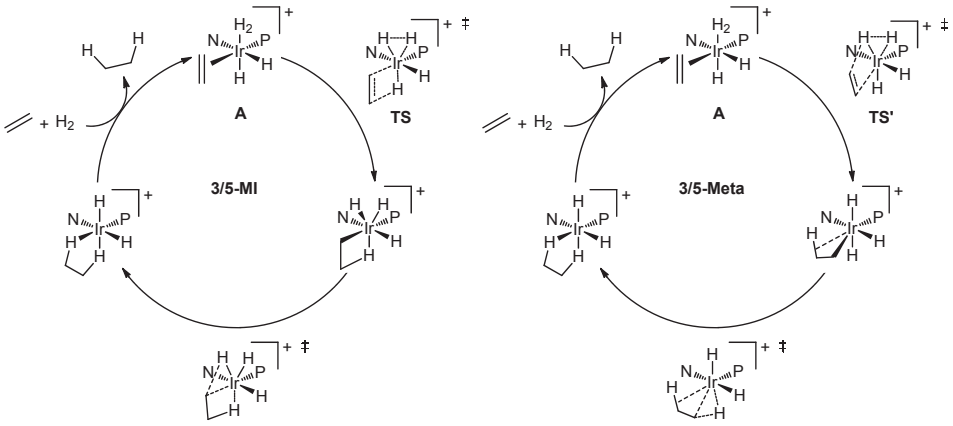
1.2.2. Ir-catalyzed asymmetric hydrogenation of unfunctionalized olefins

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,[1,22] 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.[65]

1.2.2.1. Mechanism

Although the mechanism of olefin hydrogenation (and consequently of stereocontrol) by Rh catalysts is well understood,[23,24a] 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 1.2.1), but in the second four different mechanisms have been proposed (two of them involving Ir^{I}/Ir^{III} intermediates[66] and the other two Ir^{III}/Ir^{V} species[67]). 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.[68] Their studies agree with the two already proposed catalytic cycles

involving Ir^{III}/Ir^{V} intermediates;[67] 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 1.2.3)[67c] whereas the second mechanism uses an Ir^{III}/Ir^{V} σ-metathesis/reductive-elimination pathway (labeled 3/5-Meta in Scheme 1.2.3)[67a,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.[68] It has been demonstrated that the enantioselectivity can be reliably obtained from the calculated relative energies of migratory insertion transition states.[68] Very recently Hopmann and coworkers performed a computational study using a phosphine-oxazoline (**PHOX**)-based iridium catalyst.[69] 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.[70] Both studies indicate that the hydrogenation of unfunctionalized olefins follows the 3/5-Meta pathway.



Scheme 1.2.3. 3/5-MI and 3/5-Meta catalytic cycles for the Ir-hydrogenation of unfunctionalized olefins.

1.2.2.2. Ligands

A breakthrough in the hydrogenation of unfunctionalized olefins came in 1997 when Pfaltz and coworkers used phosphine-oxazoline ligands **PHOX**[71] (Figure 1.2.20) 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)[72] that enantioselectively hydrogenated prochiral imines.[73] 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 $[(3,5\text{-}(F_3C)_2\text{-}C_6H_3)_4B]^-$ ($[BAr_F]^-$). The result was [Ir(**PHOX**)(cod)]BAr_F (Figure 1.2.20), 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.[74]

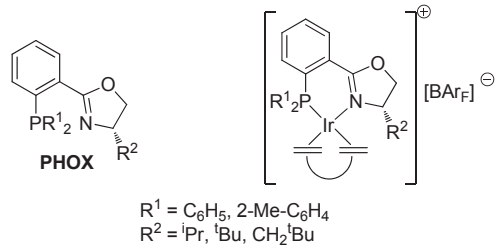


Figure 1.2.20. General structure of phosphino-oxazoline ligands **PHOX** and [Ir(**PHOX**)(cod)]BAr_F developed by Pfaltz and coworkers.

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). The structure of the chiral ligand's backbone has also been modified. These modifications have led to the discovery of new ligands[75] that have considerably broadened the scope of Ir-catalyzed hydrogenation.[74g,76] Figure 1.2.21 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.[65] The most successful P,N-ligands contain a phosphine or phosphinite moiety as P-donor group and either an oxazoline,[76b,g] oxazole,[76d] thiazole[76h] or pyridine[76c] as N-donor group (Figure 1.2.21). The latest innovation in the design of ligands for this process was the replacement of the phosphine/phosphinite moiety by a biaryl phosphite group.[65e,77] 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.[65]

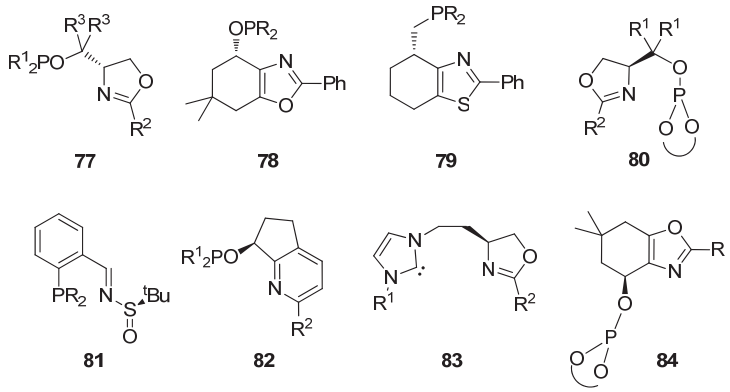


Figure 1.2.21. Representative chiral ligands applied to the Ir-catalyzed asymmetric hydrogenation of minimally functionalized olefins.

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 **85** developed by Pfaltz and coworkers (Figure 1.2.22). These ligands provided enantioselectivities up to 95% in the hydrogenation of a limited range of *E*- and *Z*-trisubstituted alkenes (Figure 1.2.22).[78] However, they required high catalyst loadings (4 mol %) and high pressures (100 bars) to achieve full conversion.

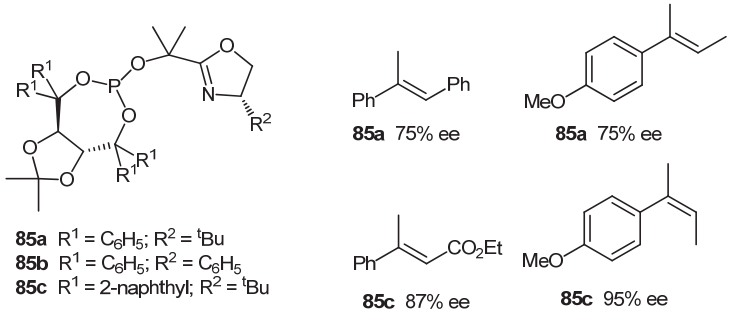


Figure 1.2.22. TADDOL-based phosphite-oxazoline **85**. Summary of the best results obtained.

Recently, Diéguez and Andersson applied pyranoside biaryl phosphite-oxzoline ligands derived from D-(+)-glucosamine (Figure 1.2.23).[70,77a] 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 (**90c** and **90e**) that perform well over the entire range of *E*- and *Z*-trisubstituted substrates (Figure 1.2.24). 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%).

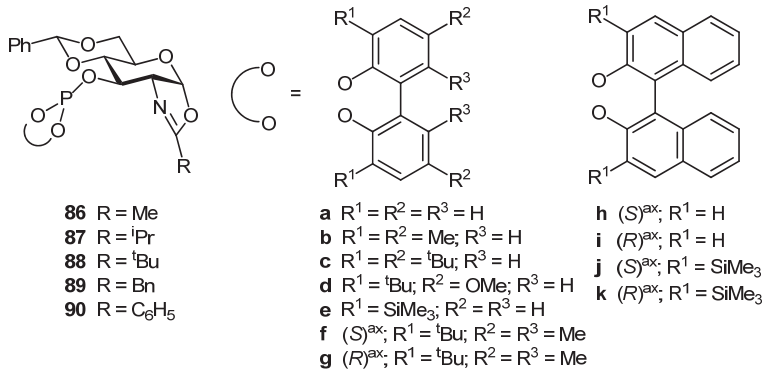


Figure 1.2.23. Pyranoside phosphite-oxazoline ligands **86-90a-k**.

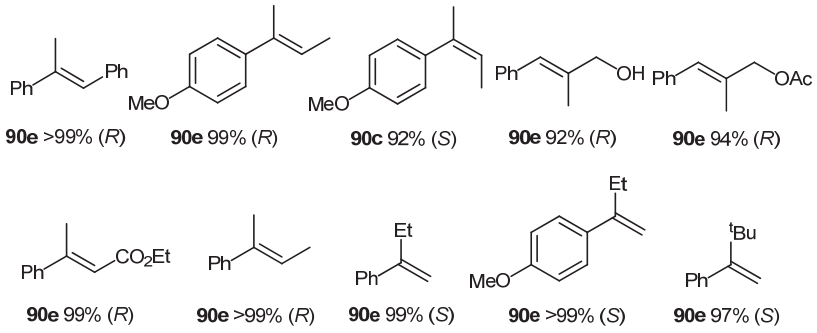
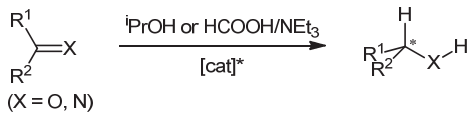


Figure 1.2.24. Summary of the best results obtained in the asymmetric hydrogenation of unfunctionalized olefins using ligands **90c**,**e**. In all cases full conversions were obtained.

1.3. Asymmetric transfer hydrogenation (ATH) of ketones

Asymmetric transfer hydrogenation (ATH) can be defined as "the reduction of prochiral compounds with a hydrogen donor other than hydrogen gas in the presence of a chiral catalyst" (Scheme 1.3.1).[79] The asymmetric transfer hydrogenation[80] of prochiral ketones and imines is one of the most attractive methods for synthesizing optically active secondary alcohols and amines, which are important intermediates for synthesizing fine chemicals and pharmaceuticals.[81] Ever since the discovery of the Meerwin-Ponndorf-Verley reaction[82] in which a ketone is reduced by an alcohol in the presence of an aluminium alkoxide, the use of metallic compounds to promote hydrogen transfer between alcohols and carbonyl compounds has been widely studied in organic synthesis.[83] After this discovery, transition metal-catalyzed versions of these reactions were developed.[80] Of all the catalysts reported so far, those that are based on the transition metal catalysts with Ru, Rh and Ir complexes have been the most successful.[80] Recently, however, iron-based catalysts have also shown useful activity and selectivity.[84] Metal-catalysed ATH reactions are most often performed in 2-propanol or the azeotropic mixture of formic acid and triethylamine ($HCOOH:NEt_3$ in the molar ratio 2.5:1), which act as both the solvent and reductant.[80]



Scheme 1.3.1. Asymmetric transfer hydrogenation of prochiral compounds.

1.3.1. Mechanism

From a mechanistic point of view, two general pathways have been proposed for transfer hydrogenation: (i) direct hydrogen transfer (Figure 1.3.1, **I**) and (ii) a hydridic route (Figure 1.3.1, **II**).[85]

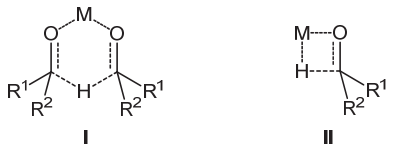
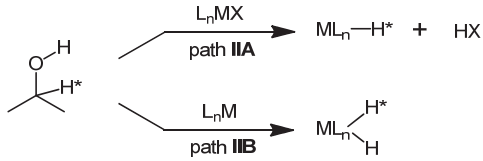


Figure 1.3.1. Key intermediates of the two general intermediates proposed for transfer hydrogenation reactions.

Direct hydrogen transfer, proposed for the Meerwein-Ponndorf-Verley (MPV) reduction, is a concerted process, involving a six-membered cyclic transition state (**I**) in which both the hydrogen donor and the hydrogen acceptor are coordinated to the metal center. This mechanism is claimed to occur with main group catalysts.[85c,d]

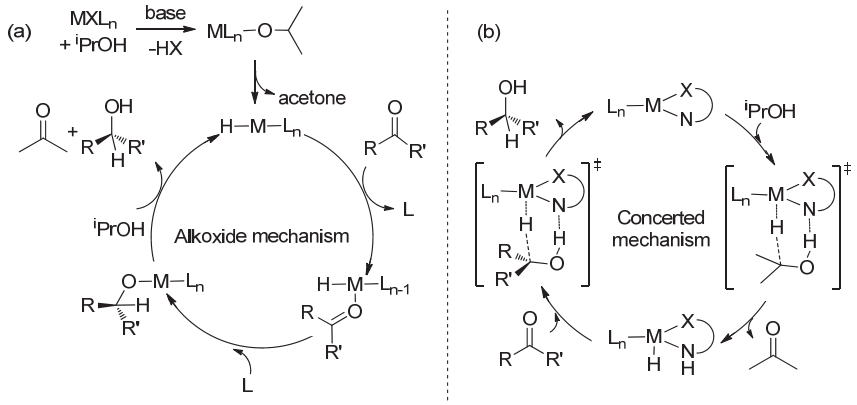
The hydrydic route, which is generally accepted to occur for transition metal catalysts, involves metal hydrides as key intermediates. There are two different hydridic pathways: (i) the metal monohydride mechanism (path **IIA**, Scheme 1.3.2) and (ii) a metal dihydride mechanism (path **IIB**, Scheme 1.3.2).[85a-c] However, most of the representative enantioselective catalysts developed for ATH (i.e. Ru catalysts modified with amino alcohols, pseudo-dipeptides and monotosylated diamines, etc.) follow the metal monohydride mechanism.[85]



Scheme 1.3.2. Hydridic pathways **IIA** and **IIB**.

Hydrogen transfer reactions catalyzed by metal monohydride may proceed via two slightly different pathways (Scheme 1.3.3): the alkoxide mechanism and the concerted mechanism. In both, the α-C-H is the origin of the hydride (and, according to the principle of microscopic reversibility, the M-H adds exclusively to the carbonyl carbon of the ketone). In the first mechanism (Scheme 1.3.3 (a)), the formation of the metal monohydride involves the formation of a transition metal alkoxide followed by β-elimination. Then, insertion of a ketone into the metal hydride bond results in the formation of the corresponding alkoxide. Finally, ligand exchange between alkoxide species and the hydrogen donor (isopropanol in Scheme 1.3.3 (a)) followed by β-elimination completes the catalytic cycle. In the second mechanisms (Scheme 1.3.3 (b)),

the formation of the metal monohydride involves a concerted pathway with simultaneous transfer of α-C-H of the hydrogen donor to the metal and transfer of O-H to the ligand. This involves a single 6-membered transition state. The same transition state is the responsible for the transfer of H^+ from ligand to carbonyl oxygen and M-H to carbonyl carbon of the ketone. Thus, the latter mechanism would not involve the intermediacy of a transition metal alkoxide. The concerted pathway has been supported by several groups studying Ru-complexes modified with aminoalcohols and monotosylated diamines.[86] Recently, a special case of the concerted pathway has been suggested for Ru-pseudo-dipeptide catalysts, which involves the simultaneous transfer of a hydride and an alkali cation instead of a proton.[87]



Scheme 1.3.3. Hydrogen transfer reactions catalyzed by metal monohydride species (X = O or NTs).

1.3.2. Ligands

Different types of chiral ligands have been reported for transition metal-catalyzed asymmetric transfer hydrogenation.[80] Some of the earliest reported catalytic systems for ATH involved phosphine ligands combined with Ru, Rh or Ir.[88] However, these catalytic systems led to low conversions and enantioselectivities. The first important breakthrough came with the work of Noyori and coworkers in the mid 1990's. They discovered that the monotosylated diamine ligand **91** (**TsDPEN**, Figure 1.3.2) in combination with Ru-arene complexes lead to excellent catalysts for the asymmetric reduction of a wide range of aryl-alkyl ketones (ee's up to 99%).[80e,89] Since then, the range of successful ligands has been expanded (Figure 1.3.2) by including

other monotosylated diamines (i.e. **92**),[89,90,91] 1,2-amino alcohols (**93-94**),[92] chiral amino-pyridines (**95**),[93] diphosphonites (**96**),[94] tetradentated P,N,N,P ligands (**97**)[95] and more recently, pseudo-dipeptides (**98**)[87b,96] and thioamide ligands (**99**).[87a,97]

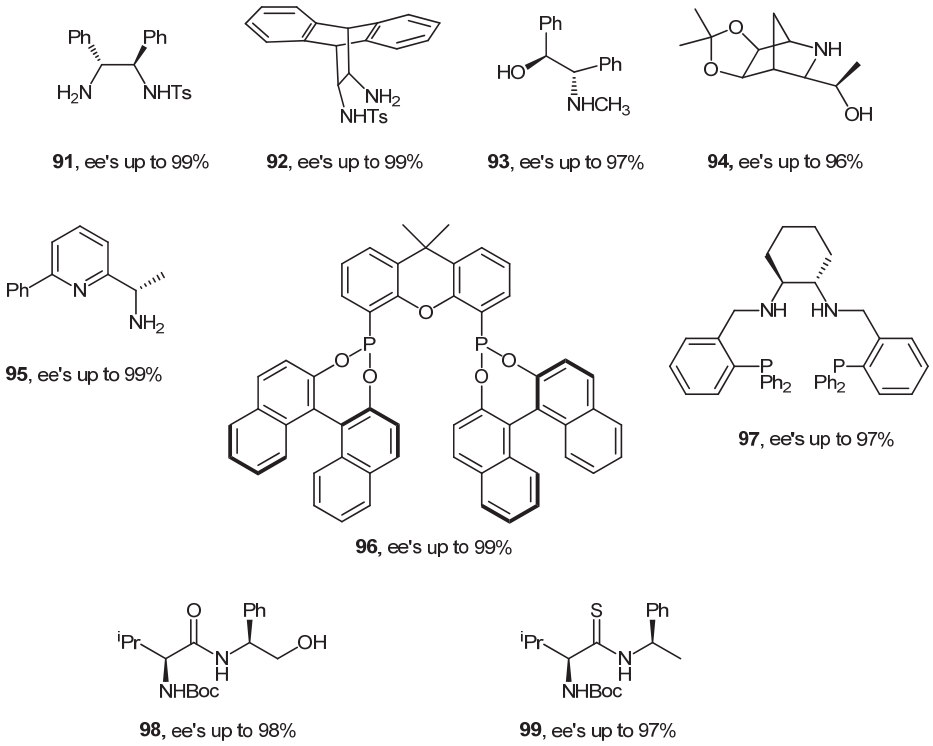
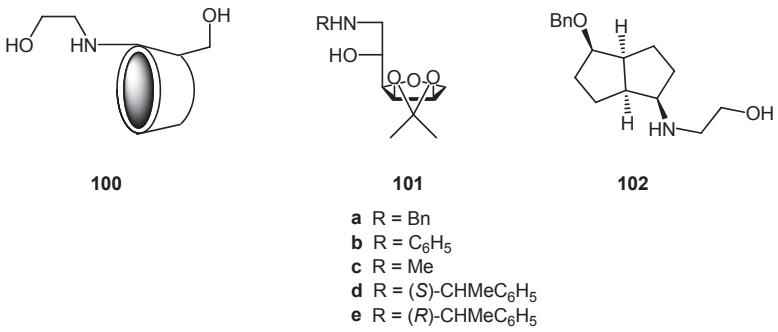


Figure 1.3.2. Representative chiral ligands developed for ATH reactions.

Although carbohydrate ligands have been succesfully used in asymmetric reductions with molecular hydrogen, only three reports have been published on asymmetric transfer hydrogenation using these systems.

The most notable example is the work of Woggon and coworkers (ligand **100**, Figure 1.3.3).[98] They modified the classical Noyori-type amino alcohol ligand **93** in which the chiral information is introduced in the substituent of the amine group rather than the ligand backbone. The introduction of a β-cyclodextrin in the amino group has therefore led to ligands that are extremely efficient (ee's up to 98%) at reducing aliphatic ketones in water using sodium formate as the hydrogen source. The β-cyclodextrin unit is an essential component of the catalyst. It contributes to the unprecedented levels of enantioselectivity observed by preorganizing the substrates in the hydrophobic cavity.



100 **101** **102**

a R = Bn
b R = C_6H_5
c R = Me
d R = (*S*)-$CHMeC_6H_5$
e R = (*R*)-$CHMeC_6H_5$

Figure 1.3.3. Sugar-based 1,2-amino alcohol ligands **100-102**.

In 2008, Saluzzo and coworkers developed a series of furanoside amino alcohols **101** (Figure 1.3.3), derived from isosorbide, as ligands for asymmetric transfer hydrogenation.[99] The best enantioselectivities (up to 78%) were obtained using ligand **101a**, with a benzyl substituent at the amino group.

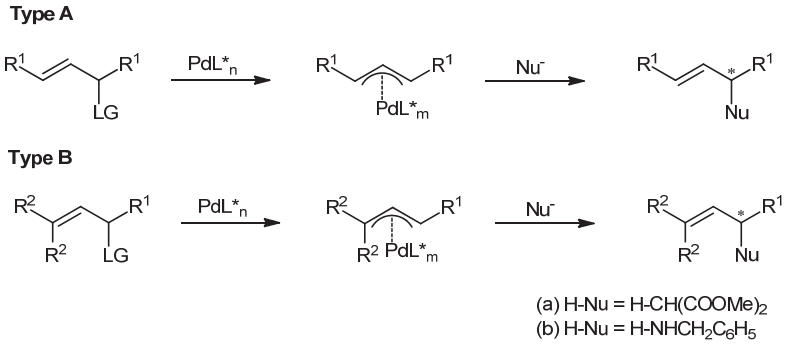
More recently, Toffano, Vo-Thanh and coworkers developed amino alcohols **102** (Figure 1.3.3) related to **100** in which the β-cyclodextrin was replaced by an isosorbide derivative.[100] Enantioselectivities up to 70% were obtained in the ATH of acetophenone.

1.4. 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,71b,101]

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 1.4.1 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 1.4.1. Two classes of asymmetric allylic substitution reactions.

In this reaction, the range of substrates tested (linear and cyclic) is quite wide (Figure 1.4.1). 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,71b,101]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 a few examples of enantioselective reactions with non-stabilized nucleophiles such as diorganozinc or Grignard reagents.[1b,71b,101]

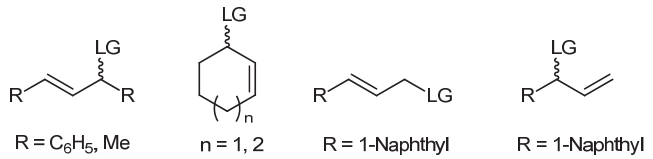


Figure 1.4.1. The most common substrates for the enantioselective allylic substitution.

1.4.1. Mechanism

The catalytic cycle for Pd-catalyzed asymmetric allylic substitution with stabilized nucleophiles is well established and involves four steps (Figure 1.4.2).[1b,71b,101] The first step is the coordination of an allylic substrate **104** to the catalyst precursor **103**, 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 $Pd_2(dba)_3 \cdot dba$, (dba = dibenzylidenacetone), $Pd(OAc)_2$ and $[Pd(\eta^3\text{-}C_3H_5)(\mu\text{-}Cl)]_2$. The next step is the oxidative addition of complex **105** to form the π-allyl intermediate **106**, 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 **107** is produced, which readily releases the final product **108**.

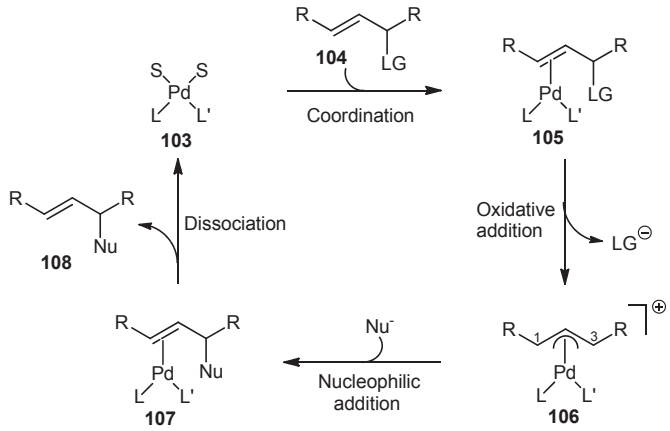


Figure 1.4.2. Accepted mechanism for Pd-catalyzed allylic substitutions.

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 **106**.[1b,71b,101] Hence, the π-allyl intermediate **106** 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-**106** can show a dynamic behaviour in solution, which leading in a mixture of isomers (Figure 1.4.3).

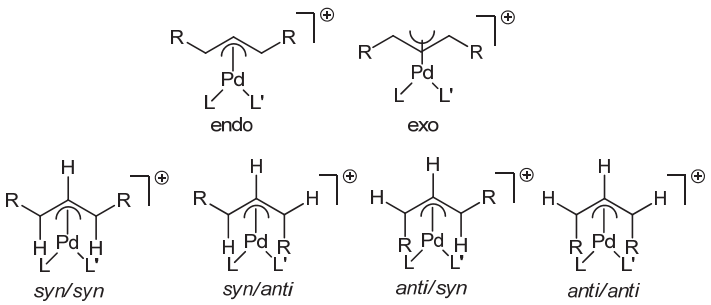


Figure 1.4.3. Possible isomers adopted by the Pd-allyl complex **106**.

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 **103** to **108** 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.

1.4.2. Ligands

Since the first enantioselective catalytic process described by Trost in 1977, the enantioselectivity of which was moderate,[102] many catalytic systems have been tested. These have provided excellent enantiomeric excesses.[1b,71b,101] Unlike the asymmetric hydrogenation process, few diphosphines have provided good enantioselectivities in allylic substitutions. Though high ee's can be obtained in certain cases for instance, with **BINAP** and **CHIRAPHOS** (Section 1.2.1.2, Figure 1.2.2), the scope of standard diphosphines in this process seems limited.

However, one of the most versatile ligands for this process is a diphosphine **109** developed by Trost (Figure 1.4.4).[101b,103] The noteworthy properties of this ligand are related to the bite angle, which is larger than in unstrained Pd-diphosphine complexes. Consequently, the P-aryl groups generated a chiral cavity, in which the allyl system is embedded, and which provides high ee's for several sterically undemanding substrates.

For diphosphines and other homodonor systems, the chiral discrimination is therefore induced by the C_2 or C_1 backbone of the ligand.

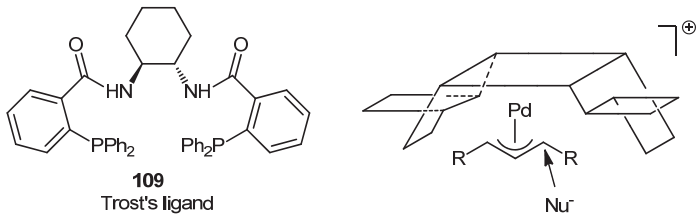


Figure 1.4.4. Trost's diphosphine ligand developed for Pd-catalyzed allylic substitution reactions.

The chiral ligands most often selected for highly enantioselective allylic substitution are mixed bidentate donor ligands such as phosphorus-nitrogen, phosphorus-sulfur and sulfur-nitrogen.[4c,71b,101] In this context, the phosphine-oxazoline **PHOX** ligands (Section 1.2.2.2, Figure 1.2.20) are, together with Trost's ligand, one of the most representative ligands developed for this process.[71b] The efficiency of this type of hard-soft heterodonor ligands has mainly been attributed to the different electronic effects of the donor atoms that predominantly produced the nucleophilic attack at one of the allyl carbon atoms (the one located *trans* to the best π-acceptor, Figure 1.4.5).

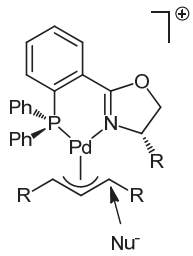


Figure 1.4.5. Enantiodiscrimination model for the Pd-catalyzed allylic substitution reactions using **PHOX** ligands.

Other ligands, such as bidentate nitrogen and sulfur, have also exhibited very good catalytic behavior.[4c,101b,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]

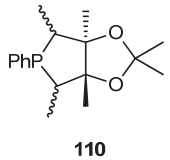
In the next section, we summarize the most relevant catalytic data published for the Pd-catalyzed allylic substitution reactions with carbohydrate ligands.

1.4.2.1. P-donor ligands

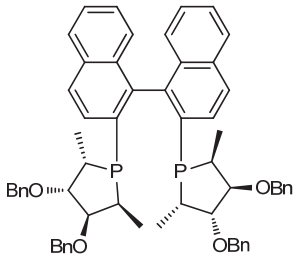
Phosphine ligands

In 2000, the above mentioned C_1-symmetric diphosphine ligands **38-40** with a furanoside backbone (Figure 1.2.6) were applied in Pd-catalyzed asymmetric allylic substitution reactions with moderate success.[104] 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%).

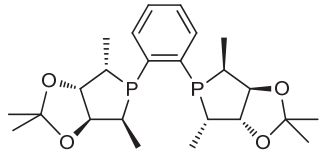
At the same time, one of the best results obtained in the allylic substitution that used phosphine ligands was achieved with the family independently developed by RajanBabu and Zhang. These authors reported the use of the above mentioned diphospholane ligands **32** (Figure 1.2.4) and phospholanes **110-112**, derived from D-mannitol, in the Pd-catalyzed allylic alkylation of substrate 1,3-diphenylprop-2-enyl acetate (Figure 1.4.6), with high enantioselectivities (ee's up to 99%).[7,40c] It was also observed that the sense of the asymmetric induction is controled by the absolute stereochemistry of the P-carrying carbons. Both enantiomers of the product can therefore be obtained.



110



111



112

Figure 1.4.6. 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 1.4.7, ligands **113** and **114**).[105] 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 (**113**) to D-mannose (**114**) derivative ligands.

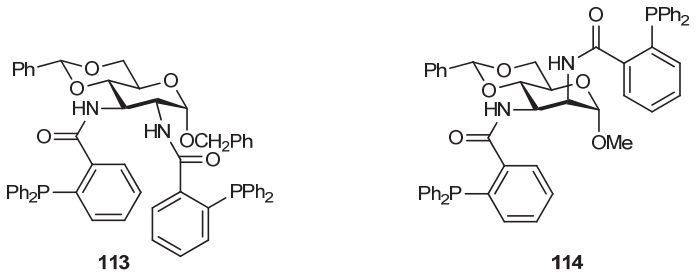
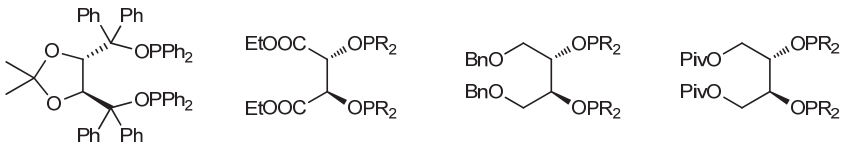


Figure 1.4.7. Bis(phosphinylamides) ligands **113** and **114** developed by Ruffo et al.

Phosphinite ligands

In 1995, Seebach and coworkers first prepared C_2-symmetric diphosphinite **115** from **TADDOL**, tested it in the asymmetric allylic substitution and obtained ee's of up to 76% ee (Figure 1.4.8).[106] Subsequently, RajanBabu and coworkers tested the above mentioned ligands **42** (R^2 = Ph) (Figure 1.2.8) and ligands **116-118** (Figure 1.4.8), 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 **42**, the best enantioselectivity (59% ee) was achieved with the ligand containing cyclohexyl as substituent R^1.[107] 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 **116-118**, the electronic effects were similar to those with ligands **42**, but enantioselectivities were up to 77% (Figure 1.4.8).[108]



115 (76% (*R*)) **116** (73% (*R*)) **117** (31% (*S*)) **118** (77% (*R*))

Figure 1.4.8. Diphosphinite ligands **115-118**. Enantioselectivities are shown in parentheses.

Phosphite ligands

The series of previously reported furanoside diphosphite ligands **51-56** (Figure 1.2.12) were also successfully applied in the Pd-catalyzed allylic substitution of diethyl malonate and benzylamine to several acyclic and cyclic allylic esters (Figure 1.4.9).[20a,104a,109]

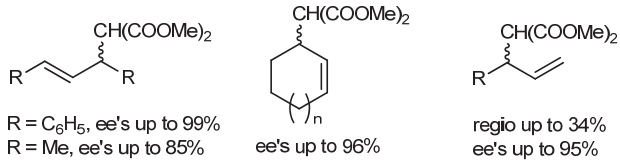


Figure 1.4.9. Acyclic and cyclic allylic esters tested with ligands **51-56**.

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 **53c**, which has a glucofuranoside backbone and bulky *tert*-butyl substitutents at both *ortho* and *para* positions of the biphenyl moieties. The results also indicated that the nucleophilic attack takes place *trans* to the carbon atom C-5. Ligand **51c** 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.[110]

Next, the above mentioned furanoside ligands of C_2-symmetry **57** and **59** (Figure 1.2.13), 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 **57** provided excellent activities and enantioselectivities (ee's up to 99% (*S*)).[111]

More recently, Claver and coworkers have reported further modifications to the privileged ligand **53c** by: (a) replacing the methyl substituent at C-5 with increasingly

sterically demanding ether substituents (ligands **119**, **120** and **121**, Figure 1.4.10) and (b) replacing the 1,2-acetal protection with an alkyl chain in C-2 (ligands **122** and **123**, Figure 1.4.10).[112] These ligands were applied to the Pd-catalysed 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 **122a**.

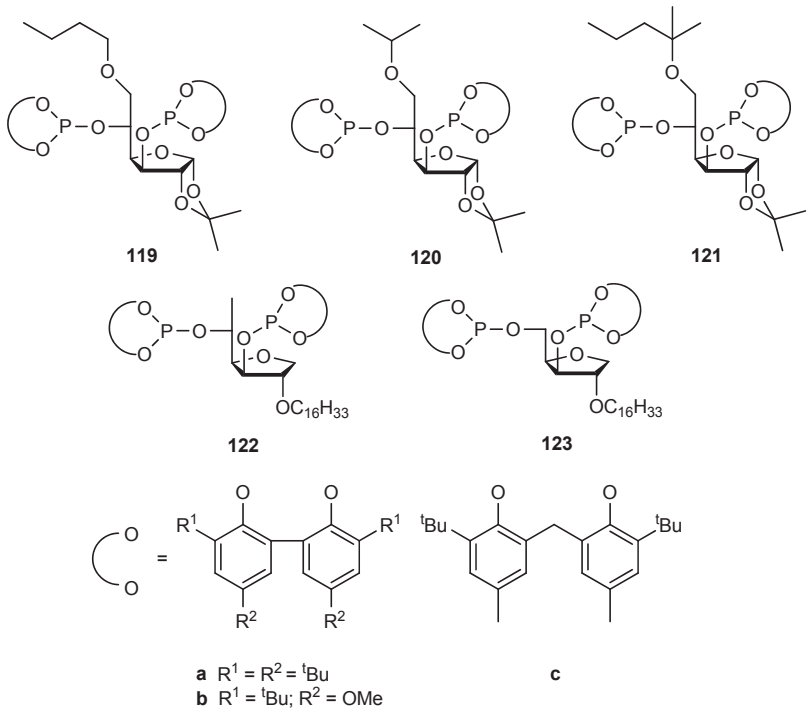


Figure 1.4.10. Furanoside diphosphite ligands **119-123a-c**.

Phosphoroamidite ligands

In recent decades, there has been a huge advance in the use of phosphoroamidite ligands for several asymmetric processes.[113] However, to the best of our knowledge, only one family of diphosphoroamidite ligands (**124**) based on carbohydrates has been successfully applied in asymmetric catalysis (Figure 1.4.11). 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 1.4.11).[114]

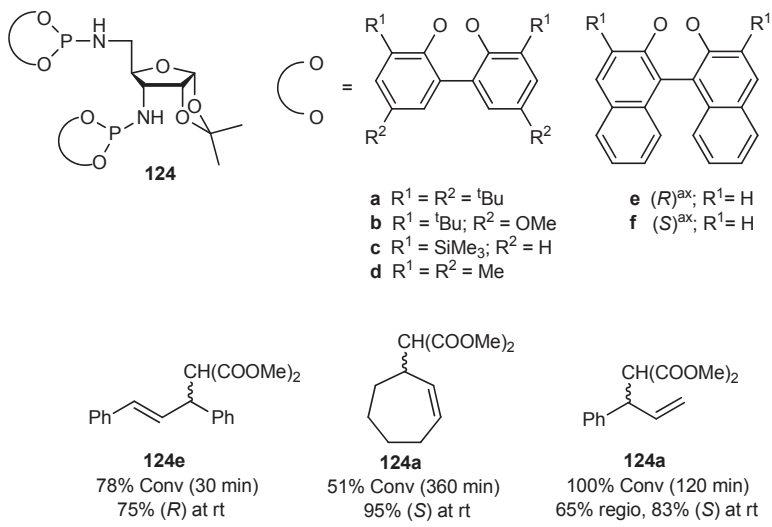


Figure 1.4.11. Furanoside diphosphoroamidite ligands **124**. Summary of the best results obtained with acyclic and cyclic substrates.

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.

1.4.2.2. 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.[4c,101f] In this context, Khiar and coworkers used a combinatorial approach to find the best dithioether ligand **125** (Figure 1.4.13) from a library of 64 potential ligands made by combining four linkers, four carbohydrate residues and four protective groups (Figure 1.4.12) for the Pd-catalyzed allylic alkylation of dimethyl malonate to 1,3-diphenylprop-2-enyl acetate (ee's up to 90%).[115a] To have access at both enantiomers of the alkylation product, the authors successfully prepared pseudo-enantiomers **126** and **127** derived from D-galactose and D-arabinose, respectively (Figure 1.4.13).[115b]

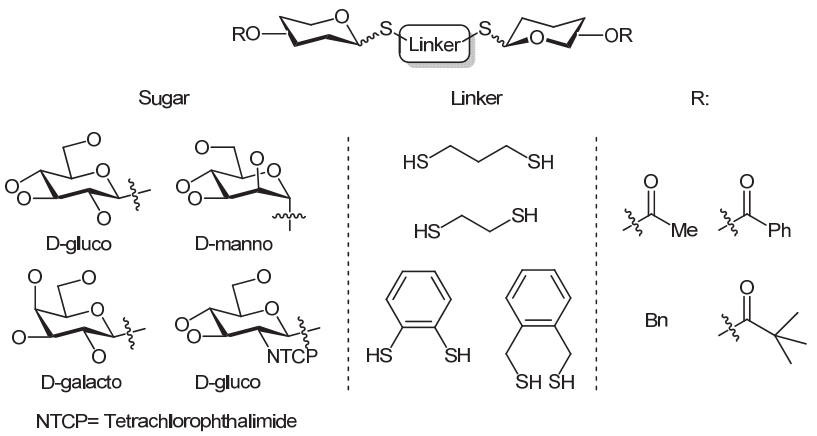


Figure 1.4.12. Dithioether ligand library studied by Khiar and coworkers.

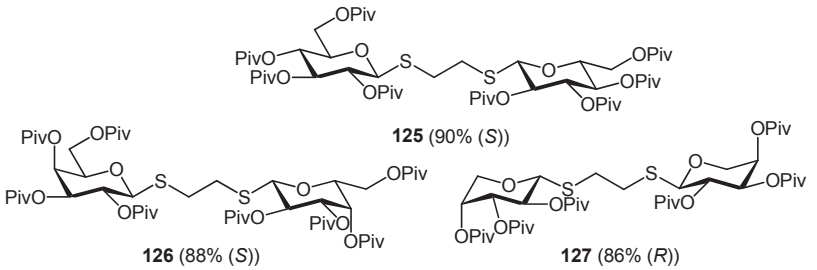


Figure 1.4.13. Summary of the best results obtained in the Pd-catalyzed alylic alkylation of 1,3-diphenylprop-2-enyl acetate using dithioether ligands **125-127**.

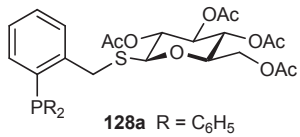
1.4.2.3. Heterodonor ligands

P-S ligands

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

The above mentioned ferrocenylphosphine-thioglucoside ligand **1** (Figure 1.1.1) with multiple stereogenic units afforded an ee of 88% in the palladium allylic substitution of diethyl malonate with 1,3-diphenylprop-2-enyl acetate.[5a] However, when

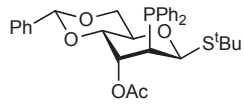
the thiosugar moiety was the sole stereogenic unit on ligands **128** (Figure 1.4.14), enantioselectivities were only moderate (ee's up to 64%).[116]



128a R = C_6H_5
128b R = Cy

Figure 1.4.14. Phosphine-thioether ligands **128**.

Khiar and coworkers reported the successful use of the above mentioned phosphine-thioether ligand **15** (Figure 1.1.7) in the Pd-catalyzed asymmetric allylic alkylation of 1,3-diphenylprop-2-enyl acetate (ee's up to 90% (*S*)).[11] The same group also reported the application of ligand **129** (Figure 1.4.15), but with little success (ee's up to 30% (*R*)).[117]



129

Figure 1.4.15. Phosphine-thioether ligand **129**.

In 2003, the above phosphine-oxathiane ligand **12** (Figure 1.1.4), 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).[8b-d]

More recently, the series of above mentioned phosphinite-thioether ligands with a furanoside backbone **23** (Figure 1.1.11), 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%).[16] 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 **23c-d** were used. The replacement of the phosphinite group by a bulky biaryl phosphite led to a much lower enantioselectivity.[20a]

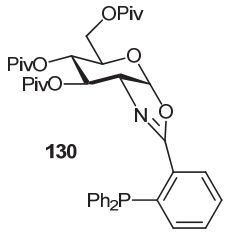
At the same time, the above mentioned phosphinite-thioether ligands **21** and **22** with a pyranoside backbone (Figure 1.1.10) were successfully applied in the Pd-catalyzed allylic substitution of 1,3-diphenylprop-2-enyl acetate (ee's up to 96%).

Enantioselectivities were best when bulky *tert*-butyl substituents were present in the thioether moiety. Both enantiomers of the products were obtained by using pseudo-enantiomeric ligands **21a** and **22**.[15]

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.

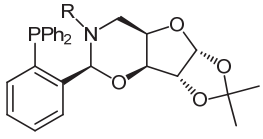
Kunz and coworkers developed a phosphine-oxazoline ligand **130** derived from D-glucosamine for the Pd-catalyzed allylic alkylation of dimethyl malonate to symmetrically and non-symmetrically substituted allyl acetates with high enantioselectivities (ee's up to 98%) (Figure 1.4.16).[118] These results are in line with a nucleophilic attack *trans* to the phosphorus atom.



130

Figure 1.4.16. Phosphine-oxazoline ligand **130** developed by Kunz and coworkers.

In 2003, phosphine-oxazine ligands **131**, related to ligand **12**, were developed for the Pd-catalyzed allylic substitution of 1,3-diphenylprop-2-enyl acetate (Figure 1.4.17). Enantioselectivities up to 75% were obtained.[8c]



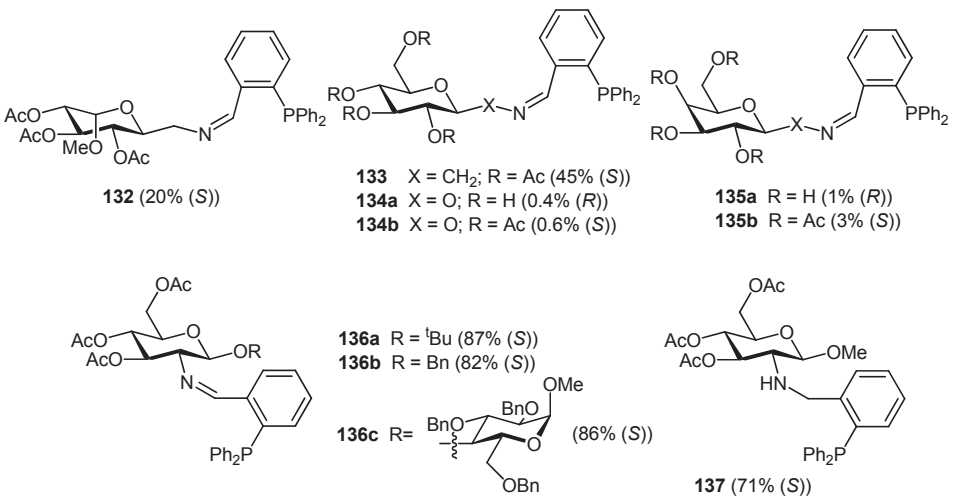
131

	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 1.4.17. Phosphine-oxazine ligands **131**. This figure also shows the enantioselectivities obtained.

Several phosphine-imine ligands with a pyranoside backbone **132-137** have been developed for Pd-catalyzed allylic substitution reactions (Figure 1.4.18).[119] The results

indicated that having the imine-phosphine residue at C-2 (ligands **136**) provided better enantioselectivities than having it at the C-1 position of the pyranoside backbone (ligands **132-135**). It should be noted that ligands with the general structure **136** have provided enantioselectivities up to 99% in the amination of 1,3-diphenylprop-2-enyl acetate using morpholine as the nucleophile.[119c] Recently, the imine group in ligands with the general structure **136** has been replaced by an amine group (ligand **137**, Figure 1.4.18). The results were also good.[119d]



132 (20% (*S*))

133 X = CH_2; R = Ac (45% (*S*))
134a X = O; R = H (0.4% (*R*))
134b X = O; R = Ac (0.6% (*S*))

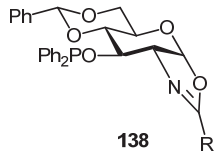
135a R = H (1% (*R*))
135b R = Ac (3% (*S*))

136a R = ^{t}Bu (87% (*S*))
136b R = Bn (82% (*S*))
136c R= (86% (*S*))

137 (71% (*S*))

Figure 1.4.18. Phosphine-imine **132-136** and phosphine-amine **137** ligands. This figure also shows the enantioselectivities obtained in the Pd-allylic alkylation of 1,3-diphenylprop-2-enyl acetate.

Uemura and coworkers developed a series of phosphinite-oxazoline ligands **138,** derived from D-glucosamine, for Pd-catalyzed allylic substitution reactions (Figure 1.4.19).[120] These ligands showed high enantioselectivities with 1,3-diphenylprop-2-enyl acetate as a substrate, but low-to-moderate enantioselectivites 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 **138a**). Their results also indicate that the nucleophilic attack took place *trans* to the phosphorus atom thought an *endo* π-allyl Pd-intermediate.



	R	%ee
a	Me	96 (*S*)
b	^{i}Pr	90 (*S*)
c	^{i}Bu	95 (*S*)
d	^{t}Bu	83 (*S*)
e	C_6H_5	94 (*S*)
f	Bn	78 (*S*)

Figure 1.4.19. Phosphinite-oxazoline ligands **138**. This figure also shows the enantioselectivities obtained in the allylic alkylation of substrate 1,3-diphenylprop-2-enyl acetate.

Water-soluble ligand **139** (Figure 1.4.20), related to **138a**, 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%).[121]

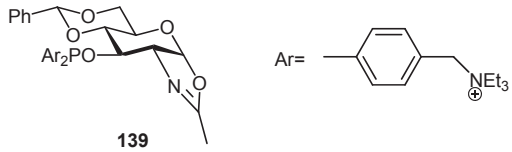
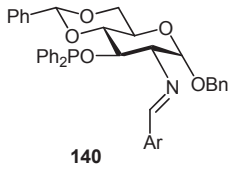


Figure 1.4.20. Water-soluble ligand **139**.

In 2010, Chen and coworkers developed the new carbohydrate-based phosphinite-imine ligands **140a-g** (Figure 1.4.21). 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%).[122]



Ligand	Ar	%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 1.4.21. Carbohydrate-based phosphinite-imine ligands **140a-g**. This figure also shows the enantioselectivities obtained in the allylic alkylation of 1,3-diphenylprop-2-enyl acetate.

Recently, the replacement of the phosphinite group in ligands **138** by a phosphite moiety led to the formation of the above mentioned phosphite-oxazoline ligands **86-90** (Figure 1.2.23).[123] The introduction of a biaryl phosphite moiety in the ligand design proved to be highly advantageous.[124] Ligands **86-90**, 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 1.4.22). These ligands were also used to stabilize Pd-nanoparticles.[125]

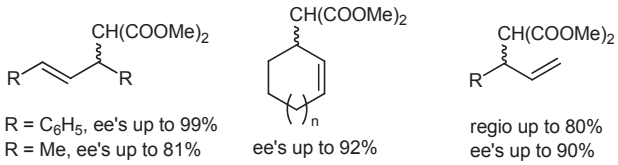


Figure 1.4.22. Acyclic and cyclic allylic esters tested with ligands **86-90**.

Pfaltz and coworkers have also applied the previously reported phosphite-oxazoline ligand **85a** (Figure 1.2.22) 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%).[126]

P-O ligands

Phosphine-amide ligands **141-146** (Figure 1.4.23) with a pyranoside backbone have been extensively studied for the Pd-catalyzed allylic alkylation of 1,3-diphenylprop-2-enyl acetate with dimethyl malonate.[119c,127] 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 **141**, **145** and **146** that forms a six-membered chelate ring and with a β anomeric carbon afforded higher enantioselectivitives than ligands **142** with an α anomeric carbon and **144** that form a seven membered chelate ring. Moreover, the results achieved with ligands **145** and **146** indicated a cooperative effect between the additional stereocenters in **145** and the carbohydrate backbone that resulted in a matched combination for ligand (*S*)-**145**.

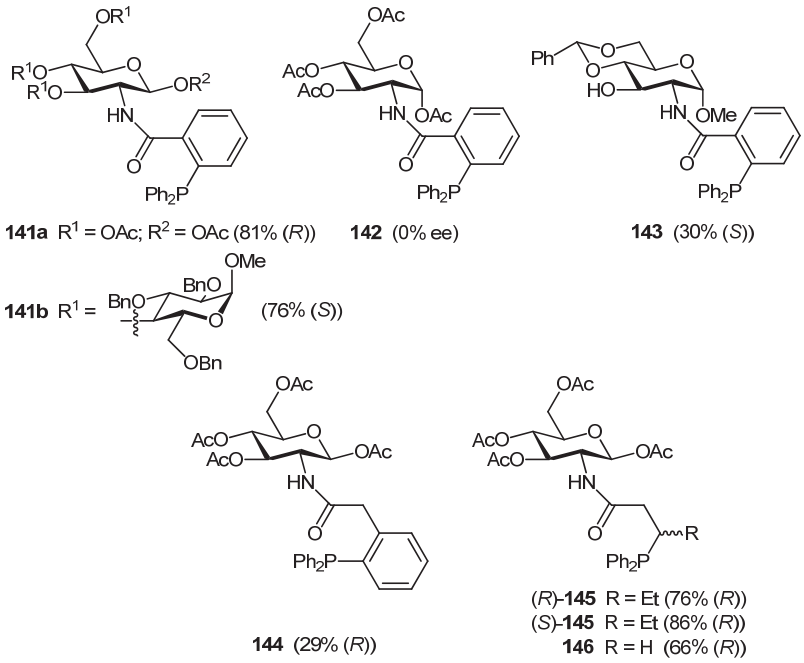
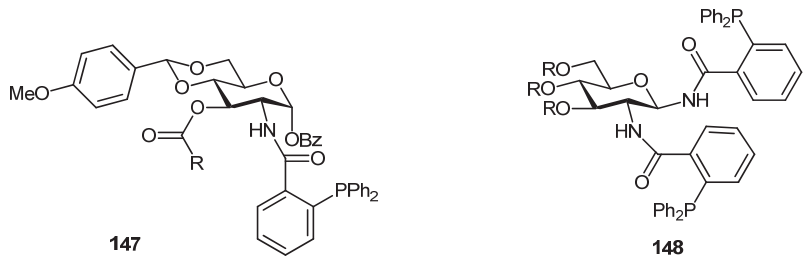


Figure 1.4.23. Phosphine-amide ligands **141-146**. The enantioselectivities are also shown in brackets.

Recently, Ruffo and coworkers reported the modular ligand library naplephos (**147**, Figure 1.4.24), 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%).[128] These ligands were also effective in the desymmetritzation of *meso*-cyclopent-2-ene-1,4-diol (ee's up to 98%).[105b] In the search for the opposite enantiomer of the alkylation product, the same authors developed the pseudo-enantiomeric ligands elpanphos (**148**, Figure 1.4.24).[129]



a R = 2-C_6H_4-PPh_2; **b** R = Me; **c** R = Bn; **d** R = CH_2Cy;
e R = ^tBu; **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 = $CH_2C_6F_5$

a R = Ac
b R = H

Figure 1.4.24. Naplephos (**147a-l**) and elpanphos (**148a-b**) ligands.

P-P' ligands

The first successful family of P-P' carbohydrate ligands contains the above mentioned phosphite-phosphoroamidite ligands **75** and **76** (Figure 1.2.19) and ligands **149-150** (Figure 1.4.25). These ligands were successfully applied in the Pd-asymmetric allylic substitution (ee's up to 98%).[130] 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 1.4.25). The related phosphine-phosphite ligands **73** (Figure 1.2.18) 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.[20a]

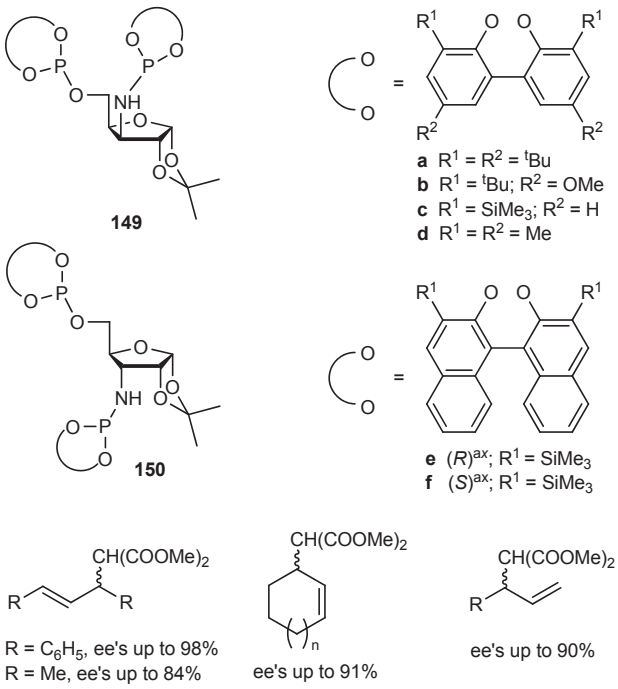


Figure 1.4.25. Phosphite-phosphoroamidite ligands **149-150**. This figure also shows the best results obtained in the allylic alkylation of several substrates.

Pyranoside phosphite-phosphoroamidite ligands **151** (Figure 1.4.26) 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.[131]

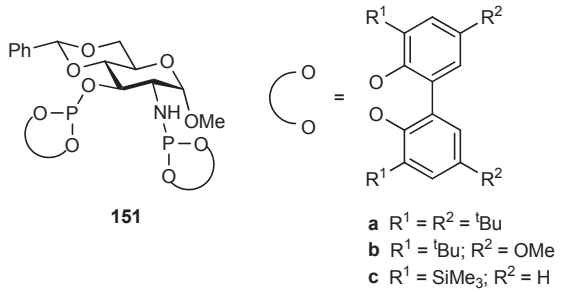
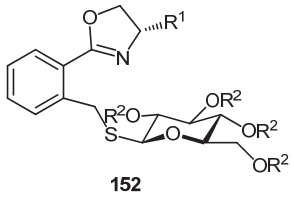


Figure 1.4.26. Phosphite-phosphoroamidite ligands **151**.

N-S ligands

Thioglucoside-derived ligands **152**, containing a chiral oxazoline moiety (Figure 1.4.27), 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.[132] 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.

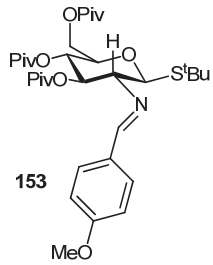


152

	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 1.4.27. Thioether-oxazoline ligands **152**. 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 **153** (Figure 1.4.28), related to P-S ligand **15**, was applied in the allylic alkylation of 1,3-diphenylprop-2-enyl acetate with low enantioselectivity (ee's up to 34%).[11]



153

Figure 1.4.28. Thioether-imine ligand **153**.

1.5. References

[1] See for example: a) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, **1994**; b) Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. *Comprehensive Asymmetric Catalysis*; Springer-Verlag: Berlin, **1999**; c) Cornil, B.; Herrmann, W. A. *Applied Homogeneous Catalysis with Organometallic Compounds*; 2nd edition, Wiley-VCH, Weinheim, **2002**; d) Blaser, H. U.; Schmidt, E. *Asymmetric Catalysis on Industrial Scale: Challenges, Approaches and Solutions*; Wiley-VCH, Weinheim, **2004**; e) Ojima, I. *Catalytic Asymmetric Synthesis*; 3rd edition, John Wiley & Sons, Hoboken, **2010**.

[2] a) Diéguez, M.; Ruiz, A.; Claver, C. *Dalton Trans.* **2003**, 2957; b) Pàmies, O.; Diéguez, M.; Ruiz, A.; Claver, C. *Chim. Oggi* **2004**, *22*, 12; c) Diéguez, M.; Pàmies, O.; Ruiz, A.; Díaz, Y.; Castillón, S.; Claver, C. *Coord. Chem. Rev.* **2004**, *248*, 2165; d) Diéguez, M.; Pàmies, O.; Claver. C. *Chem. Rev.* **2004**, *104*, 3189; e) Diéguez, M.; Pàmies, O.; Ruiz, A.; Claver, C. *Methodologies in Asymmetric Catalysis*, Chapter 11, American Chemical Society, Washington DC, **2004;** f) Castillón, S.; Díaz, Y.; Claver, C. *Chem. Soc. Rev.* **2005**, *34*, 702; g) Diéguez, M.; Claver, C.; Pàmies, O. *Eur. J. Org. Chem.* **2007**, 4621; h) Boysen, M. M. K. *Chem. Eur. J.* **2007**, *13*, 8648; i) Benessere, V.; Del Litto, R.; De Roma, A.; Ruffo, F. *Coord. Chem. Rev.* **2010**, *254*, 390; j) Woodward, S.; Diéguez, M.; Pàmies, O. *Coord. Chem. Rev.* **2010**, *254*, 2007.

[3] a) Pignolet, L. H. (Ed), *Homogeneous Catalysis with Metal Phosphine Complexes*, Plenum: New York, NY, **1983**; b) Simpson, M. C.; Cole-Hamilton, D. J. Coord. *Chem. Rev.* **1996**, *155*, 163; c) Cornils, B., Herrmann, W. A. (Eds.), *Applied Homogeneous Catalysis with Organometallic Compounds*, VCH: Weinheim, **1996**; d) *Phosphorous Ligands in Asymmetric Catalysis*, Ed.: Börner, A., Wiley-VCH, Weinheim, **2008**.

[4] For reviews, see: a) Rakowski, M. *Chem. Rev.* **1989**, *89*, 1; b) Bayon, J. C.; Claver, C.; Masdeu-Bultó, A. M. *Coord. Chem. Rev.* **1999**, *193*, 73; c) Masdeu-Bultó, A. M.; Diéguez, M.; Martin, E.; Gómez, M. *Coord. Chem. Rev*. **2003**, *242*, 159; d) Pellisier, H. *Tetrahedron* **2007**, *63*, 1297; e) Mellah, M.; Voituriez, A.; Schulz, E. *Chem. Rev*. **2007**, *107*, 5133; f) Gomez, R.; Carretero, J. C. *Chem. Commun.* **2011**, *47*, 2207.

[5] a) Albinati, A.; Pregosin, P. S.; Wick, K. *Organometallics* **1996**, *15*, 2419; b) Enders, D.; Peters, R.; Runsink, J.; Bats, J. W. *Org. Lett.* **1999**, *1*, 1863; c) Enders, D.; Peters, R.; Lochtman,R.; Raabe, G.; Runsink, J.; Bats, J. W. *Eur. J. Org. Chem.* **2000**, 3399; d)

Tu, T.; Zhou, Y. G.; Hou, X. L.; Dai, L. X.; Dong, X. C.; Yu, Y. H.; Sun, J. *Organometallics* **2003**, *22*, 1255; e) Priego, J.; Garcia, O.; Cabrera, S.; Gomez, R.; Llamas, T.; Carretero, J. C. *Chem. Commun.* **2002**, 2512; f) Garcia, O.; Priego, J.; Cabrera, S.; Gomez, R.; Llamas, T.; Carretero, J. C. *J. Org. Chem.* **2003**, *68*, 3679; g) Routaboul, L.; Vincendeau, S.; Daran, J. C.; Manoury, E. *Tetrahedron: Asymmetry* **2005**, *16*, 2685; h) Roux. E. L.; Malacea, R.; Manoury, E.; Poli, R.; Gonsalvi, L.; Peruzzini, M. *Adv. Synth. Catal.* **2007**, *349*, 309; i) Lam. F. L.; Au-Yeung, T. T.L.; Cheung, H. Y.; Kok, S. H. L. ; Lam, W. S.; Wong, K. Y.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2006**, *17*, 497; j) Lam. F. L.; Au-Yeung, T. T. L.; Kwong, F. Y.; Zhou, Z.; Wong, K. Y.; Chan, A. S. C. *Angew. Chem. Int. Ed.* **2008**, *47*, 1280; k) Cheung, H. Y.; Yu, W. Y.; Lam, F. L.; Au-Yeung, T. T. L.; Zhou, Z.; Chan, T. H.; Chan, A. S. C. *Org. Lett.* **2007**, *9*, 4295.

[6] Hiroi, K.; Suzuki, Y.; Abe, I. *Tetrahedron: Asymmetry* **1999**, *10*, 1173.

[7] Yan, Y.-Y.; RajanBabu, T. V. *Org. Lett*. **2000**, *2*, 199.

[8] a) Nakano, H.; Okuyama, Y.; Yanagida, M.; Hongo, H. *J. Org. Chem.* **2001**, *66*, 620; b) Nakano, H.; Yokoyama, J.; Fujita, R.; Hongo, H. *Tetrahedron Lett.* **2002**, *43*, 7761; c) Nakano, H.; Yokohama, J.; Okuyama, Y.; Fujita, R.; Hongo, H. *Tetrahedron: Asymmetry* **2003**, *14*, 2361; d) Nakano, H.; Takahashi, K.; Suzuki, Y.; Fujita, R. *Tetrahedron: Asymmetry* **2005**, *16*, 609.

[9] Zhang, W.; Shi, M. *Tetrahedron: Asymmetry* **2004**, *15*, 3467.

[10] Molander, G. A.; Burke, J. P.; Carroll, P. J. *J. Org. Chem.* **2004**, *69*, 8062.

[11] Khiar, N.; Suárez, B.; Fernández, I. *Inorg. Chim. Acta* **2006**, *359*, 3048.

[12] Solà, J.; Revés, M.; Riera, A.; Verdaguer. X. *Angew. Chem. Int. Ed.* **2007**, *46*, 5020.

[13] a) Evans, D. A.; Campos, K. R.; Tedrow, J. R.; Michael, F. E.; Gagné, M. R. *J. Org. Chem.* **1999**, *64*, 2994; b) Evans, D. A.; Campos, K. R.; Tedrow, J. R.; Michael, F. E.; Gagné, M. R. *J. Am. Chem. Soc.* **2000**, *122*, 7905.

[14] Evans, D. A.; Michael, F. E.; Tedrow, J. S.; Campos, K. R. *J. Am. Chem. Soc.* **2003**, *125*, 3534.

[15] a) Khiar, N.; Suárez, B.; Stiller, M.; Valdivia, V.; Fernández, I. *Phosphorus Sulfur Silicon Relat. Elem.* **2005**, *180*, 1253; b) Khiar, N.; Suárez, B.; Valdivia, V.; Fernández, I. *Synlett* **2005**, 2963; c) Khiar, N.; Navas, R.; Suárez, B.; Álvarez, E.; Fernández, I. *Org. Lett*. **2008**, *10*, 3697.

[16] a) Guimet, E.; Diéguez, M.; Ruiz, A.; Claver, C. *Tetrahedron: Asymmetry* **2005**, *16*, 959; b) Diéguez, M.; Pàmies, O.; Claver, C. *J. Organomet. Chem*. **2006**, *691*, 2257.

[17] Guimet, E.; Diéguez, M.; Ruiz, A.; Claver, C. *Dalton Trans.* **2005**, 2557.

[18] Guimet, E.; Diéguez, M.; Ruiz, A.; Claver, C. *Tetrahedron: Asymmetry* **2005**, *16*, 2161.

[19] Caldentey, X.; Pericàs, M. A. *J. Org. Chem.* **2010**, *75*, 2628.

[20] a) Pàmies, O.; Van Strijdonck, G. P. F.; Diéguez, M.; Deerenberg, S.; Net, G.; Ruiz, A.; Claver, C.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *J. Org. Chem*. **2001**, *66*, 8867; b) Pàmies, O.; Diéguez, M.; Net, G.; Ruiz, A.; Claver, C. *Organometallics* **2000**, *19*, 1488; c) Diéguez, M.; Pàmies, O.; Net, G.; Ruiz, A.; Claver, C. *J. Mol. Catal. A: Chem*. **2002**, *185*, 11.

[21] T. Kanayama, Q. Yoshida, H. Miyabe, Y. Takemoto *Angew. Chem., Int. Ed.* **2003**, *42*, 2054.

[22] *Handbook of Homogeneous Hydrogenation*; de Vries, J. G.; Elsevier, C. J.; Eds.; Wiley-VCH: Weinheim, **2007**.

[23] a) Halpern, J.; Riley, D. P.; Chan, A. S. C.; Pluth, J. J. *J. Am. Chem. Soc*. **1977**, *99*, 8055; b) Chan, A. S. C.; Pluth, J. J.; Halpern, J. *J. Am. Chem. Soc*. **1980**, *102*, 5952; c) Wilczynski, R.; Fordyce, W. A.; Halpern, J. *J. Am. Chem. Soc.* **1983**, *105*, 2066; d) Landis, C. R.; Halpern, J. *J. Am. Chem. Soc.* **1987**, *109*, 1746; d) Brown, J. M. *Chem. Soc. Rev.* **1993**, *22*, 25; e) Giovannetti, J. S.; Kelly, C. M.; Landis, C. R. *J. Am. Chem. Soc.* **1993**, *115*, 4040; f) Kimmich, B. F.; Somsook, E.; Landis, C. R. *J. Am. Chem. Soc.* **1998**, *120*, 10115; g) Landis, C. R.; Brauch, T. W. *Inorg. Chim. Acta* **1998**, *270*, 285; h) Landis, C. R.; Hilfenaus, P.; Feldgus, S. *J. Am. Chem. Soc*. **1999**, *121*, 8741; i) Feldgus, S.; Landis, C. R. *J. Am. Chem. Soc.* **2000**, *122*, 12714; j) Landis, C. R.; Feldgus, S. *Angew. Chem. Int. Ed.* **2000**, *39*, 2863; k) Feldgus, S.; Landis, C. R. *Organometallics* **2001**, *20*, 2374.

[24] See for instance: a) Fernández-Pérez, H.; Donald, S. M. A.; Munslow, I. J.; Benet-Buchholz, J.; Maseras, F.; Vidal-Ferran, A. *Chem. Eur. J.* **2010**, *16*, 6495; b) Deerenberg, S.; Pàmies, O.; Diéguez, M.; Claver, C.; Kamer, P.C.J.; van Leeuwen, P.W.N.M. *J. Org. Chem*. **2001**, *66*, 7626; c) Pàmies, O.; Diéguez, M.; Net, G.; Ruiz, A.; Claver, C. *J. Org. Chem*. **2001**, *66*, 8364.

[25] Knowles, W. S.; Sabacky, M. J. *Chem Commun*. **1968**, 1445.

[26] Horner, L.; Siegel, H.; Büthe, H. Angew. *Chem. Int. Ed. Engl.* **1968**, *7*, 941.

[27] Osborn, J. A.; Jardine, F. H.; Young, J. F.; Wilkinson, G. *J. Chem. Soc. A* **1966**, 1711.

[28] Kagan, H. B.; Dang, T. P. *J. Am. Chem. Soc.* **1972**, *94*, 6429.

[29] Knowles, W. S.; Sabacky, M. J.; Vineyard, B. D. *J. Chem. Soc. Chem. Commun.* **1972**, 10.

[30] Knowles, W. S. *J. Chem. Educ.* **1986**, *63*, 222.

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

[32] a) Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029; b) Zhang, W.; Chi, Y.; Zhang, X. *Acc. Chem. Res.* **2007**, *40*, 1278; c) Xie, J. H.; Zhou, Q. L. *Acc. Chem. Res*. **2008**, *41*, 581.

[33] a) Miyashita, A.; Yashuda, A.; Takaya, H.; Toriumi, K.; Ito, T.; Souchi, T.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 7932; b) Noyori, R. *Science* **1990**, *248*, 1194.

[34] a) Nugent, W. A.; RajanBabu, T. V.; Burk, M. J. *Science* **1993**, *259*, 479. b) Burk, M. J. *Acc. Chem. Res.* **2000**, *33*, 363.

[35] van Leeuwen, P.W.N.M.; Kamer, P.C.J.; Claver, C.; Pàmies, O.; Diéguez, M. *Chem. Rev.* **2011**, *111*, 2077.

[36] Fernández-Pérez, H.; Etayo, P.; Panossian, A.; Vidal-Ferran, A. *Chem. Rev.* **2011**, *111*, 2119.

[37] See for intance: a) Peña, D.; Minnaard, A.; de Vries, J. G.; Feringa, L. J. *J. Am. Chem. Soc.* **2002**, *124*, 14552; b) Reetz, M. T.; Sell, T.; Meiswinkel, A.; Mehler, G. *Angew. Chem. Int. Ed.* **2003**, *42*, 790; c) Claver, C.; Fernandez, E.; Gillon, A.; Heslop, K.; Hyett, D. J.; Martorell, A.; Orpen, A. G.; Pringle, P. G. *Chem. Commun*. **2000**, 961; d) Reetz, M: T.; Mehler, G.; Meiswinkel, A.; Sell, T. *Tetrahedron Lett.* **2002**, *43*, 7941.

[38] a) Yan, Y. Y.; RajanBabu, T. V. *Org. Lett.* **2000**, *2*, 4137; b) Li, W.; Zhang, X. *J. Org. Chem.* **2000**, *65*, 5871; c) Zhang, X. US Patent WO 01/34612 A2, **2001**.

[39] Li, W.; Waldkirch, J. P.; Zhang, X. *J. Org. Chem*. **2002**, *67*, 7618.

[40] a) Holz, J.; Quirmbach, M.; Schmidt, U.; Heller, D.; Stürmer, R.; Börner, A. *J. Org. Chem.* **1998**, *63*, 8031; b) Li, W.; Zhang, Z.; Xiao, D.; Zhang, X. *J. Org. Chem*. **2000**, *65*, 3489; c) Liu, D.; Li, W.; Zhang, X. *Org. Lett*. **2002**, *4*, 4471; d) Zhang, X. Patent WO 03/040149 A2, **2003**.

[41] Bayer, A.; Murszat, P.; Thewalt, U.; Rieger, B. *Eur. J. Inorg. Chem.* **2002**, 2614.

[42] Holz, J.; Stürmer, R.; Schmidt, U.; Drexler, H. J.; Heller, D.; Krimmer, H. P.; Börner, A. *Eur. J. Org. Chem*. **2001**, 4615.

[43] Carmichael, D.; Doucet, H.; Brown, J. M. *Chem. Commun*. **1999**, 261.

[44] a) Pàmies, O.; Net, G.; Ruiz, A.; Claver, C. *Eur. J. Inorg. Chem*. **2000**, 2011; b) Diéguez, M.; Pàmies, O.; Ruiz, A.; Castillón, S.; Claver, C. *Tetrahedron: Asymmetry* **2000**, *11*, 4701.

[45] Wong, Y. T.; Yang, C.; Ying, K-C.; Jia, G. *Organometallics* **2002**, *21*, 1782.

[46] Cullen, W. R.; Sugi, Y. *Tetrahedron Lett.* **1978**, 1635.

[47] Jackson, R.; Thompson, D. J. *J. Organomet. Chem.* **1978**, *159*, C29.

[48] Selke, R. *React. Kinet. Catal. Lett.* **1979**, *10*, 135.

[49] Sinou, D.; Descotes, G. *React. Kinet. Catal. Lett.* **1980**, *14*, 463.

[50] a) Selke, R.; Pracejus, H. *J. Mol. Catal.* **1986**, *37*, 213; b) Selke, R. *J. Prakt. Chem.* **1987**, *329*, 717; c) Selke, R. *J. Organomet. Chem.* **1989**, *370*, 249; d) Selke, R.; Schwarze, M.; Baudisch, H.; Grassert, I.; Michalik, M.; Oehme, G.; Stoll, N.; Costisella, B. *J. Mol. Catal.* **1993**, *84*, 223.

[51] a) RajanBabu, T. V.; Ayers, T. A.; Casalnuovo, A. L. *J. Am. Chem. Soc.* **1994**, *116*, 4101; b) RajanBabu, T. V.; Ayers, T. A.; Halliday, G. A.; You, K. K.; Calabrese, J. C. *J. Org. Chem.* **1997**, *62*, 6012; c) Ayers, T. A.; RajanBabu, T. V. US Patent 5510507, **1996**.

[52] Guimet, E.; Diéguez, M.; Ruiz, A.; Claver, C. *Tetrahedron: Asymmetry* **2004**, *15*, 2247.

[53] Guiu, E.; Muñoz, B.; Castillón, S.; Claver, C. *Adv. Synth. Catal.* **2003**, *345*, 169.

[54] Aghmiz, M.; Aghmiz, A.; Díaz, Y.; Masdeu-Bultó, A.; Claver, C.; Castillón, S. *J. Org. Chem.* **2004**, *69*, 7502.

[55] Guiu, E.; Aghmiz, M.; Díaz, Y.; Claver, C.; Meseguer, B.; Militzer, C.; Castillón, S. *Eur. J. Org. Chem*. **2006**, 627.

[56] Reetz, M. T.; Neugebauer, T. *Angew. Chem. Int. Ed.* **1999**, *38*, 179.

[57] a) Pàmies, O.; Net, G.; Ruiz, A.; Claver, C. *Eur. J. Inorg. Chem.* **2000**, 1287; b) Pàmies, O.; Net, G.; Ruiz, A.; Claver, C. *Tetrahedron: Asymmetry* **2000**, *11*, 1097; c) Diéguez, M.; Ruiz, A.; Claver, C. *J. Org. Chem*. **2002**, *67*, 3796.

[58] Axet, M. R.; Benet-Buchholz, J.; Claver, C.; Castillón, S. *Adv. Synth. Catal*. **2007**, *349*, 1983.

[59] Engeldinger, E.; Armspach, D.; Matt, D.; Toupet, L.; Wesolek, M. *C. R. Chim*. **2002**, 359.

[60] Reetz, M. T.; Mehler, G. *Angew. Chem. Int. Ed.* **2000**, *39*, 3889.

[61] a) Reetz, M. T.; Goosen, L. J.; Meiswinkel, A.; Paetzol, J.; Jensen, J. F. *Org. Lett*. **2003**, *5*, 3099; b) Huang, H.; Zheng, Z.; Luo, H.; Bai, C.; Hu, X.; Chen, H. *Org. Lett*. **2003**, *5*, 4137; c) Huang, H.; Liu, X.; Chen, S.; Chen, H.; Zheng, Z. *Tetrahedron: Asymmetry* **2004**, *15*, 2011; d) Huang, H.; Zheng, Z.; Luo, H.; Bai, C.; Hu, X.; Chen, H. *J. Org. Chem*. **2004**, *69*, 2335; e) Huang, H.; Liu, X.; Chen, H.; Zheng, Z. *Tetrahedron: Asymmetry* **2005**, *16*, 693.

[62] Bayer, A.; Murszat, P.; Thewalt, U.; Rieger, B. *Eur. J. Inorg. Chem*. **2002**, *10*, 2614.

[63] Pàmies, O.; Diéguez, M.; Net, G.; Ruiz, A.; Claver, C. *Chem. Commun*. **2000**, 2383.

[64] Diéguez, M.; Ruiz, A.; Claver, C. *Chem. Commun*. **2001**, 2702.

[65] For recent reviews, see: a) Cui, X.; Burgess, K. *Chem. Rev*. **2005**, *105*, 3272; b) Källström, K. ; Munslow, I.; Andersson, P. G. *Chem. Eur. J.* **2006**, *12*, 3194; c) Roseblade, S. J.; Pfaltz, A. *Acc. Chem. Res*. **2007**, *40*, 1402; d) Church, T. L.; Andersson, P. G. *Coord. Chem. Rev.* **2008**, *252*, 513; e) Pàmies, O.; Andersson, P. G.; Diéguez, M. *Chem. Eur. J.* **2010**, *16*, 14232.

[66] a) Roseblade, S. J.; Pfaltz, A. *C. R. Chim.* **2007**, *10*, 178; b) Vazquez-Serrano, L. D.; Owens, B. T.; Buriak, J. M. *Chem. Commun.* **2002**, 2518.

[67] a) Cui, X.; Fan, Y.; Hall, M. B.; Burgess, K. *Chem. Eur. J.* **2005**, *11*, 6859; b) Fan, Y.; Cui, X.; Burgess, K.; Hall, M. B. *J. Am. Chem. Soc.* **2004**, *126*, 16688; c) Brandt, P.; Hedberg, C.; Andersson, P. G. *Chem. Eur. J.* **2003**, *9*, 339.

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

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

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

[71] For reviews on phosphine-oxazoline ligands, see: a) Pfaltz, A. *J. Heterocycl. Chem.* **1999**, *36*, 1437; b) Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000**, *33*, 336; c) Pfaltz, A.; Drury III, W. J. *Proc. Natl. Acad. Sci. U. S. A.* **2004**, *101*, 5723.

[72] Crabtree, R. H. *Acc. Chem. Res.* **1979**, *12*, 331.

[73] Schnider, P.; Koch, G.; Prétôt, R.; Wang, G.; Bohnen, F. M.; Krüger, C.; Pfaltz, A. *Chem. Eur. J.* **1997**, *3*, 887.

[74] See for instance: a) Tang, W.; Wang, W.; Zhang, X. *Angew. Chem. Int. Ed.* **2003**, *42*, 943; b) Hou, D.-R.; Reibenspies, J.; Colacot, T. J.; Burgess, K. *Chem. Eur. J.* **2001**, *7*, 5391; c) Cozzi, P. G.; Menges, F.; Kaiser, S. *Synlett* **2003**, 833; d) Lighfoot, A.; Schnider, P.; Pfaltz, A. *Angew. Chem. Int. Ed*. **1998**, *37*, 2897; e) Menges, F.;

Neuburger, M.; Pfaltz, A. *Org. Lett.* **2002**, *4*, 4713; f) Liu, D.; Tang, W.; Zhang, X. *Org. Lett*. **2004**, *6*, 513; g) Drury III, W. J.; Zimmermann, N.; Keenan, M.; Hayashi, M.; Kaiser, S.; Goddard, R.; Pfaltz, A. *Angew. Chem. Int. Ed*. **2004**, *43*, 70; h) Cheruku, P.; Gohil, S.; Andersson. P. G. *Org. Lett*. **2007**, *9*, 1659.

[75] Chiral diphosphines have been used but with less success. See for instance: a) Co, T. T.; Kim, T. J. *Chem. Commun.* **2006**, 3537; b) Forman, G. S.; Ohkuma, T.; Hems, W. P.; Noyori, R. *Tetrahedron Lett.* **2000**, *41*, 9471.

[76] See for instance: a) Perry, M. C.; Cui, X.; Powell, M. T.; Hou, D.-R.; Reibenspies, J. H.; Burgess, K. *J. Am. Chem. Soc.* **2003**, *125*, 5391; b) Blankestein, J.; Pfaltz, A. *Angew. Chem. Int. Ed.* **2001**, *40*, 4445; c) Kaiser, S.; Smidt, S. P.; Pfaltz, A. *Angew. Chem. Int. Ed.* **2006**, *45*, 5194; d) Källström, K.; Hedberg, C.; Brandt, P.; Bayer, P.; Andersson, P. G. *J. Am. Chem. Soc.* **2004**, *126*, 14308; e) Engman, M.; Diesen, J. S.; Paptchikhine, A.; Andersson, P. G. *J. Am. Chem. Soc*. **2007**, *129*, 4536; f) Trifonova, A.; Diesen, J. S.; Andersson, P. G. *Chem. Eur. J.* **2006**, *12*, 2318; g) Menges, F.; Pflatz, A. *Adv. Synth. Catal.* **2002**, *334*, 40; h) Hedberg, C.; Källström, K.; Brandt, P.; Hansen, L. K.; Andersson, P. G. *J. Am. Chem. Soc*. **2006**, *128*, 2995.

[77] a) Diéguez, M.; Mazuela, J.; Pàmies, O.; Verendel, J. J.; Andersson, P. G. *J. Am. Chem. Soc.* **2008**, *130*, 7208; b) Diéguez, M.; Mazuela, J.; Pàmies, O.; Verendel, J. J.; Andersson, P. G. *Chem. Commun.* **2008**, 3888; c) Mazuela, J.; Verendel, J. J.; Coll, M.; Schäffner, B.; Börner, A.; Andersson, P. G.; Pàmies, O.; Diéguez, M. *J. Am. Chem. Soc.* **2009**, *131*, 12344; d) Mazuela, J.; Paptchikhine, A.; Pàmies, O.; Andersson, P. G.; Diéguez, M. *Chem. Eur. J.* **2010**, *16*, 4567.

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

[79] Wu, X.; Wang, C.; Xiao, J. *Platinum Metals Rev.* **2010**, *54*, 3.

[80] a) Zassinovich, G.; Mestroni, G.; Gladiali, S. *Chem. Rev*. **1992**, *92*, 1051; b) Bäckvall, J. E.; Chowdhury, R. L.; Karlsson, U.; Wang, G. Z. in "*Perspective in Coordination Chemistry*", Eds. Williams, A. F.; Floriani, C.; Merbach, A. E. Verlag Helvetica Chimica Acta, Basel, **1992**, pp. 463-486; c) Chaloner, P. A.; Esterulas, M. A.; Joo, F.; Oro, L. A. *Homogeneous Hydrogenation*, Kluwer Academic Publishers, Dordrecht, The Netherlands, **1994**, pp 87-118; d) Gladiali, S.; Mestroni, G. in *Transition Metals for Organic Synthesis*. Eds.; Beller, M.; Bolm, C. Wiley VCH: Weinheim, **1998**, 97-119; e) Noyori, R.; Hashiguchi, S. *Acc. Chem. Res.* **1997**, *30*, 97; f) Naota, T.; Takaya, H.;

Murahashi, S. I. *Chem. Rev.* **1998**, *98*, 2599; g) Gladiali, S.; Alberico, E. *Chem. Soc. Rev.* **2006**, *35*, 226; h) Wang, C.; Wu, X.; Xiao, J. *Chem. Asian J.* **2008**, *3*, 1750.

[81] a) Siegel, H.; Himmele, W. *Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 178; b) Botteghi, C.; Paganelli, S.; Schionato, A.; Marchetti, M. *Chirality* **1991**, *3*, 355.

[82] a) Meerwein, H.; Schmidt, R. *Liebigs Ann. Chem*., **1925**, *444*, 221; b) Verley, A. *Bull. Soc. Chem. Fr.* **1925**, *37*, 537; c) Ponndorf, W. *Angew. Chem.* **1926**, *39*, 138.

[83] a) Oppenauer, R. V. *Recl. Trav. Chim. Pays-Bas* **1937**, *56*, 137; b) de Graauw, C. F.; Peters, J. A.; van Bekkum, H.; Huskens, J. *Synthesis* **1994**, 1007.

[84] See, for instance: a) Casey, C. P.; Guan, H. *J. Am. Chem. Soc.* **2007**, *129*, 5816; b) Zhou, S.; Fleischer, S.; Junge, K.; Das, S.; Addis, D.; Beller, M. *Angew. Chem. Int. Ed.* **2010**, *49*, 8121; c) Mikhailine, A. A.; Morris, R. H. *Inorg. Chem.* **2010**, *49*, 11039; d) Naik, A.; Maji, T.; Reiser, O. *Chem. Commun.* **2010**, *46*, 4475; e) Mikhailine, A.; Lough, A. L.; Morris, R. H. *J. Am. Chem. Soc.* **2009**, *131*, 1394.

[85] a) Bäckvall, J.-E. *J. Organomet. Chem.* **2002**, *652*, 105; b) Samec, J. S. M.; Bäckvall, J.-E.; Andersson, P. G.; Brandt, P. *Chem. Soc. Rev*. **2006**, *35*, 237; c) Pàmies, O.; Bäckvall, J.-E. *Chem. Eur. J.* **2001**, *7*, 5052; d) Palmer, M. J.; Wills, M. *Tetrahedron: Asymmetry* **1999**, *10*, 2045.

[86] See for example: a) Haack, K. J.; Hashiguchi, S.; Fujii, A.; Ikariya, T.; Noyori, R. *Angew. Chem. Int. Ed.* **1997**, *36*, 285; b) Alonso, D. A.; Brandt, P.; Nordin, S. J. M.; Andersson, P. G. *J. Am. Chem. Soc*. **1999**, *121*, 9580; c) Yamakawa, M.; Ito, H.; Noyori, R. *J. Am. Chem. Soc.* **2000**, *122*, 1466; d) Petra, D. G. I.; Reek, J. N. H.; Handgraaf, J. W.; Meijer, E. J.; Dierkes, P.; Kamer, P. C. J.; Brussee, J.; Schoemaker, H. S.; van Leeuwen, P. W. N. M. *Chem. Eur. J*. **2000**, *6*, 2818.

[87] a) Wettergren, J.; Buitrago, E.; Ryberg, P.; Adolfsson, H. *Chem. Eur. J.* **2009**, *15*, 5709; b) Västilä, P.; Zaitsev, A. B.; Wettergren, J.; Privalov, T.; Adolfsson, H. *Chem. Eur. J.* **2006**, *12*, 3218.

[88] a) Bianchi, M.; Matteoli, U.; Menchi, G.; Frediani, P.; Pratesi, S.; Piacenti, F.; Bottegi, C. *J. Organomet. Chem.* **1980**, *198*, 73; b) Spogliarichi, R.; Kaspar, J.; Graziani, M.; Morandini, F. *J. Organomet. Chem.* **1986**, *306*, 407; c) Krause, H. W.; Bhatnagar, A. K. *J. Organomet. Chem.* **1986**, *302*, 407.

[89] a) Fujii, A.; Hashiguchi, S.; Uematsu, N.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc*. **1996**, *118*, 2521; b) Hashiguchi, S.; Fujii, A.; Takehara, J.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 7562; c) Uematsu, N.; Fujii, A.; Hashiguchi, S.; Ikariya, T.;

Noyori, R. *J. Am. Chem. Soc*. **1996**, *118*, 4916; d) Matsumura, K.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc*. **1997**, *119*, 8738; e) Murata, K.; Okano, K.; Miyagi, M.; Iwane, H.; Noyori, R.; Ikariya, T. *Org. Lett*. **1999**, *1*, 1119; f) Yamada, I.; Noyori, R. *Org. Lett.* **2000**, *2*, 3425.

[90] See, for example: a) Matsunaga, H.; Ishizuka, T.; Kunieda, T. *Tetrahedron Lett*. **2005**, *46*, 3645; b) Hannedouche, J.; Clarkson, G. J.; Wills, M. *J. Am. Chem. Soc.* **2004**, *126*, 986; c) Hayes, A. M.; Morris, D. J.; Clarkson, G. J.; Wills, M. *J. Am. Chem. Soc.* **2005**, *127*, 7318; d) Cheung, F. K.; Hayes, A. M.; Hannedouche, J.; Yim, A. S. Y.; Wills, M. *J. Org. Chem.* **2005**, *70*, 3188; e) Cheung, F. K.; Lin, C.; Minissi, F.; Lorente, C. A.; Graham, M. A.; Fox, D. J.; Wills, M. *Org. Lett.* **2007**, *9*, 4659.

[91] For water-soluble ligand modifications, see: a) Thorpe, T.; Blacker, J.; Brown, S. M.; Bubert, C.; Crosby, J.; Fitzjohn, S.; Muxworthy, J. P.; Williams, J. M. J. *Tetrahedron Lett.* **2001**, *42*, 4041; b) Bubert, C.; Blacker, J.; Brown, S. M.; Crosby, J.; Fitzjohn, S.; Muxworthy, J. P.; Thorpe, T.; Williams, J. M. J. *Tetrahedron Lett.* **2001**, *42*, 4037; c) Barrón-Jaime, A.; Narvaez-Garayzar, O. F.; Gonzáles, J.; Ibarra-Galván, V.; Aguirre, G.; Parra-Hake, M.; Chávez, D.; Somanathan, R. *Chirality* **2011**, *23*, 178; d) Zhou, Z.; Ma, Q.; Sun, Y.; Zhang, A.; Li, L. *Heteroat. Chem.* **2010**, *21*, 505; e) Zhou, Z.; Sun, Y. *Catal. Commun.* **2009**, *10*, 1685; f) Ma, Y.; Liu, H.; Chen, L.; Cui, X.; Zhu, J.; Deng, J. *Org. Lett.* **2003**, *5*, 2103.

[92] See, for instance: a) Takehara, J.; Hashiguchi, S.; Fujii, A.; Inoue, S.; Ikariya, T.; Noyori, R. *J. Chem. Soc., Chem. Commun.* **1996**, 233; b) Nordin, S. J. M.; Roth, P.; Tarnai, T.; Alonso, D. A.; Brandt, P.; Andersson, P. G. *Chem. Eur. J.* **2001**, *7*, 1431; c) Palmer, M.; Walsgrove, T.; Wills, M. *J. Org. Chem.* **1997**, *62*, 5226.

[93] a) Cuervo, D.; Gamasa, M. P.; Gimeno, J. *Chem. Eur. J.* **2004**, *10*, 425; b) Baratta, W.; Benedetti, F.; Del Zotto, A.; Fanfoni, L.; Felluga, F.; Magnolia, S.; Putignano, E.; Rigo, P. *Organometallics* **2010**, *29*, 3563; c) Baratta, W.; Bosco, M.; Chelucci, G.; Del Zotto, A.; Siega, K.; Toniutti, M.; Zangrando, E.; Riego, P. *Organometallics* **2006**, *25*, 4611; d) Baratta, W.; Chelucci, G.; Gladiali, S.; Siega, K.; Toniutti, M.; Zanette, M.; Zangrando, E.; Rigo, P. *Angew. Chem. Int. Ed.* **2005**, *44*, 6214.

[94] Reetz, M. T.; Li, X. *J. Am. Chem. Soc.* **2006**, *128*, 1044.

[95] Gao, J-X.; Ikariya, T.; Noyori, R. *Organometallics* **1996**, *15*, 1087.

[96] a) Pastor, I. M.; Adolfsson, H. *Tetrahedron Lett*. **2002**, *43*, 1743; b) Västilä, P.; Pastor, I. M.; Adolfsson, H. *J. Org. Chem.* **2005**, *70*, 2921; c) Pastor, I. M.; Västilä, P.; Adolfsson, H. *Chem. Commun.* **2002**, 2046.

[97] a) Zaitsev, A. B.; Adolfsson, H. *Org. Lett.* **2006**, *8*, 5129; b) Ahlford, K.; Livendahl, M.; Adolfsson, H. *Tetrahedron Lett.* **2009**, *50*, 6321; c) Tinnis, F.; Adolfsson, H. *Org. Biomol. Chem.* **2010**, *8*, 4536; d) Wettergren, J.; Zaitsev, A. B.; Adolfsson, H. *Adv. Synth. Catal.* **2007**, *349*, 2556.

[98] a) Schlatter, A.; Kundu M. K.; Woggon, W.-D. *Angew. Chem. Int. Ed.* **2004**, *43*, 6731; b) Schlatter, A.; Woggon, W.-D. *Adv. Synth. Catal.* **2008**, *350*, 995.

[99] Guillarme, S. ; Mai Nguyen, T. X. ; Saluzzo, C. *Tetrahedron : Asymmetry* **2008**, *19*, 1450.

[100] Huynh, K. D.; Ibrahim, D.; Toffano, M.; Vo-Thanh, G. *Tetrahedron: Asymmetry* **2010**, *21*, 1542.

[101] See, for instance: a) Tsuji, J. *Palladium Reagents and Catalysis, Innovations in Organic Synthesis*; Wiley: New York, **1995**; b) Trost, B. M.; van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395; c) Johannsen, M.; Jorgensen, K. A. *Chem. Rev.* **1998**, *98*, 1689; d) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921; e) Martin, E.; Diéguez, M. *C. R. Chemie* **2007**, *10*, 188; f) Lu, Z.; Ma, S. *Angew. Chem. Int. Ed.* **2008**, *47*, 258.

[102] Trost, B. M.; Strege, P. E. *J. Am. Chem. Soc.* **1977**, *99*, 1649.

[103] Trost, B. M. *Acc. Chem. Res.* **1996**, *29*, 355.

[104] a) Diéguez, M.; Jansat, S.; Gómez, M.; Ruiz, A.; Muller, G.; Claver, C. *Chem. Commun.* **2001**, 1132; b) Pàmies, O.; Ruiz, A.; Net, G.; Claver, C.; Kalchhauser, H.; Widhalm, M. *Monatsh. Chem*. **2000**, *131*, 1173.

[105] a) Ruffo, F.; Del Lito, R.; De Roma, A.; D'Errico, A.; Magnolia, S. *Tetrahedron: Asymmetry* **2006**, *17*, 2265; b) Benessere, V.; De Roma, A.; Ruffo, F. *ChemSusChem* **2008**, *1*, 425.

[106] Seebach, D.; Devaquet, E.; Ernst, A.; Hayakawa, M.; Kühnle. F. N. M.; Schweizer, W. B.; Weber, B. *Helv. Chim. Acta* **1995**, *78*, 1636.

[107] Nomura, N.; Mermet-Bouvier, Y. C.; RajanBabu, T. V. *Synlett* **1996**, 745.

[108] Clyne, D. S.; Mermet-Bouvier, Y. C.; Nomura, N.; RajanBabu, T. V. *J. Org. Chem.* **1999**, *64*, 7601.

[109] Diéguez, M.; Pàmies, O.; Claver, C. *Adv. Synth. Catal*. **2005**, *347*, 1257.

[110] a) Jansat, S.; Gómez, M.; Philippot, K.; Muller, G.; Guiu, E.; Claver, C.; Castillón, S.; Chaudret, B. *J. Am. Chem. Soc.* **2004**, *126*, 1592; b) Favier, I.; Gómez, M.; Muller, G.; Axet, M. R.; Castillón, S.; Claver, C.; Jansat, S.; Chaudret, B.; Philippot, K. *Adv. Synth. Catal.* **2007**, *349*, 2459.

[111] Balanta, A.; Favier, I.; Teuma, E.; Castillón, S.; Godard, C.; Aghmiz, A.; Claver, C.; Gómez, M. *Chem. Commun*. **2008**, 6197.

[112] Gual, A.; Castillón, S.; Pàmies, O.; Diéguez, M.; Claver, C. *Dalton Trans*. **2011**, *40*, 2852.

[113] See for instance: a) Feringa, B. L. *Acc. Chem. Res.* **2000**, *33*, 346; b) Jagt, R. B. C.; Toullec, P. Y.; Geerdink, D.; de Vries, J. G.; Feringa, B. L.; Minnaard, A. J. *Angew. Chem. Int. Ed.* **2006**, *45*, 2789; c) Tissot-Croset, K.; Polet, D.; Alexakis, A. *Angew. Chem. Int. Ed.* **2004**, *43*, 2426; d) Polet, D.; Alexakis, A.; Tissot-Croset, K.; Corminboeuf, C.; Ditrich, K. *Chem. Eur. J.* **2006**, *12*, 3596; e) Boele, M. D. K.; Kamer, P. C. J.; Lutz, M.; Spek, A. L.; de Vries, J. G.; van Leeuwen, P. W. N. M.; van Strijdonck, G. P. F. *Chem. Eur. J.* **2004**, *10*, 6232; f) Pàmies, O.; Diéguez, M. *Chem. Eur. J.* **2008**, *14*, 944; g) Biswas, K.; Prieto, O.; Goldsmith, P. J.; Woodward, S. *Angew. Chem. Int. Ed.* **2005**, *44*, 2232; h) Alexakis, A.; Benhaim, C.; Rosset, S.; Humam, M. *J. Am. Chem. Soc.* **2002**, *124*, 5262.

[114] Raluy, E.; Diéguez, M.; Pàmies, O. *J. Org. Chem.* **2007**, *72*, 2842.

[115] a) Khiar, N.; Araújo, C. S.; Alvarez, E.; Fernández, I. *Tetrahedron Lett.* **2003**, *44*, 3401; b) Khiar, N.; Araújo, C. S.; Suárez, B.; Fernández, I. *Eur. J. Org. Chem.* **2006**, 1685.

[116] Barbaro, P.; Currao, A.; Herrmann, J.; Nesper, R.; Pregosin, P. S.; Salzmann, R. *Organometallics* **1996**, *15*, 1879.

[117] Khiar, N.; Navas, R.; Alvarez, E.; Fernández, I. *Arkivoc* **2008**, 211.

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

[119] a) Borriello, C.; Cucciolito, M. E.; Panunzi, A.; Ruffo, F. *Inorg. Chim. Acta.* **2003**, *353*, 238; b) Brunner, H.; Schönherr, M.; Zabel, M. *Tetrahedron: Asymmetry* **2003**, *14*, 1115; c) Johannensen, S. A.; Glegola, K.; Sinou, D.; Framery, E.; Skrydstrup, T. *Tetrahedron Lett.* **2007**, *48*, 3569; d) Glegola, K.; Johannensen, S. A.; Thim, L.; Goux-Henry, C.; Skrydstrup, T.; Framery, E. *Tetrahedron Lett.* **2008**, *49*, 6635.

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

[121] Yonehara, K.; Hashizume, T.; Mori, K.; Ohe, K.; Uemura, S. *J. Org. Chem.* **2000**, *65*, 5197.

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

[123] a) Mata, Y.; Diéguez, M.; Pàmies, O.; Claver, C. *Adv. Synth. Catal*. **2005**, *347*, 1947; b) Mata, Y.; Pàmies, O.; Diéguez, M. *Adv. Synth. Catal.* **2009**, *351*, 3217.

[124] a) Pàmies, O.; Diéguez, M.; Claver, C. *J. Am. Chem. Soc*. **2005**, *127*, 3646; b) Diéguez, M.; Pàmies, O. *Chem. Eur. J.* **2008**, *14*, 3653.

[125] Diéguez, M.; Pàmies, O.; Mata, Y.; Teuma, E.; Gómez, M.; Ribaudo, F.; van Leeuwen, P. W. N. M. *Adv. Synth. Catal.* **2008**, *350*, 2583.

[126] Hildraf, R.; Pfaltz, A. *Synlett* **1999**, 1814.

[127] a) Tollabi, M.; Framery, E.; Goux-Henry, C.; Sinou, D. *Tetrahedron: Asymmetry* **2003**, *14*, 3329; b) Konovets, A.; Glegola, K.; Penciu, A.; Framery, E.; Jubault, P.; Goux-Henry, C.; Pietrusiewicz, K. M.; Quirion, J. C.; Sinou, D. *Tetrahedron: Asymmetry* **2005**, *16*, 3183; c) Glegola, K.; Framery, E.; Goux-Henry, C.; Pietrusiewicz, K. M.; Sinou, D. *Tetrahedron* **2007**, *63*, 7133; d) Bauer, T.; Bartoszewicz, A. *Polish J. Chem.* **2007**, *81*, 2115.

[128] a) Benessere, V.; Ruffo, F. *Tetrahedron: Asymmetry* **2010**, *21*, 171; b) Benessere, V.; Lega, M.; Silipo, A.; Ruffo, F. *Tetrahedron* **2011**, *67*, 4826.

[129] Benessere, V.; De Roma, A.; Del Litto, R.; Lega, M. Ruffo, F. *Eur. J. Org. Chem.* **2011**, 5779.

[130] a) Raluy, E.; Claver, C.; Pàmies, O.; Diéguez, M. *Org. Lett*. **2007**, *9*, 49; b) Raluy, E.; Pàmies, O.; Diéguez, M. *Adv. Synth. Catal*. **2009**, *351*, 1648.

[131] Mata, Y.; Diéguez, M.; Pàmies, O.; Claver, C. *Tetrahedron: Asymmetry* **2006**, *17*, 3282.

[132] Boog-Wick, K.; Pregosin, P. S.; Trabesinger, G. *Organometallics* **1998**, *17*, 3254.

UNIVERSITAT ROVIRA I VIRGILI
SUGAR-BASED LIGAND LIBRARIES FOR ASYMMETRIC REDUCTIONS AND C-C BOND FORMING REACTIONS
M. Mercè Coll Serrahima
DL:T. 150-2012

CHAPTER 2

Objectives

UNIVERSITAT ROVIRA I VIRGILI
SUGAR-BASED LIGAND LIBRARIES FOR ASYMMETRIC REDUCTIONS AND C-C BOND FORMING REACTIONS
M. Mercè Coll Serrahima
DL:T. 150-2012

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 furanoside phosphite-phosphoroamidite and diphosphoroamidite (**L1-L5a-f**, Figure 2.1) ligand library in the asymmetric Rh-catalyzed hydrogenation of α,β-unsaturated carboxylic acid derivatives and enamides.

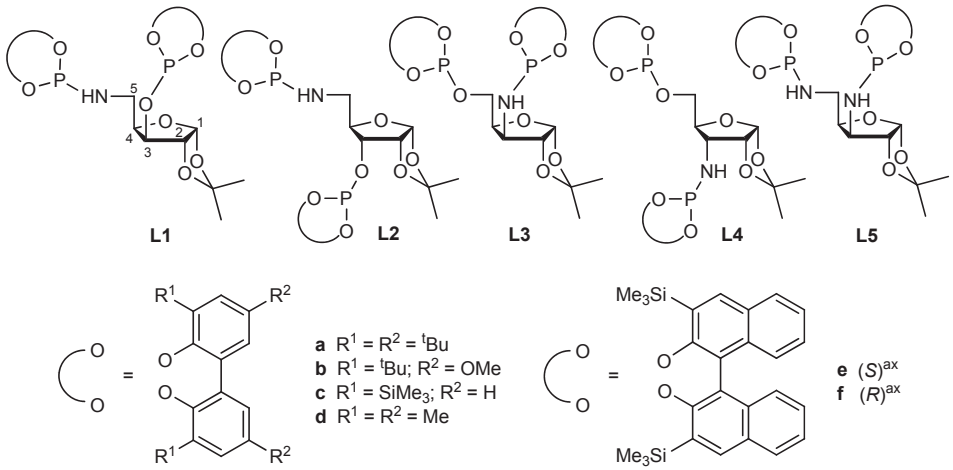


Figure 2.1. Furanoside phosphite-phosphoroamidite and diphosphoroamidite ligand library **L1-L5a-f**.

2. To synthesize and apply furanoside thioether-phosphite (**L6-L20a-h**), thioether-phosphinite (**L6-L20i**) and thioether-phosphoroamidite (**L21-L26a-f**) ligand libraries (Figure 2.2) in the asymmetric Ir-catalyzed hydrogenation of minimally functionalized olefins and in Pd-allylic substitution reactions. For purposes of comparison we also prepared and screened cyclohexane-based thioether-phosphite ligands (**L27a-c**), the backbone of which is one of the privileged ligand skeletons for P,S-ligands.

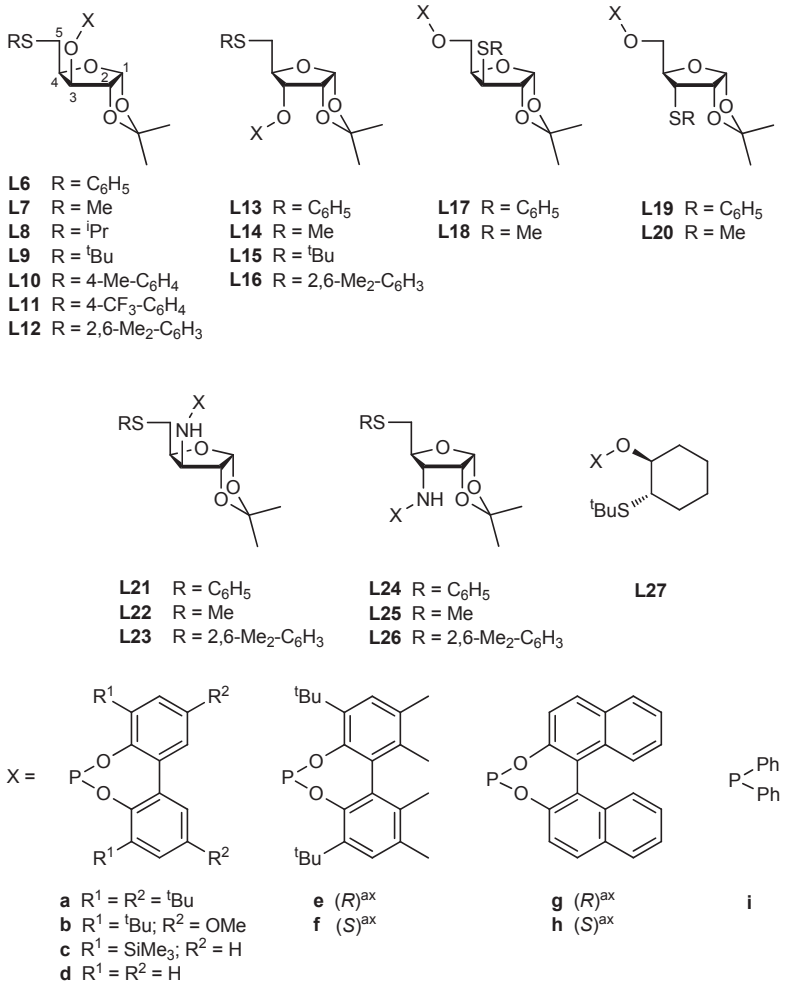
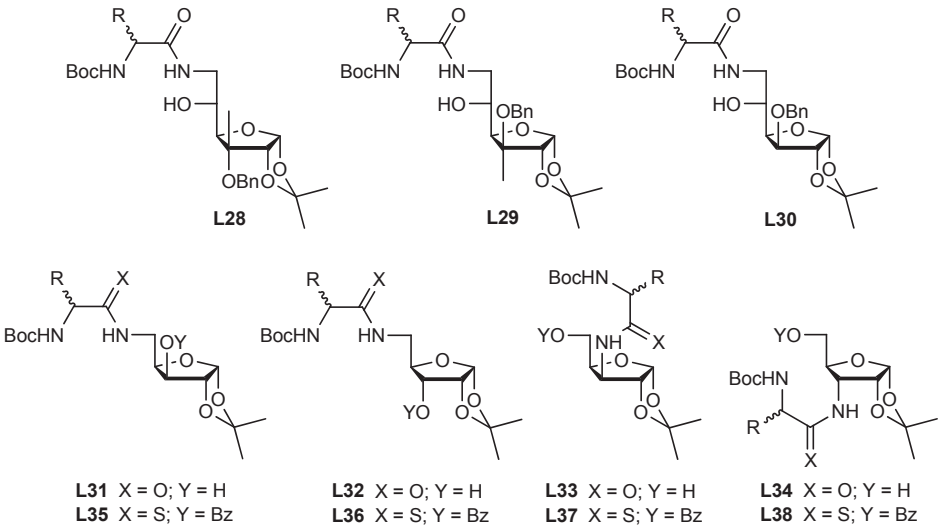


Figure 2.2. Heterodonor P,S ligands **L6-L27a-i** developed for this thesis.

3. To synthesize and apply carbohydrate-based pseudo-dipeptide (**L28-L30a-i** and **L31-L34a-i**) and thioamide (**L35-L38a-i**) ligand libraries (Figure 2.3) in the asymmetric Ru- and Rh-catalyzed transfer hydrogenation of several ketones.



a R = (*S*)-^{i}Pr; **b** R = (*S*)-Ph; **c** R = (*S*)-Bn; **d** R = (*S*)-^{i}Bu; **e** R = (*S*)-^{t}Bu;
f R = (*S*)-Me; **g** R = H; **h** R = (*R*)-^{i}Pr; **i** R = (*R*)-Ph

Figure 2.3. Carbohydrate-based pseudo-dipeptide and thioamide ligand libraries **L28**-**L38a-i** developed for this thesis.

UNIVERSITAT ROVIRA I VIRGILI
SUGAR-BASED LIGAND LIBRARIES FOR ASYMMETRIC REDUCTIONS AND C-C BOND FORMING REACTIONS
M. Mercè Coll Serrahima
DL:T. 150-2012

UNIVERSITAT ROVIRA I VIRGILI
SUGAR-BASED LIGAND LIBRARIES FOR ASYMMETRIC REDUCTIONS AND C-C BOND FORMING REACTIONS
M. Mercè Coll Serrahima
DL:T. 150-2012

CHAPTER 3

Asymmetric hydrogenation reactions

UNIVERSITAT ROVIRA I VIRGILI
SUGAR-BASED LIGAND LIBRARIES FOR ASYMMETRIC REDUCTIONS AND C-C BOND FORMING REACTIONS
M. Mercè Coll Serrahima
DL:T. 150-2012

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.[1]

As we discussed in the introduction, most of the chiral ligands developed for asymmetric hydrogenation of functionalized olefins are phosphorus donors. Among those, chiral homodonor P-donor ligands (i.e. phosphines, phosphites, phosphoroamidites,…) have played a dominant role.[1,2] Other ligands, such as heterodonors, have only more recently demonstrated their potential utility in asymmetric hydrogenation. The recent development of highly enantioselective hybrid phosphine-phosphite and phosphine-phosphoroamidite ligands illustrates this idea.[2,3] Although excellent results have been obtained using phosphites and phosphoroamidites, the combination of both in the same ligand backbone has been scarcely used in this process. This encourages further research into phosphite-phosphoroamidite ligands.

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] the asymmetric hydrogenation of minimally functionalized olefins is less developed because these substrates have not adjacent polar group to direct the reaction.[4] 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. In this respect, the most successful P-N ligands contain a phosphine, phosphinite or phosphite moiety as P-donor group and either an oxazoline, oxazole, thiazole or pyridine as N-donor group. However, the possibility of changing the nature of the N-donor atom in these heterodonor ligands has never been contemplated.

In this chapter, we therefore report the synthesis of several carbohydrate ligand libraries: phosphite-phosphoroamidite (**L1-L4a-f**), diphosphoroamidite (**L5a-f**), thioether-phosphite (**L6-L20a-h**), thioether-phosphinite (**L6-L20i**) and thioether-phosphoroamidite (**L21-L26a-f**). We also report their use in the asymmetric hydrogenation reactions. More specifically, in section 3.2 we describe the application of

a furanoside phosphite-phosphoroamidite and diphosphoroamidite ligand library in the asymmetric Rh-catalyzed hydrogenation of several α,β-unsaturated esters and enamides. As well as being prepared from commercially available D-(+)-glucose or D-(+)-xylose, 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 (**L1**-**L5a-f**), then, we investigate the effect of systematically varying the position of the phosphoroamidite group at both C-5 (ligands **L1** and **L2**) and C-3 (ligands **L3** and **L4**) of the furanoside backbone, as well as the effects of the configuration at C-3 of the furanoside backbone, the introduction of second phosphoroamidite moiety (ligands **L5**) and the substituents/configurations in the biaryl phosphite/phosphoroamidite moieties (**a**-**f**). By judicious choice of the ligand components, we achieved high enantioselectivities (ee's up to >99%) in the hydrogenation of several α,β-unsaturated carboxylic acid derivatives and enamides. This section also includes kinetic and NMR studies to provide greater insight into the origin of the enantioselectivity. In next section 3.3, we report the first successful application of non N-donor heterodonor ligands – thioether-phosphite and thioether-phosphinite– in the Ir-catalyzed hydrogenation of a broad range of minimally functionalized olefins. These ligands are derived from D-(+)-xylose and they combine the advantages of phosphite/phosphinite and sugar cores: that is to say, they are readily available from cheap feedstocks, are highly resistant to oxidation, and have a straightforward modular construction. Their modular constructions make it easy for us to study the effect of several ligand parameters on catalytic activity and selectivity. With these ligands we therefore investigated the effect of systematically varying the position of the thioether group at either C-5 (ligands **L6**-**L16**) or C-3 (ligands **L17**-**L20**) of the furanoside backbone, the configuration at C-3 of the furanoside backbone, the substituents in the thioether group (**L6**–**L12**), the substituents and configurations in the biaryl phosphite moiety (**a**-**h**) and the effect of replacing the phosphite moiety by a phosphinite (**i**) group. We found that their effectiveness at transferring the chiral information in the product can be tuned by correctly choosing the ligand components. Enantioselectivities were therefore excellent (ee's up to 99%) in a wide range of *E*- and *Z*-trisubstituted alkenes. It should be pointed out that these catalysts are also very tolerant to the presence of neighboring polar group. Thus, a range of allylic alcohols, acetates, α,β-unsaturated esters and vinylboronates were hydrogenated in high enantioselectivities. The good performance extends to the

very challenging class of terminal disubstituted aryl/alkyl olefins (ee's up to 99%). Both enantiomers of the hydrogenation product can be obtained in high enantioselectivity, simply by changing the configuration of the biaryl phosphite moiety. On the basis of previous thioether-phosphite/phosphinite ligand libraries, in next section 3.4, we designed a new furanoside P-S ligand family in which the phosphite/phosphinite moiety is replaced by a phosphoroamidite group, leading to a furanoside thioether-phosphoroamidite ligand library (**L21-L26a-f**). These ligands were applied in the asymmetric Ir-catalyzed hydrogenation of several minimally functionalized olefins. The introduction of a phosphoroamidite moiety in the ligand design has a negative effect on enantioselectivity. However, this effect is less pronounced in the reduction of 1,1-disubstituted terminal alkenes (ee's up to 87%) than in the hydrogenation of trisubstituted olefins (ee's up to 53%).

3.1.1. References

[1] See for instante: a) Blaser, H. U.; Schmidt, E. *Asymmetric Catalysis on Industrial Scale: Challenges, Approaches and Solutions*; Wiley-VCH, Weinheim, **2004**; b) *Handbook of Homogeneous Hydrogenation*; de Vries, J. G.; Elsevier, C. J.; Eds.; Wiley-VCH: Weinheim, **2007**; c) Ojima, I. *Catalytic Asymmetric Synthesis*; 3rd edition, John Wiley & Sons, Hoboken, **2010**.

[2] *Phosphorous Ligands in Asymmetric Catalysis*; Börner, A.; Eds.; Wiley-VCH, Weinheim, **2008**.

[3] See, for instance: Fernández-Pérez, H.; Etayo, P.; Panossian, A.; Vidal-Ferran, A. *Chem. Rev.* **2011**, *111*, 2119.

[4] For recent reviews, see: a) Cui, X.; Burgess, K. *Chem. Rev*. **2005**, *105*, 3272; b) Roseblade, S. J.; Pfaltz, A. *Acc. Chem. Res*. **2007**, *40*, 1402; c) Church, T. L.; Andersson, P. G. *Coord. Chem. Rev.* **2008**, *252*, 513.

UNIVERSITAT ROVIRA I VIRGILI
SUGAR-BASED LIGAND LIBRARIES FOR ASYMMETRIC REDUCTIONS AND C-C BOND FORMING REACTIONS
M. Mercè Coll Serrahima
DL:T. 150-2012

3.2. Asymmetric Rh-catalyzed hydrogenation using a furanoside phosphite-phosphoroamidite and diphosphoroamidite ligand library

Mercedes Coll, Oscar Pàmies and Montserrat Diéguez submitted for publication to *Dalton Trans.*

Abstract. A furanoside phosphite-phosphoroamidite and diphosphoroamidite ligand library **L1-L5a-f** was tested in the asymmetric Rh-catalyzed hydrogenation of α,β-unsaturated carboxylic acid derivatives and enamides. Enantioselectivity depended strongly on the ligand parameters. High enantioselectivities were obtained in the reduction of dimethyl itaconate (up to >99% ee), α-dehydroamino acid esters (up to 99% ee) and several enamides (up to 92% ee). Kinetic and NMR studies on the intermediates of the catalytic cycle of the reaction indicate that the [Rh(P-P')(substrate)]$^+$ species is the resting state of the reaction and that the rate dependence is first order in rhodium and hydrogen pressure and zeroth order in the substrate.

3.2.1. 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. For many years, the scope of this reaction has been gradually extended in both reactant structure and catalyst efficiency.[1] Chiral homodonor P-donor ligands (i.e. phosphines, phosphites, phosphoroamidites,…) 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 carbohydrates have many advantages: they are readily available and highly functionalized, and they have several stereogenic centres. This facilitates the development of chiral ligand libraries in the search for high activities and selectivities for each particular substrate.[2] Heterodonor P-P' ligands also have a potential advantage because specific substrate

coordination, mediated by two non-equivalent donor atoms, facilitates the transferring of the chiral information from the catalyst to the hydrogenation product for a wide range of substrates.[3] The recent development of highly enantioselective hybrid phosphine-phosphite[4] and phosphine-phosphoroamidite[5] ligands illustrates this idea. Although excellent results have been obtained using phosphites and phosphoroamidites, the combination of both in the same ligand backbone has been scarcely used in this process.[6] Notable examples include three types of phosphite-phosphoroamidite ligands. In this context, in 2001, we communicated the first successful application of phosphite-phosphoroamidite ligands, with furanoside skeleton (ligands **L1-L2a-b**; Figure 3.2.1), in the Rh-catalyzed hydrogenation of α,β-unsaturated carboxylic acid derivatives.[6a] Latter, in 2006, Laschat's and Reetz's groups developed the tropane- and binol-based ligands, respectively, which provided enantioselectivities up to 96% in the hydrogenation of dimethyl itaconate and α-dehydroamino acid esters.[6d,e]

To fully investigate the potential of phosphite-phosphoroamidite as a new class of ligands for this process, in this chapter we extend the 2001 study to other furanoside phosphite-phosphoroamidite ligands (Figure 3.2.1) and to other types of substrates. We have therefore extended the ligand library by including new furanoside backbones (ligands **L3** and **L4**) and new substituents at the biaryl phosphite groups (**c-f**). We also compare the effectiveness of these phosphite-phosphoroamidite ligands with their related diphosphoroamidites (Figure 3.2.1, ligands **L5**). As well as being prepared from commercially available inexpensive D-(+)-glucose or D-(+)-xylose, this ligand library also has the advantage of a flexible ligand scaffold that enables various ligand parameters to be easily tuned so that the catalyst performance can be maximized. With this ligand library (**L1-L5a-f**), then, we investigate the effect of systematically varying the position of the phosphoroamidite group at both C-5 (ligands **L1** and **L2**) and C-3 (ligands **L3** and **L4**) of the furanoside backbone, as well as the effects of the configuration at C-3 of the furanoside backbone, the introduction of second phosphoroamidite moiety (ligands **L5**) and the substituents/configurations in the biaryl phosphite/phosphoroamidite moieties (**a-f**). By judicious choice of the ligand components, we achieved high enantioselectivities (ee's up to >99%) in the hydrogenation of several α,β-unsaturated carboxylic acid derivatives and enamides.

Despite the success of Rh/phosphite-phosphoroamidite catalytic systems in asymmetric hydrogenation, no mechanistic studies have been carried out. In this

context, the mechanistic aspects of these ligands are still not understood well enough for the a priori prediction of the type of ligand needed for high selectivity. To address this important point, we also investigated the intermediate rhodium complexes under hydrogenation conditions and conducted kinetic studies.

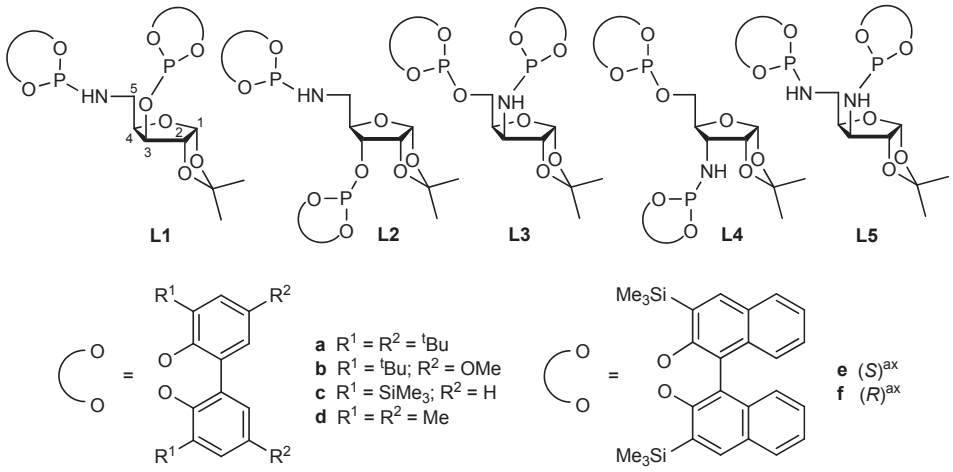


Figure 3.2.1. Library of phosphite-phosphoroamidite **(L1-L4a-f)** and diphosphoroamidite (**L5a-f**) ligands with furanoside backbone.

3.2.2. Results and Discussion

3.2.2.1. Asymmetric hydrogenation of dimethyl itaconate S1

Initially, we evaluated phosphite-phosphoroamidite and diphosphoroamidite ligands **L1-L5a-f** (Figure 3.2.1) 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 $[Rh(cod)_2]BF_4$. In our previous communication, we found a positive effect on both activity and enantioselectivity when the hydrogen pressure was raised above 2.5 bar, the ee's being unaffected in the range 2.5 – 30 bar.[6a] Therefore, reactions were carried out at 5 bar of H_2 at room temperature.

The results, which are summarized in Table 3.2.1, indicated that enantioselectivity is highly affected by the position of the phosphoroamidite group at either C-5 or C-3 of the furanoside backbone, by the configuration of C-3, by the

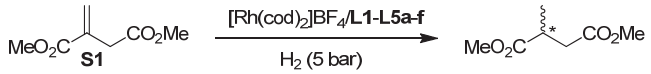
substituents and configurations in the biaryl phosphite/phosphoroamidite moieties (**a-f**) and by the introduction of a second phosphoroamidite moiety.

The results obtained using ligands **L1-L4a** indicate that there is a cooperative effect between the position of the phosphoroamidite group at either C-5 (ligands **L1** and **L2**) or C-3 (ligands **L3** and **L4**) and the configuration of carbon atom C-3 of the furanoside backbone. The matched combination is therefore achieved with ligand **L1**, whose phosphoroamidite moiety is attached to C-5 and which has an (*S*)-configuration of carbon atom C-3 on the tetrahydrofuran ring (Table 3.2.1, entries 1 *vs* 7, 12 and 17).

Interestingly, there is also a cooperative effect between the position of the phosphoroamidite (at either C-5 or C-3) and the substituents in the biphenyl phosphite/phosphoroamidite moieties. Thus, for **L1** and **L2**, in which the phosphoroamidite moiety is attached to C-5, the presence of bulky substitutents at the *para* positions of the biphenyl moieties are crucial for high enantioselectivity (i.e. ^{t}Bu > OMe > Me > H; Table 3.2.1, entries 1-4). On the other hand, the opposite behavior was observed for ligands containing the phosphoroamidite group attached to C-3 (ligands **L3** and **L4**). For these latter ligands, enantioselectivities are therefore best with the less sterically hindered *para* substituents (i.e. H >> ^{t}Bu; Table 3.2.1, entries 12-14).

The results using ligands **L1-L4e-f**, which contain enantiopure binapthyl 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 **L1f** (96% ee; Table 3.2.1, entry 6). Moreover, comparing the results of tropoisomeric biphenyl-based ligands (**a-d**) with those of enantiopure binaphthyl-ones (**e-f**) we can conclude that if enantioselectivity has to be high the tropoisomerization in biphenyl ligands has to be avoided upon coordination in the active species. Thus, for instance, ligand backbone **L1** efficiently controls tropoisomerization of the biaryl phosphite/phosphoroamidite moieties when bulky *tert*-butyl substituents at both *ortho* and *para* positions of the biaryl phosphite/phosphoroamidite moieties are present. Both biaryl moieties adopt an (*R*)-configuration in the active species (Table 3.2.1, entries 1 *vs* 5 and 6). In a similar way, the low enantioselectivities obtained using ligands **L1c** and **L1d** (Table 3.2.1, entries 3 and 4) can be explained by the lack of appropriate substituents in the biphenyl moieties to prevent the tropoisomerization of their biphenyl units.

Table 3.2.1. Asymmetric Rh-catalyzed hydrogenation of dimethyl itaconate **S1** using phosphite-phosphoroamidite and diphosphoroamidite ligands **L1-L5a-f**.[a]



Entry	Ligand	% Conv (h)[b]	%ee[c]	Entry	Ligand	% Conv (h)[b]	%ee[c]
1	**L1a**	100 (6)	97 (*R*)	12	**L3a**	42 (6)	8 (*S*)
2	**L1b**	100 (6)	86 (*R*)	13	**L3b**	43 (6)	14 (*S*)
3	**L1c**	100 (6)	21 (*R*)	14	**L3c**	100 (6)	78 (*R*)
4	**L1d**	100 (6)	29 (*R*)	15	**L3e**	100 (6)	80 (*R*)
5	**L1e**	100 (6)	89 (*S*)	16	**L3f**	100 (6)	45 (*S*)
6	**L1f**	100 (6)	96 (*R*)	17	**L4a**	89 (6)	15 (*R*)
7	**L2a**	52 (6)	34 (*R*)	18	**L4b**	100 (6)	14 (*R*)
8	**L2b**	48 (6)	30 (*R*)	19	**L4c**	100 (6)	69 (*S*)
9	**L2c**	100 (6)	5 (*S*)	20	**L5a**	100 (6)	51 (*R*)
10	**L2e**	100 (6)	31 (*S*)	21[d]	**L1a**	100 (12)	>99 (*R*)
11	**L2f**	98 (6)	35 (*R*)	22[d,e]	**L1a**	74 (24)	99 (*R*)

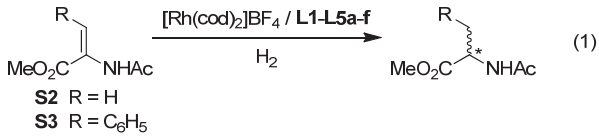
[a] $[Rh(cod)_2]BF_4$ (1 mol%), ligand (1.1 mol%), **S1** (1 mmol), CH_2Cl_2 (6 mL), room temperature. [b] % Conversion measured by GC. [c] Enantiomeric excess measured by GC. [d] Reaction carried out using 30 bar of H_2 at 5 °C. [e] Reaction carried out using 0.1 mol% catalyst.

Finally, we studied the effect of introducing a second phosphoroamidite moiety on catalytic performance. The results of using ligands **L5** indicated that replacing the phosphite moiety by a phosphoroamidite group in the ligands had a negative effect on enantioselectivity (Table 3.2.1, entry 1 *vs* 20).

In summary, the best result was obtained with ligands **L1a** and **L1f** (Table 3.2.1, entries 1 and 6), which contains the optimal combination of ligand parameters (position of the phosphoroamidite group, configuration at C-3 of the furanoside backbone and the substituents and configurations in the biaryl phosphite/phosphoroamidite moieties). Enantioselectivity was further improved to >99% (*R*) ee by lowering the reaction temperature to 5 °C (Table 3.2.1, entry 21). Enantioselectivity was also maintained when the catalyst loading was lowered to 0.1 mol%, which suggests that no decomposition of the catalyst took place (Table 3.2.1, entry 22).

3.2.2.2. Asymmetric hydrogenation of α-dehydroamino acid esters

We also screened the phosphite-phosphoroamidite and diphosphoroamidite ligand library **L1**-**L5a-f** in the asymmetric reduction of some benchmark α-dehydroamino acid derivatives (Equation 1). Table 3.2.2 shows the most representative results.



The results followed the same trends as for the hydrogenation of **S1**. Again, the highest enantioselectivities (ee values up to 98%) were obtained when the Rh-**L1a** and Rh-**L1f** catalyst precursors were used (Table 3.2.2, entries 1, 6, 19 and 20). The stereoselectivity of the hydrogenation of dehydroamino acid derivatives **S2** and **S3** products were the same as for the reduction reaction of **S1**, though the CIP descriptor was inverted because of the change in the priority of the groups.

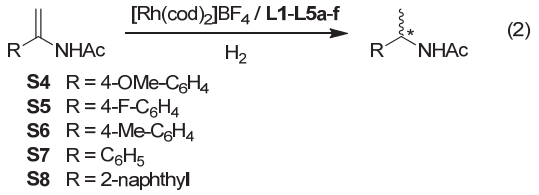
Table 3.2.2. Asymmetric Rh-catalyzed hydrogenation of α-dehydroamino acid esters using phosphite-phosphoroamidite and diphosphoroamidite ligands **L1-L5a-f**.[a]

		S2		**S3**	
Entry	Ligand	% Conv (h)[b]	%ee[c]	% Conv (h)[b]	%ee[c]
1	**L1a**	100 (6)	92 (*S*)	100 (6)	94 (*S*)
2	**L1b**	100 (6)	82 (*S*)	100 (6)	85 (*S*)
3	**L1c**	100 (6)	12 (*R*)	100 (6)	18 (*R*)
4	**L1d**	100 (6)	15 (*S*)	100 (6)	13 (*S*)
5	**L1e**	100 (6)	86 (*R*)	100 (6)	83 (*R*)
6	**L1f**	100 (6)	92 (*S*)	100 (6)	93 (*S*)
7	**L2a**	100 (6)	15 (*S*)	100 (6)	18 (*S*)
8	**L2b**	93 (6)	12 (*S*)	95 (6)	17 (*S*)
9	**L2c**	100 (6)	4 (*S*)	100 (6)	8 (*S*)
10	**L2e**	84 (6)	14 (*R*)	89 (6)	17 (*R*)
11	**L2f**	99 (6)	21 (*S*)	99 (6)	22 (*S*)
12	**L3a**	30 (6)	4 (*R*)	48 (6)	6 (*R*)
13	**L3b**	24 (6)	10 (*R*)	36 (6)	11 (*R*)
14	**L3c**	100 (6)	85 (*S*)	100 (6)	78 (*S*)
15	**L4a**	78 (6)	14 (*S*)	69 (6)	13 (*S*)
16	**L4b**	100 (6)	13 (*S*)	100 (6)	16 (*S*)
17	**L4c**	100 (6)	78 (*S*)	100 (6)	71 (*S*)
18	**L5a**	100 (6)	43 (*S*)	100 (6)	44 (*S*)
19[d]	**L1a**	100 (12)	98 (*S*)	100 (20)	98 (*S*)
20[d,e]	**L1a**	96 (20)	98 (*S*)	65 (20)	98 (*S*)

[a] $[Rh(cod)_2]BF_4$ (1 mol%), ligand (1.1 mol%), substrate (1 mmol), CH_2Cl_2 (6 mL), 5 bar of H_2, room temperature. [b] % Conversion measured by GC. [c] Enantiomeric excess measured by GC. [d] Reaction carried out at 5 °C. [e] Reaction carried out using 0.1 mol% catalyst.

3.2.2.3. Asymmetric hydrogenation of enamides

We subsequently applied ligand library **L1-L5a-f** in the Rh-catalyzed asymmetric reduction of several enamides (Equation 2). Enamides are an important class of substrates because their reductions give rise to optically active secondary amines, which are useful building blocks for the synthesis of fine chemicals.[7]



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-L5a-f**. The results are summarized in Table 3.2.3. In general the results followed the same trend as for substrates **S1-S3**. However, the effect of the substituents on the biaryl phosphite/phosphoroamidite moieties was different. The cooperative effect between the biaryl substituents and the position of the phosphoroamidite moiety is not observed. So, for all ligand backbones, if enantioselectivities have to be high, bulky substituents need to be present at the *para* position of the biaryl phosphite/phosphoroamidite moieties (i.e. ^{t}Bu > OMe > Me ≈ H). Moreover, the detrimental effect of introducing a second phosphoroamidite moiety in the ligand is less pronounced for enamide **S4** than for substrates **S1-S3** (i.e. Table 3.2.1, entries 1 and 20 *vs* Table 3.2.3, entries 1 and 21). To sum up, once again the best enantioselectivities were obtained using the Rh-**L1a** and Rh-**L1f** catalyst precursors (Table 3.2.3, entries 1 and 6).

Next, we used one of the ligands that provided the best results (ligand **L1a**) to study the effect of the ligand-to-rhodium ratio and hydrogen pressure on the product outcome (Table 3.2.3, entries 26-28). Our results show that as for substrates **S1-S3** no excess of ligand is needed for enantioselectivities to be high (Table 3.2.3, entries 1 *vs* 26).[6a] However, unlike **S1-S3**, enantioselectivities increased when the hydrogenation was conducted at lower pressures (73% ee at 30 bar and 76% ee at 5 bar; Table 3.2.3, entry 1 *vs* 28). Enantioselectivity was further improved by lowering the reaction temperature to 5 °C (88% ee; Table 3.2.3, entry 30).

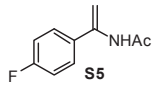
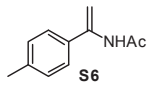
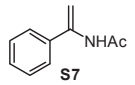
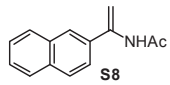
Table 3.2.3. Asymmetric Rh-catalyzed hydrogenation of *N*-(1-(4-methoxyphenyl)vinyl)-acetamide **S4** using phosphite-phosphoroamidite and diphosphoroamidite ligands **L1-L5a-f**.[a]

Entry	Ligand	% Conv (h)[b]	%ee[c]	Entry	Ligand	% Conv (h)[b]	%ee[c]
1	**L1a**	100 (12)	73 (*S*)	16	**L3d**	100 (12)	12 (*R*)
2	**L1b**	100 (12)	65 (*S*)	17	**L4a**	100 (12)	52 (*S*)
3	**L1c**	99 (12)	14 (*R*)	18	**L4b**	100 (12)	50 (*S*)
4	**L1d**	100 (12)	16 (*S*)	19	**L4c**	98 (12)	19 (*S*)
5	**L1e**	100 (12)	46 (*R*)	20	**L4d**	100 (12)	7 (*R*)
6	**L1f**	100 (12)	70 (*S*)	21	**L5a**	100 (12)	60 (*S*)
7	**L2a**	100 (12)	18 (*R*)	22	**L5b**	100 (12)	47 (*S*)
8	**L2b**	100 (12)	13 (*R*)	23	**L5c**	100 (12)	31 (*S*)
9	**L2c**	97 (12)	14 (*S*)	24	**L5e**	100 (12)	36 (*S*)
10	**L2d**	100 (12)	7 (*R*)	25	**L5f**	100 (12)	66 (*S*)
11	**L2e**	94 (12)	17 (*R*)	26[d]	**L1a**	100 (12)	72 (*S*)
12	**L2f**	99 (12)	33 (*S*)	27[e]	**L1a**	42 (24)	76 (*S*)
13	**L3a**	100 (12)	54 (*S*)	28[f]	**L1a**	95 (18)	76 (*S*)
14	**L3b**	100 (12)	49 (*S*)	29[g]	**L1a**	100 (24)	86 (*S*)
15	**L3c**	98 (12)	6 (*S*)	30[f,g]	**L1a**	71 (36)	88 (*S*)

[a] $[Rh(cod)_2]BF_4$ (1 mol%), ligand (1.1 mol%), substrate (0.25 mmol), CH_2Cl_2 (2 mL), room temperature, 30 bar of H_2. [b] % Conversion measured by GC. [c] Enantiomeric excess measured by GC. [d] Reaction carried out at a ligand/Rh ratio of 2. [e] Reaction carried out using 2.5 bar of H_2. [f] Reaction carried out using 5 bar of H_2. [g] Reaction carried out at 5 °C.

To further investigate the catalytic efficiency of the Rh/**L1a** catalytic system, we tested it in the Rh-catalyzed hydrogenation of other enamides with different aryl substituents. The results are summarized in Table 3.2.4. 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. 92% (*S*) for *N*-(1-(4-fluorophenyl)vinyl)-acetamide **S5**; Table 3.2.4, entry 3).

Table 3.2.4. Hydrogenation results of enamides **S5-S8** using $[Rh(cod)_2]BF_4$/**L1a** catalyst precursor.[a]

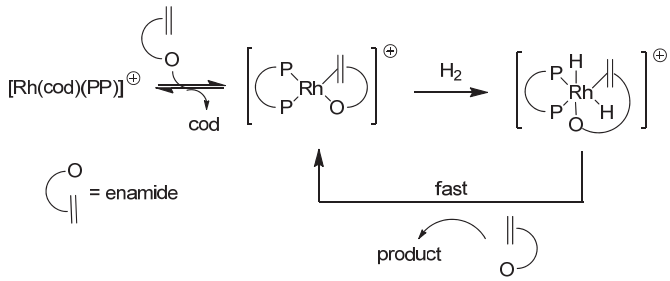
Entry	Substrate	P_{H2} (bar)	T (°C)	% Conv (h)[b]	%ee[c]
1	 **S5**	30	25	100 (12)	85 (*S*)
2		5	25	100 (24)	88 (*S*)
3		5	5	81 (36)	92 (*S*)
4	 **S6**	30	25	100 (12)	69 (*S*)
5		5	25	100 (24)	70 (*S*)
6		5	5	79 (36)	74 (*S*)
7	 **S7**	30	25	100 (12)	70 (*S*)
8		5	25	100 (24)	72 (*S*)
9		5	5	76 (36)	75 (*S*)
10	 **S8**	30	25	100 (12)	70 (*S*)
11		5	25	99 (24)	73 (*S*)
12		5	5	65 (36)	77 (*S*)

[a] $[Rh(cod)_2]BF_4$ (1 mol%), **L1a** (1.1 mol%), substrate (0.25 mmol), CH_2Cl_2 (2 mL). [b] % Conversion measured by GC. [c] Enantiomeric excess measured by GC.

3.2.2.4. Mechanistic considerations

The mechanism of the enantioselective hydrogenation catalyzed by cationic diphosphine rhodium complexes has been thoroughly studied. The widely accepted catalytic cycle, a result of the work by Brown, Halpern, Landis, and Bosnich and their groups, involves the reversible binding of the substrate to the catalyst, followed by the rate-determining oxidative addition of H_2 and the subsequent rapid elimination of the hydrogenated product (Scheme 3.2.1).[8] In the last decade, this mechanism has proved to be valid for other phosphorus-based ligands (i.e. diphosphinites, diphosphites, etc.).[4b,9] However, the catalytic sequence may be affected by the use of heterodonor phosphite-phosphoroamidite ligands, which have two electronically different donor sites. To learn more about the catalytic cycle, we made a kinetic study and investigated the species

formed under hydrogenation conditions using $[Rh(L)(cod)]BF_4$ as catalyst precursors and methyl *N*-acetamidoacrylate **S2** as substrate.



Scheme 3.2.1. Landis-Halpern hydrogenation mechanism.

Firstly, we investigated the rate dependence on hydrogen pressure and rhodium and substrate concentration using $[Rh(\mathbf{L1a})(cod)]BF_4$ as catalyst precursor. The results collected in Table 3.2.5 indicated that the hydrogenated product formation is linearly proportional to the hydrogen pressure and rhodium concentration. These data are therefore in agreement with a first-order dependency on hydrogen and catalyst concentration. To establish the substrate concentration dependency, we followed the conversion over time. The graph of conversion *vs* time (Figure 3.2.2) clearly shows a zeroth-order dependency on substrate concentration.

Table 3.2.5. Hydrogen pressure and Rh-concentration dependency on the hydrogenation reaction rate.

P_{H2}[a]	$[Rh(\mathbf{L1a})(cod)]BF_4$[b]	TOF[c]
2.5	0.00167	7
5	0.00167	16
15	0.00167	49
30	0.00167	101
5	0.00835	83
5	0.00084	9

[a] Hydrogen pressure in bar. [b] Concentration of $[Rh(\mathbf{L1a})(cod)]BF_4$ in mol · l^{-1}. [c] TOF measured in mol · (molRh · h) $^{-1}$ at around 10% conversion.

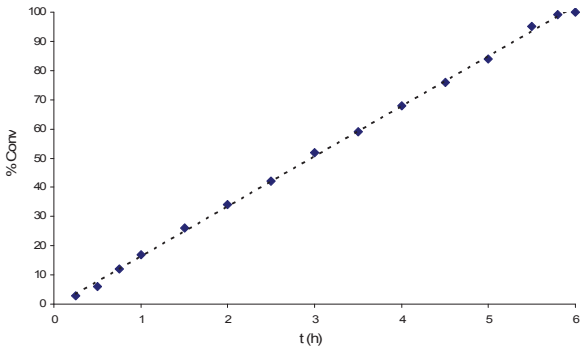


Figure 3.2.2. Variation of the conversion over time. Conditions: P_{H2}= 5 bar, [Rh]= 1.67 mM. [**S2**]= 0.167 M.

Next, we studied the species formed under hydrogenation conditions to gain further insight into the sequence of the catalytic cycle and at the same time to obtain information about the origin of enantioselectivity. For this purpose, we studied the reactivity of catalyst precursors [Rh(L)(cod)]BF_4 (L = **L1-L4a** and **L3c**). With complexes [Rh(L)(cod)]BF_4 (L = **L1-L4a**), we contemplated the four possible combinations of varying the position of the phosphoroamidite group and the configuration of carbon atom C-3 and their study will allow us to understand the observed effect of these parameters on the catalytic performance. Finally with complex [Rh(**L3c**)(cod)]BF_4, we studied the matched combination of the observed cooperative effect between the position of the phosphoroamidite and the substituent in the biphenyl phosphite/phosphoroamidite moieties.

First we investigated the reactivity of catalyst precursors [Rh(L)(cod)]BF_4 (L = **L1-L4a** and **L3c**) with molecular hydrogen. Their reactivity was examined by pressurizing a CD_2Cl_2 solution of the corresponding [Rh(L)(cod)]BF_4 with H_2 gas at 5 and 30 bar. The VT-^{1}H NMR spectra did not show the formation of hydride species. Neither did the VT-^{31}P NMR spectra show any new signal, which indicated that catalyst precursors [Rh(L)(cod)]BF_4 did not react with molecular hydrogen under these conditions. After dehydroamino acid derivative **S2** had been added, two new double doublets were observed in the $^{31}P\{^1H\}$ NMR spectra (Table 3.2.6). These new signals were assigned to cationic rhodium complexes [Rh(L)(**S2**)]$^+$. The P-P coupling constants are around 40 Hz, whereas J{OP-Rh} and J{NP-Rh} are around 250 and 260 Hz, respectively. VT-$^{31}P\{^1H\}$ NMR spectra between +25 and -80 °C showed that there was only one diastereomer for each catalytic precursor. The shifts of the phosphoroamidite

signals in the $^{31}P\{^{1}H\}$NMR spectrum of complexes [Rh(L)(**S2**)]$^+$ are consistent with a diastereoisomer whose phosphoroamidite is *trans* to the C=O fragment and whose phosphite is *trans* to the C=C fragment.[8a] Also, neither the $[RhH_2(L)(\mathbf{S2})]BF_4$ species nor the $[RhH(L)(alkyl)]BF_4$ species were observed under hydrogenation conditions.

Table 3.2.6. Selected spectroscopic NMR data for complexes $[Rh(L)(\mathbf{S2})]BF_4$.[a]

	P_1= Phosphite		P_2= Phosphoroamidite		
Complex	δ (P_1)	$J_{P1\text{-}Rh}$	δ (P_2)	$J_{P2\text{-}Rh}$	$J_{P1\text{-}P2}$
[Rh(**L1a**)(**S2**)]$^+$	128.9	246	125.8	259	38
[Rh(**L2a**)(**S2**)]$^+$	129.2	249	124.9	258	39
[Rh(**L3a**)(**S2**)]$^+$	128.8	247	122.4	252	41
[Rh(**L4a**)(**S2**)]$^+$	132.3	243	124.4	254	39
[Rh(**L3c**)(**S2**)]$^+$	133.9	245	130.2	261	42

[a] NMR measured in CD_2Cl_2 at 25 °C, chemical shift (δ) in ppm, coupling constants (*J*) in hertz.

In summary, the kinetic and NMR results agree with the Landis-Halpern mechanism (Scheme 3.2.1). However, the evidence is not conclusive since the rate law would be the same if there were a fast equilibration between [Rh(L)(**S2**)]$^+$ as the dominant species and a minor amount (below the detection limit of the NMR equipment) of $[RhH_2(L)(cod)]^+$ species, followed by a rate-determining addition of the substrate (**S2**) to the latter complex. In addition the similar chemical shift and coupling constants of all complexes [Rh(L)(**S2**)]$^+$ studied (see Table 3.2.6) together with the presence of only one diastereoisomer suggest that for our Rh/phosphite-phosphoroamidite, the coordination mode of the enamide is mainly controlled by the electronic properties of the ligand. However, the formation of the diastereomeric Rh(III)-dihydride complexes, and therefore that of the hydrogenated product, is mainly controlled by the steric hindrance of the chiral ligand, which controls the rotation of the substrate with respect to the ligand that follows the oxidative addition of H_2.[8p] This agrees with our hydrogenation results, which indicate that enantioselectivity was controlled by a suitable combination of ligand parameters (position of the

phosphoroamidite group, configuration of C-3 and substituents/configurations in the biaryl phosphite/phosphoroamidite moieties).

3.2.3. Conclusions

A library of furanoside phosphite-phosphoroamidite **L1-L4a-f** and diphosphoroamidite **L5a-f** ligands was applied to the Rh-catalyzed hydrogenation of several substrate types. Enantioselectivity is highly affected by the position of the phosphoroamidite group, the configuration of C-3 of the furanoside backbone, the introduction of a second phosphoroamidite moiety and the substituents/configurations in the biaryl phosphite/phosphoroamidite 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 **L1a** and **L1f**, which contain the optimal combination of ligand parameters. Kinetic studies indicate that the rate dependence is first order in rhodium and hydrogen pressure and zero order in substrate concentration. NMR studies on the intermediates formed under hydrogenation conditions indicate that: (a) the [Rh(P-P')(substrate)]BF_4 species is the resting state; (b) the olefin coordination mode is controlled by the electronic properties of ligand; and (c) the enantioselectivity is mainly dictated by steric factors which controls the substrate rotation that follows the oxidative addition of hydrogen.

3.2.4. Experimental section

3.2.4.1. General considerations

All reactions were carried out using standard Schlenk techniques under an argon atmosphere. Solvents were purified and dried by standard procedures. Phosphite-phosphoroamidite[6a,10] (**L1-L4a-f**) and diphosphoroamidite[11] (**L5a-f**) ligands were prepared as previously described. Methyl (*Z*)-*N*-acetylaminocinnamate **S3**[12] and enamides **S4-S8**[13] were prepared following literature procedures. All other reagents were used as commercially available. All catalytic experiments were performed three times.

3.2.4.2. Asymmetric hydrogenation

In a typical run, $[Rh(cod)_2]BF_4$ (1 mol%) and the corresponding ligand (1.1 mol%) were dissolved in dichloromethane (1 mL) and stirred. After 3 minutes, a dichloromethane (5 mL) solution of the corresponding substrate (1 mmol) was added. 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.[14]

3.2.4.3. Preparation of [Rh(L)(cod)]BF_4 complexes

Phosphite-phosphoroamidite ligand (0.1 mmol) was added to a solution of $[Rh(cod)_2]BF_4$ (40.4 mg, 0.1 mmol) in dichloromethane (3 mL). After 5 minutes, the solvent was partially removed and the desired complex was obtained by precipitation with hexane as a pale orange solid.

[Rh(L1a)(cod)]BF_4. Yield: 93% (127 mg). ^{31}P NMR (CD_2Cl_2), δ: 121.6 (1P, dd, $^1J_{NP\text{-}Rh}$= 271 Hz, $^2J_{OP\text{-}NP}$= 44 Hz), 129.5 (1P, dd, $^1J_{OP\text{-}Rh}$= 232 Hz, $^2J_{OP\text{-}NP}$= 44 Hz). ^1H NMR (CD_2Cl_2), δ: 1.14 (s, 3H, CH_3), 1.23 (s, 3H, CH_3), 1.31 (s, 18H, CH_3, ^{t}Bu), 1.33 (s, 18H, CH_3, ^{t}Bu), 1.39 (m, 4H, CH_2, cod), 1.46 (s, 9H, CH_3, ^{t}Bu), 1.50 (s, 9H, CH_3, ^{t}Bu), 1.64 (s, 9H, CH_3, ^{t}Bu), 1.70 (s, 9H, CH_3, ^{t}Bu), 1.96 (m, 2H, CH_2, cod), 2.11 (m, 2H, CH_2, cod), 3.34 (m, 1H, H-5'), 3.68 (m, 1H, NH), 3.79 (m, 1H, H-5), 3.93 (b, 1H, H-2), 4.14 (b, 1H, H-4), 4.84 (m, 1H, H-3), 5.06 (m, 1H, CH=, cod), 5.25 (m, 1H, CH=, cod), 5.74 (d, 1H, $^3J_{1\text{-}2}$= 3.2 Hz), 6.05 (m, 1H, CH=, cod), 6.24 (m, 1H, CH=, cod), 7.1-7.6 (m, 8H, CH=). Anal. Calc (%) for $C_{72}H_{105}BF_4NO_8P_2Rh$: C 63.39, H 7.76, N 1.03; found: C 63.31, H 7.73, N 1.00.

[Rh(L2a)(cod)]BF_4. Yield: 91% (124 mg). ^{31}P NMR (CD_2Cl_2), δ: 123.1 (1P, dd, $^1J_{NP\text{-}Rh}$= 266 Hz, $^2J_{OP\text{-}NP}$= 31 Hz), 129.4 (1P, dd, $^1J_{OP\text{-}Rh}$= 235 Hz, $^2J_{OP\text{-}NP}$= 31 Hz). ^1H NMR (CD_2Cl_2), δ: 1.10 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 1.36 (s, 9H, CH_3, ^{t}Bu), 1.38 (s, 18H, CH_3, ^{t}Bu), 1.44 (s, 9H, CH_3, ^{t}Bu), 1.52 (s, 9H, CH_3, ^{t}Bu), 1.55 (s, 9H, CH_3, ^{t}Bu), 1.71 (s, 9H, CH_3, ^{t}Bu), 1.74 (s, 11H, CH_3, ^{t}Bu and CH_2 cod), 2.22 (m, 2H, CH_2, cod),

2.48 (m, 2H, CH_2, cod), 2.52 (m, 2H, CH_2, cod), 3.07 (m, 1H, H-2), 3.29 (m, 1H, NH), 3.79 (m, 1H, H-5), 3.87 (m, 1H, H-5'), 4.28 (b, 2H, H-4 and H-3), 5.33 (d, 1H, $^3J_{1\text{-}2}$= 3.6 Hz), 5.38 (m, 1H, CH=, cod), 5.48 (m, 1H, CH=, cod), 6.34 (m, 2H, CH=, cod), 7.1-7.5 (m, 8H, CH=). Anal. Calc (%) for $C_{72}H_{105}BF_4NO_8P_2Rh$: C 63.39, H 7.76, N 1.03; found: C 63.33, H 7.69, N 1.01.

[Rh(L3a)(cod)]BF_4. Yield: 94% (129 mg). ^{31}P NMR (CD_2Cl_2), δ: 121.6 (1P, dd, $^1J_{NP\text{-}Rh}$= 267 Hz, $^2J_{OP\text{-}NP}$= 33 Hz), 129.5 (1P, dd, $^1J_{OP\text{-}Rh}$= 238 Hz, $^2J_{OP\text{-}NP}$= 33 Hz). ^{1}H NMR (CD_2Cl_2), δ: 1.02 (s, 3H, CH_3), 1.19 (s, 3H, CH_3), 1.29 (s, 9H, CH_3, ^{t}Bu), 1.31 (s, 9H, CH_3, ^{t}Bu), 1.33 (s, 18H, CH_3, ^{t}Bu), 1.50 (s, 9H, CH_3, ^{t}Bu), 1.53 (s, 9H, CH_3, ^{t}Bu), 1.63 (s, 9H, CH_3, ^{t}Bu), 1.69 (s, 9H, CH_3, ^{t}Bu), 2.18 (m, 4H, CH_2, cod), 2.46 (m, 2H, CH_2, cod), 2.67 (m, 2H, CH_2, cod), 2.77 (m, 1H, NH), 2.85 (d, 1H, H-2, $^3J_{2\text{-}1}$= 3.6 Hz), 3.60 (m, 1H, H-4), 3.68 (m, 1H, H-3), 3.87 (b, 1H, H-5') 3.92 (b, 1H, H-5), 5.32 (d, 1H, $^3J_{1\text{-}2}$= 3.6 Hz), 5.43 (m, 1H, CH=, cod), 5.52 (m, 1H, CH=, cod), 6.38 (m, 2H, CH=, cod), 7.1-7.5 (m, 8H, CH=). Anal. Calc (%) for $C_{72}H_{105}BF_4NO_8P_2Rh$: C 63.39, H 7.76, N 1.03; found: C 63.29, H 7.68, N 1.01.

[Rh(L4a)(cod)]BF_4. Yield: 89% (119 mg). ^{31}P NMR (CD_2Cl_2), δ: 123.6 (1P, dd, $^1J_{NP\text{-}Rh}$= 267 Hz, $^2J_{OP\text{-}NP}$= 23 Hz), 133.1 (1P, dd, $^1J_{OP\text{-}Rh}$= 241 Hz, $^2J_{OP\text{-}NP}$= 23 Hz). ^{1}H NMR (CD_2Cl_2), δ: 1.04 (s, 3H, CH_3), 1.24 (s, 3H, CH_3), 1.29 (s, 9H, CH_3, ^{t}Bu), 1.31 (s, 18H, CH_3, ^{t}Bu), 1.33 (s, 9H, CH_3, ^{t}Bu), 1.52 (s, 9H, CH_3, ^{t}Bu), 1.53 (s, 9H, CH_3, ^{t}Bu), 1.66 (s, 9H, CH_3, ^{t}Bu), 1.71 (s, 9H, CH_3, ^{t}Bu), 2.14 (m, 4H, CH_2, cod), 2.44 (m, 2H, CH_2, cod), 2.62 (m, 2H, CH_2, cod), 3.05 (m, 1H, NH), 3.22 (m, 1H, H-2), 3.39 (m, 1H, H-4), 3.45 (m, 1H, H-5'), 3.64(b, 1H, H-3) 3.95 (b, 1H, H-5), 5.22 (m, 1H, CH=, cod), 5.35 (d, 1H, $^3J_{1\text{-}2}$= 3.6 Hz), 5.45 (m, 1H, CH=, cod), 6.23 (m, 1H, CH=, cod), 6.36 (m, 1H, CH=, cod), 7.1-7.5 (m, 8H, CH=). Anal. Calc (%) for $C_{72}H_{105}BF_4NO_8P_2Rh$: C 63.39, H 7.76, N 1.03; found: C 63.35, H 7.73, N 1.02.

[Rh(L3c)(cod)]BF_4. Yield: 89% (107 mg). ^{31}P NMR (CD_2Cl_2), δ: 128.3 (1P, dd, $^1J_{NP\text{-}Rh}$= 261 Hz, $^2J_{OP\text{-}NP}$= 34 Hz), 135.6 (1P, dd, $^1J_{OP\text{-}Rh}$= 2240 Hz, $^2J_{OP\text{-}NP}$= 34 Hz). ^{1}H NMR (CD_2Cl_2), δ: 0.46 (s, 3H, CH_3-Si), 0.48 (s, 3H, CH_3-Si), 0.59 (s, 3H, CH_3-Si), 0.62 (s, 3H, CH_3-Si), 1.13 (s, 3H, CH_3), 1.39 (s, 3H, CH_3), 2.15 (b, 6H, CH_2, cod), 2.33 (m, 2H, CH_2, cod), 2.82 (m, 1H, NH), 3.54 (d, 1H, H-2, $^3J_{2\text{-}1}$= 3.6 Hz), 3.95 (m, 1H, H-4), 4.28 (m, 2H, H-5' and H-5), 4.38 (m, 1H, H-3), 5.06 (m, 1H, CH=, cod), 5.14 (m, 1H, CH=, cod), 5.62 (m, 1H, CH=, cod), 5.65 (d, 1H, H-1, $^3J_{1\text{-}2}$= 3.6 Hz), 5.94 (m, 1H,

CH=, cod), 7.3-7.8 (m, 12H, CH=). Anal. Calc (%) for $C_{52}H_{73}BF_4NO_8P_2RhSi_4$: C 51.87, H 6.11, N 1.16; found: C 51.84, H 6.08, N 1.12.

3.2.4.4. In situ NMR characterization experiments

3.2.4.4.1. [Rh(L)(cod)]BF4 under hydrogen pressure. In a typical experiment a sapphire tube (Φ = 10 mm) was filled under argon with a solution of $[Rh(L)(cod)]BF_4$ (0.02 mmol) in CD_2Cl_2 (1.5 mL). The tube was purged three times and pressurized to 5 bar or 30 bar of H_2. The reaction was monitored by ^1H NMR and $^{31}P\{^1H\}$ NMR.

3.2.4.4.2. [Rh(L)(cod)]BF4 and S2. In a typical experiment a sapphire tube (Φ = 10 mm) was filled under argon with a solution of $[Rh(L)(cod)]BF_4$ (0.02 mmol) and **S2** (0.25 mmol) in CD_2Cl_2 (1.5 mL). The tube was purged three times and pressurized to 5 bar of H_2 The reaction was monitored by $^{31}P\{^1H\}$ NMR.

3.2.5. Acknowledgements

We would like to thank the Spanish Government for providing grants 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.

3.2.6. References

[1] a) *Asymmetric Catalysis in Industrial Scale: Challenges, Approaches and Solutions*; Blaser, H. U., Schmidt, E., Eds.; Wiley: Weinheim, Germany, **2003**; b) Shang, G.; Li, W.; Zhang, X. in *Catalytic Asymmetric Synthesis*; 3rd Edition; Ojima, I., Ed.; John Wiley & Sons, Inc.: Hoboken, **2010**, pp 343-436; c) Brown, J. M. in *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds.; Springer-Verlag: Berlin, **1999**; Vol. I, pp 121-182; d) *Asymmetric Catalysis in Organic Synthesis*; Noyori, R., Ed.; Wiley: New York, **1994**; e) *Applied Homogeneous Catalysis with Organometallic Compounds*, 2nd edition; Cornils, B.; Herrmann, W. A., Eds.; Wiley-VCH, Weinheim, **2002**; f) de Vries, J. G.; Elsevier, C. J. *The Handbook of*

Homogeneous Hydrogenation; Wiley-VCH: Weinheim, Germany, **2007**; g) Tang, W. J.; Zhang, X. M. *Chem. Rev.* **2003**, *103*, 3029.

[2] For reviews on the use of carbohydrate-based ligands in asymmetric catalysis, see for instance: a) Diéguez, M.; Pàmies, O.; Claver, C. *Chem. Rev.* **2004**, *104*, 3189; b) Diéguez, M.; Pàmies, O.; Ruiz, A.; Díaz, Y.; Castillón, S.; Claver, C. *Coord. Chem. Rev.* **2004**, *248*, 2165 ; c) Diéguez, M.; Ruiz, A.; Claver, C. *Dalton Trans.* **2003**, 2957 ; d) Diéguez, M.; Claver, C.; Pàmies, O. *Eur. J. Org. Chem*. **2007**, 4621; e) Woodward, S.; Diéguez, M.; Pàmies, O. *Coord. Chem. Rev.* **2010**, *254*, 2007; f) Boysen, M. M. K. *Chem. Eur. J.* **2007**, *13*, 8648; g) Benessere, V.; Del Litto, R.; De Roma, A.; Ruffo, F. *Coord. Chem. Rev.* **2010**, *254*, 390.

[3] For recent reviews, see: a) Fernández-Pérez, H.; Etayo, P.; Panossian, A.; Vidal-Ferran, A. *Chem. Rev.* **2011**, *111*, 2119; b) van Leeuwen, P.W.N.M.; Kamer, P.C.J.; Claver, C.; Pàmies, O.; Diéguez, M. *Chem. Rev.* **2011**, *111*, 2077.

[4] For example, see: a) Pàmies, O.; Diéguez, M.; Net, G.; Ruiz, A.; Claver, C. *Chem. Commun.* **2000**, 2383; b) Pàmies, O.; Diéguez, M.; Net, G.; Ruiz, A.; Claver, C. *J. Org. Chem.* **2001**, *66*, 8364; c) Jia, X.; Li, X.; Lam, W. S.; Kok, S. H. L.; Xu, L.; Lu, G.; Yeung, C.-H.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2004**, *15*, 2273; d) Deerenberg, S.; Pàmies, O.; Diéguez, M.; Claver, C.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *J. Org. Chem.* **2001**, *66*, 7626; e) Suárez, A.; Pizzano, A. *Tetrahedron: Asymmetry* **2001**, *12*, 2501; f) Suárez, A.; Méndez-Rojas, M. A.; Pizzano, A. *Organometallics* **2002**, *21*, 4611; g) Rubio, M.; Suárez, A.; Álvarez, E.; Pizzano, A. *Chem. Commun.* **2005**, 628; h) Rubio, M.; Vargas, S.; Suárez, A.; Álvarez, E.; Pizzano, A. *Chem. Eur. J.* **2007**, *13*, 1821; i) Vargas, S.; Rubio, M.; Suárez, A.; Pizzano, A. *Tetrahedron Lett.* **2005**, *46*, 2049; j) Vargas, S.; Rubio, M.; Suárez, A.; del Rio, D.; Álvarez, E.; Pizzano, A. *Organometallics* **2006**, *25*, 961; k) Yan, Y.; Chi, Y.; Zhang, X. *Tetrahedron: Asymmetry* **2004**, *15*, 2173; l) Müller, C.; López, L. G.; Kooijman, H.; Spek, A. L.; Vogt, D. *Tetrahedron Lett.* **2006**, *47*, 2017; m) Férnandez-Pérez, H.; Pericàs, M. A.; Vidal-Ferran, A. *Adv. Synth. Catal.* **2008**, *350*, 1984; n) Vidal-Ferran, A.; Férnandez-Pérez, H.; Pericàs, M. A. PCT Int. Appl. WO 2009030626 A1, **2009**.

[5] For instante, see: a) Francio, G.; Faraone, F.; Leitner, W. *Angew. Chem., Int. Ed.* **2000**, *39*, 1428; b) Hu, X. P.; Zheng, Z. *Org. Lett.* **2004**, *6*, 3585; c) Burk, S.; Francio, G.; Leitner, W. *Chem. Commun.* **2005**, 3460; d) Hu, X. P.; Zheng, Z. *Org. Lett.* **2005**, *7*,

419; e) Zeng, Q. H.; Hu, X. P.; Duan, Z. C.; Liang, X. M.; Zheng, Z. *Tetrahedron: Asymmetry* **2005**, *16*, 1233; f) Huang, J. D.; Hu, X. P.; Duan, Z. C.; Zeng, Q. H.; Yu, S. B.; Deng, J.; Wang, D. Y.; Zheng, Z. *Org. Lett.* **2006**, *8*, 4367; g) Vallianatou, K. A.; Kostas, I. D.; Holz, J.; Börner, A. *Tetrahedron Lett.* **2006**, *47*, 7947; h) Yu, S.-B.; Huang, J.-D.; Wang, D.-Y.; Hu, X.-P.; Deng, J.; Duan, Z.-C.; Zheng, Z. *Tetrahedron: Asymmetry* **2008**, *19*, 1862; i) Qiu, M.; Wang, D. Y.; Hu, X. P.; Huang, J. D.; Yu, S. B.; Deng, J.; Duan, Z. C.; Zheng, Z. *Tetrahedron: Asymmetry* **2009**, *20*, 210; j) Wang, D. Y.; Hu, X. P.; Huang, J. D.; Deng, J.; Yu, S. B.; Duan, Z. C.; Xu, X. F.; Zheng, Z. *Angew. Chem., Int. Ed.* **2007**, *46*, 7810; k) Qiu, M.; Hu, X. P.; Wang,D. Y.; Deng, J.; Huang, J. D.; Yu, S. B.; Duan, Z. C.; Zheng, Z. *Adv. Synth. Catal.* **2008**, *350*, 1413; l) Wassenaar, J.; Reek, J. N. H. *J. Org. Chem.* **2009**, *74*, 8403.

[6] a) Diéguez, M. ; Ruiz, A. ; Claver, C. *Chem. Commun.* **2001**, 2702; b) Cessaroti, E.; Araneo, S.; Rimoldi, I.; Tassi, S. *J. Mol. Catal. A* **2003**, *204-205*, 211; c) Reetz, M. T. Meiswinkel, A.; Mehler, G. WO Patent 2005047299; d) Cramer, N.; Laschat, S.; Baro, A. *Organometallics* **2006**, *25*, 2284; e) Reetz, M. T.; Mehler, G.; Bondarev, O. *Chem. Commun.* **2006**, 2292; f) Kostas, I. D.; Vallianatou, K. A.; Holz, J.; Börner, A. *Tetrahedron Lett.* **2008**, *49*, 331.

[7] Nogradi, M. *Stereoselective Synthesis*, 2nd ed.; VCH: Weinheim, **1995**.

[8] a) Landis, C. R.; Halpern, J. *J. Am. Chem. Soc*. **1987**, *109*, 1746; b) Brown, J. M.; Chaloner, P. A.; Morris, G. A. *J. Chem. Soc., Chem. Commun.* **1983**, 644; c) Brown, J. M.; Evans, P. L. *Tetrahedron Lett.* **1988**, *44*, 4905; d) Bodgan, P. L.; Irwin, J. J.; Bosnich, B. *Organometallics* **1989**, *8*, 1450; e) Alcock, N. W.; Brown, J. M.; Derome, A. E.; Lucy, A. R. *J. Chem. Soc., Chem. Commun*. **1985**, 575; f) Allen, D. G.; Wild, S. B.; Wood, D. L. *Organometallics* **1986**, *5*, 1009; g) Brown, J. M.; Maddox, P. J. *J. Chem. Soc., Chem. Commun.* **1987**, 1278; h) Brown, J. M.; Chaloner, P. A.; Morris, G. A. *J. Chem. Soc., Perkin Trans*. 2 **1987**, 1583; i) McCulloch, B. M.; Halpern, J. T., M. R.; Landis, C. R. *Organometallics* **1990**, *9*, 1392; j) Brown, J. M. *Chem. Soc. Rev*. **1993**, *22*, 25; k) Landis, C. R.; Brauch, T. W. *Inorg. Chim. Acta* **1998**, *270*, 285; l) Kimmich, B. F. M.; Somsook, E.; Landis, C. R. *J. Am. Chem. Soc.* **1998**, *120*, 10115; m) Landis, C. R.; Hilfenhaus, P.; Feldgus, S. *J. Am. Chem. Soc.* **1999**, *121*, 8741; n) RajanBabu, T. V.; Radetich, B.; You, K. K.; Ayers, T. A.; Casalnuovo, A. L.; Calabrese, J. C. *J. Org.*

Chem. **1999**, *64*, 3429; o) Feldgus, S.; Landis C. R. *J. Am. Chem. Soc.* **2000**, *122*, 12714; p) Landis, C. R.; Feldgus, S. *Angew. Chem., Int. Ed.* **2000**, *39*, 2863.

[9] See for instance: a) Fernández-Pérez, H.; Donald, S. M. A.; Munslow, I. J.; Benet-Buchholz, J.; Maseras, F.; Vidal-Ferran, A. *Chem. Eur. J.* **2010**, *16*, 6495; b) Deerenberg, S.; Pàmies, O.; Diéguez, M.; Claver, C.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *J. Org. Chem*. **2001**, *66*, 7626.

[10] a) Diéguez, M.; Ruiz, A.; Claver, C. *Tetrahedron: Asymmetry* **2001**, *12*, 2827; b) Raluy, E.; Claver, C.; Pàmies, O.; Diéguez, M. *Org. Lett.* **2007**, *9*, 49; c) Raluy, E.; Pàmies, O.; Diéguez, M. *Adv. Synth. Catal.* **2009**, *351*, 1648.

[11] Raluy, E.; Diéguez, M.; Pàmies, O. *J. Org. Chem.* **2007**, *72*, 2842.

[12] Vineyard, B. D.; Knowles, W. S.; Sabacky, M. J.; Bachman, G. L.; Weinkauff, D. J. *J. Am. Chem. Soc.* **1977**, *99*, 5946.

[13] van den Berg, M.; Haak, R. M.; Minnaard, A. J.; de Vries, A. H. M.; de Vries, J. G.; Feringa, B. L. *Adv. Synth. Catal.* **2002**, *344*, 1003.

[14] a) Paetzold, J.; Bäckvall, J. E. *J. Am. Chem. Soc.* **2005**, *127*, 17620; b) ref. 6b.

3.3. A Modular furanoside thioether-phosphite/phosphinite ligand library for asymmetric Ir-catalyzed hydrogenation of minimally functionalized olefins

Mercedes Coll, Oscar Pàmies and Montserrat Diéguez in *Chem. Commun.* **2011**, *47*, 9215 and full paper manuscript in preparation.

Abstract: We have described the first successful application of non N-donor heterodonor ligands –thioether-phosphite ligands- in the Ir-catalyzed hydrogenation of minimally functionalized olefins. Excellent enantioselectivities (ee's up to 99%) have been obtained for a range of substrates, including challenging terminal disubstituted substrates.

3.3.1. Introduction

Pharmaceuticals, agrochemicals, fragrances, fine chemicals, and natural product chemistry all rely on enantiomerically enriched compounds. Because of its high efficiency, atom economy and operational simplicity, the asymmetric hydrogenation of properly selected prochiral starting materials could be a sustainable and direct synthetic tool for preparing these compounds.[1] For many years now olefins containing an adjacent polar group (i.e. dehydroamino acids) have been successfully reduced by Rh- and Ru- catalyst precursors modified with phosphorus ligands, but the asymmetric hydrogenation of minimally functionalized olefins is less developed because these substrates have no adjacent polar group to direct the reaction.[1]

In the last decade, Ir complexes containing chiral P,N- ligands emerged as powerful tools in the asymmetric hydrogenation of minimally functionalized olefins.[2] They were essentially complementary to Rh- and Ru-diphosphine catalysts. Due to the early success of Pfaltz[3a] and others[3b-e] in developing chiral heterodonor phosphine-oxazoline ligands as chiral mimics of Crabtree's catalyst $[Ir(cod)(py)(PCy_3)]PF_6$,[4] research in this field has focused on maximizing the efficiency of these ligands by: (i) modifying the structure of the chiral ligand's backbone, (ii) replacing the phosphine moiety with a phosphinite, phosphite or carbene group and (iii) changing the oxazoline

moiety for other N-donor groups (such as oxazole, pyridine or thiazole).[5] However, the possibility of changing the nature of the N-donor atom in these heterodonor ligands has never been contemplated.

In this chapter, we report a new classes of non N-donor heterodonor ligands – thioether-phosphite and thioether-phosphinite– (Figure 3.3.1) for the asymmetric Ir-catalyzed hydrogenation of minimally functionalized olefins.[6,7]

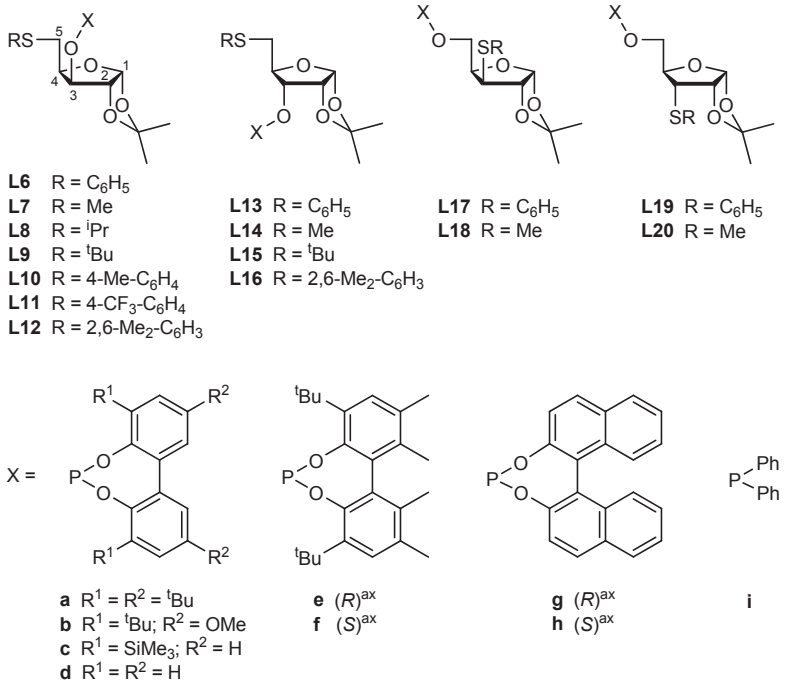


Figure 3.3.1. Thioether-phosphite/phosphinite ligands **L6-L20a-i**.

These ligands are derived from natural D-(+)-xylose and they combine the advantages of phosphite/phosphinite and sugar cores: that is to say, they are readily available from cheap feedstocks, are highly resistant to oxidation, and have a straightforward modular construction.[8] Moreover, the introduction of a thioether moiety in the ligand design may be beneficial because: (i) the S atoms become a stereogenic center when coordinated to metal, which moves the chirality closer to the metal, and (ii) the thioether group is more stable than the oxazoline moiety.[9] The highly modular construction of these ligands makes it easy for us to study the effect of several ligand parameters on catalytic activity and selectivity. With these ligands we therefore investigated the effect of systematically varying the position of the thioether group at

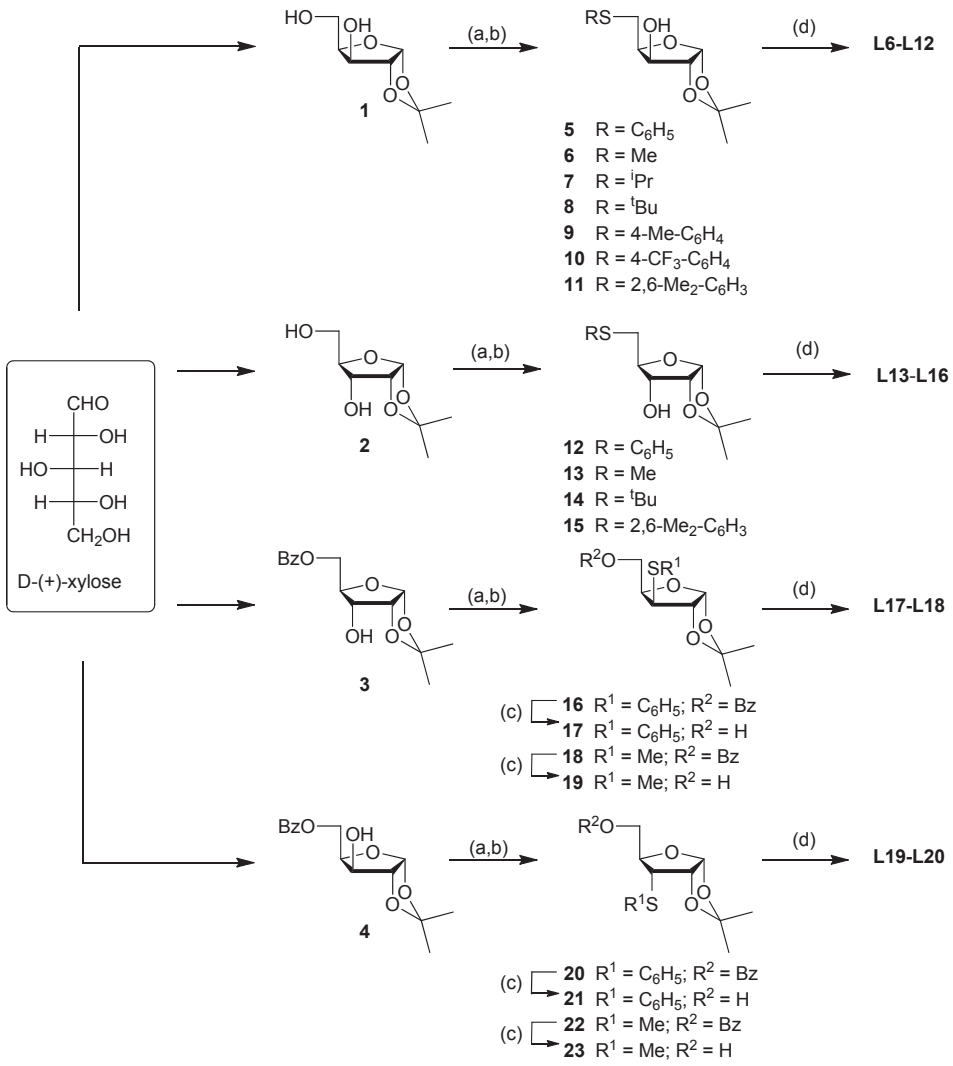
either C-5 (ligands **L6**-**L16**) or C-3 (ligands **L17**-**L20**) of the furanoside backbone, the configuration at C-3 of the furanoside backbone, the substituents in the thioether group (**L6**–**L12**), the substituents and configurations in the biaryl phosphite moiety (**a**-**h**) and the effect of replacing the phosphite moiety by a phosphinite (**i**) group. By carefully selecting these ligand parameters, we achieved high enantioselectivities for a range of minimally functionalized alkenes.

3.3.2. Results and discussion

3.3.2.1. Synthesis of ligands

The synthesis of the thioether-phosphite/phosphinite ligands **L6**-**L20a-i** is straightforward (Scheme 3.3.1).[10] They were efficiently synthesized from the corresponding easily accessible sugar-derived alcohols **1**-**4**.[11] These latter compounds are easily made in few steps from inexpensive D-(+)-xylose. Compounds **1**-**4** were chosen as intermediates for the preparation of ligands because they will easily allow to incorporate the various elements that will enable us to study the position of the thioether (at either C-5 or C-3) as well as the configuration of C-3. Compounds **1**-**4** were treated with one equiv. of tryflic anhydride to produce the desired monotriflates. Subsequent reaction with the corresponding NaSR provided direct access to the corresponding thioether-hydroxyl **5**-**15**[12] and thioether-benzoyl intermediates **16**, **18**, **20** and **22** (Scheme 3.3.1, step (a,b)). Therefore, in this step the desired diversity in electronic and steric properties of the thioether moiety was also attained. The benzoyl protecting group of compounds **16**, **18**, **20** and **22** was removed under basic standard conditions to achieve thioether-hydroxyls **17**, **19**, **21** and **23** (Scheme 3.3.1, step (c)). The last step of the ligand synthesis is the reaction of the corresponding sugar thioether-hydroxyl (**5**-**15**, **17**, **19**, **21** and **23**) with 1 equiv of the corresponding biaryl phosphorochloridite ($ClP(OR)_2$; $(OR)_2$ = **a**-**g**) or chlorodiphenylphosphine in the presence of pyridine (Scheme 3.3.1, step (d)).

All the ligands were stable during purification on neutral alumina under an atmosphere of argon and isolated in good yields as white solids or colourless oils. They were stable at room temperature and very stable to hydrolysis. The elemental analyses were in agreement with the assigned structure. The ^{1}H, ^{13}C and ^{31}P NMR spectra were as expected for these C_1 ligands.

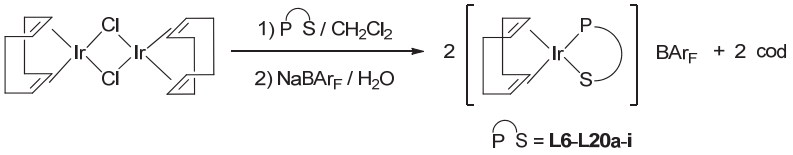


Scheme 3.3.1. Synthesis of thioether-phosphite/phosphinite ligands **L6-L20a-i**. (a) Tf_2O, Py, CH_2Cl_2, -15 °C. (b) NaSR, THF, rt. (c) NH_4OH/MeOH. (d) $ClP(OR)_2$, Py, toluene, 80 °C or $ClPPh_2$, Py, THF, r.t.

3.3.2.2. Synthesis of the Ir-catalyst precursors

The catalyst precursors were made by refluxing a dichloromethane solution of the appropriate ligand (**L6-L20a-i**) 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 3.3.2). All complexes were isolated as air-stable red-orange solids and were

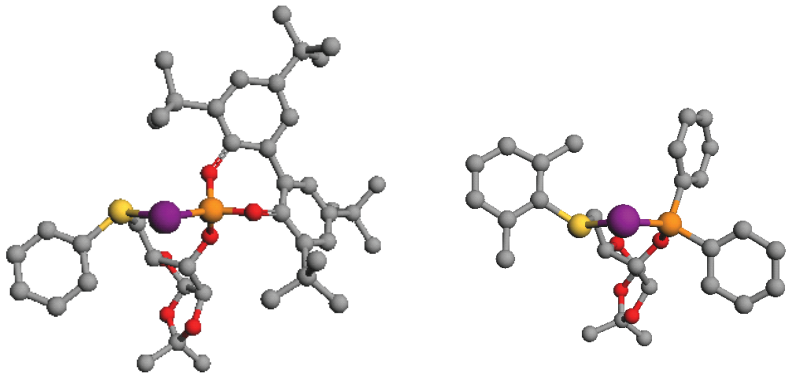
used without further purification. The complexes were characterized by elemental analysis and ^{1}H, ^{13}C, and ^{31}P NMR spectroscopy. The spectral assignments were based on information from ^{1}H-^{1}H and ^{13}C-^{1}H correlation measurements and were as expected for these C_1 iridium complexes.



Scheme 3.3.2. Synthesis of catalyst precursors [Ir(cod)(P-S)]BAr_F (P-S = **L6-L20a-i**).

VT-NMR (+40 °C to -70 °C) experiments indicate the presence of a single isomer in all cases except for [Ir(cod)(**L6-L12a**,**c**,**g-h**)]BAr_F in which two isomers are present. These isomers may be attributed to the two possible diastereoisomers formed when the thioether coordinates to the metal atom (note that the coordinated S atom is a stereogenic center), to the different tropoisomers of the biphenyl moieties, or to both. However, comparing compound Ir/**L6a** with related compounds Ir/**L6g** and Ir/**L6h**, which contain enantiomerically pure binaphthyl moieties, the presence of two isomers in them all suggests that these isomers are due to the different configurations of the sulfur stereocentre. From this we can also conclude that ligand backbones **L13**-**L20** effectively control the thioether coordination to iridium leading to the formation of a single diastereoisomer.

We were able to obtain [Ir(cod)(**L6a**)]BAr_F and [Ir(cod)(**L12i**)]BAr_F crystals that were suitable for X-ray analysis (Figure 3.3.2). The crystal structures confirmed the equatorial position of the thioether substituent in both cases. However, while for [Ir(cod)(**L6a**)]BAr_F the seven-membered chelate ring adopted a boat conformation, it adopted a twist-boat conformation for [Ir(cod)(**L12i**)]BAr_F. This results in a different spatial disposition of the thioether substituent. Thus, while for [Ir(cod)(**L6a**)]BAr_F the thioether moiety occupies the lower left quadrant, for [Ir(cod)(**L12i**)]BAr_F the thioether substituents occupies the upper left quadrant. In addition, the [Ir(cod)(**L6a**)]BArF structure also showed that the biphenyl-phosphite moiety adopts an (*R*)-configuration when coordinated to the iridium center.



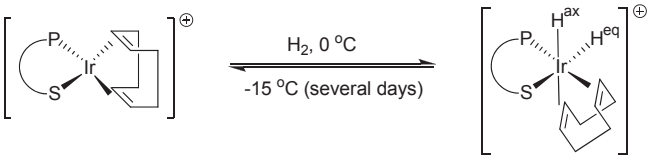
(a) (b)

Figure 3.3.2. Structure of (a) [Ir(cod)(**L6a**)]BAr_F and (b) [Ir(cod)(**L12i**)]BAr_F in the crystal (H atoms, BAr_F ion and cyclooctadiene ligand have been omitted for clarity).

3.3.2.3. Reactivity of the Ir-catalyst precursors with molecular hydrogen

To study the reactivity of the Ir-catalyst precursors with hydrogen, we choose those containing ligands **L7a**, **L14a**, **L18a** and **L20a**, because they contemplate the four ligand backbones and because the ^{1}H NMR signal of the S-Me group appears in a fairly clean region of the ^{1}H NMR spectra, which facilitates its assignment and to identify possible NOE contacts.

Iridium complexes [Ir(cod)(**L**)]BAr_F (**L**= **L7a**, **L14a**, **L18a** and **L20a**) reacted with H_2 at 0 °C to afford the corresponding *cis*-dihydridoolefin species [Ir(H)$_2$(cod)(**L**)]BAr_F in quantitative yield (Scheme 3.3.3).



Scheme 3.3.3. Reactivity of catalyst precursors [Ir(cod)(P-S)]BAr_F with H_2.

The complexes were characterized in solution using the ^{1}H, ^{13}C and ^{31}PNMR measurements. The spectral assignments were based on information from ^{1}H-^{1}H, ^{1}H-^{13}C correlation measurements, in combination with ^{1}H–^{1}H NOESY experiments.

In these species, as well as the sugar backbone and the sulfur atom, even the metal is stereogenic, so the number of possible diastereomers in solution increases. The four potential *cis*-dihydride addition products are depicted in Figure 3.3.3. If dihydrogen addition occurs to the top face of the iridium complex (opposite the sulfur substituent), isomers **A** or **B** would be produced. If the hydrogen addition occurs to the bottom face, isomers **C** and **D** would predominate. Adding H_2 along the Ir-P axis gave isomers **B** and **D** and adding H_2 parallel to the Ir-S axis gave isomers **A** and **C**.

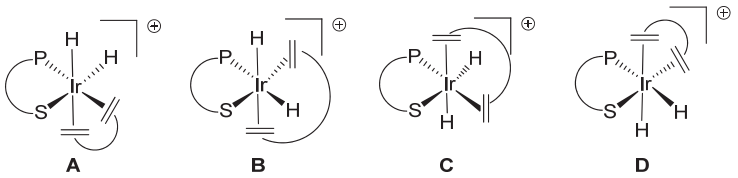


Figure 3.3.3. Possible products of dihydrogen addition to [Ir(cod)(P-S)]BAr_F.

The $^{31}P\{^1H\}$ NMR spectra consist of one sharp signal for these complexes, which do not show any splitting when the temperature is lowered to -80 °C and raised to 40 °C. The expected NMR pattern for the furanoside nucleus has been observed. The shapes of the ^1H and the ^{13}C NMR spectra for all the complexes do not change when their solutions are cooled to -80 °C. In particular, hydride and methyl resonances do not split, which indicates that only one diastereoisomer is present. In the high-field region of the ^1H NMR spectra of the CD_2Cl_2 solutions of [Ir$(H)_2$(cod)(L)]BAr_F there are two doublets due to ^{31}P coupling (Table 3.3.1). The low phosphorus-hydride coupling constants and the relatively low chemical shifts are in agreement with a structure in which the hydrides are located *cis* to the phosphorus atom.[13] Therefore, only structures **A** and **C**, both of which are the products of addition parallel to the sulfur donor, agreed with these conditions. The nature of the hydrido ligands was confirmed by measuring T_{1min} with ^1H relaxation rates. For all complexes the hydride resonances have T_{1min} values ranging from 345 ms to 482 ms in CD_2Cl_2 at -70 °C and 400 MHz, which are consistent with classical hydrides.[14]

The 2D-NOESY experiments provided the isomer adopted for the *cis*-dihydrogen complexes. For all complexes the 2D-NOESY spectra showed that H^{ax} had cross peaks with the methyl signals of the thioether groups and the H-3 of the furanoside backbone. These observations correspond to isomer **C** for complexes

$[Ir(H)_2(cod)(L)]BAr_F$ (L= **L7a** and **L18a**) and to isomer **A** for complexes containing ligands **L14a** and **L20a** with an equatorial disposition of the sulfur substituent.

Table 3.3.1. The ^{1}H-NMR spectroscopic data in the high-field region for complexes $[Ir(H)_2(cod)(L)]BAr_F$.[a]

L	H^{ax}	H^{eq}
L7a	-13.41 (d, $^2J_{H-P}$= 19.2 Hz)	-14.07 (d, $^2J_{H-P}$= 9.8 Hz)
L14a	-12.76 (d, $^2J_{H-P}$= 19.6 Hz)	-14.10 (d, $^2J_{H-P}$= 1.6 Hz)
L18a	-13.27 (d, $^2J_{H-P}$= 18.8 Hz)	-14.32 (d, $^2J_{H-P}$= 9.2 Hz)
L20a	-12.95 (d, $^2J_{H-P}$= 21.6 Hz)	-14.40 (d, $^2J_{H-P}$= 6.4 Hz)

[a] Chemical shifts in ppm. Abbreviation: d= doublet.

3.3.2.4. Asymmetric hydrogenation of trisubstituted olefins

3.3.2.4.1. Asymmetric hydrogenation of minimally functionalized trisubstituted olefins

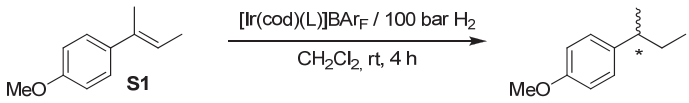
In a first set of experiments, we used the Ir-catalyzed hydrogenation of (*E*)-2-(4-methoxyphenyl)-2-butene **S1** to study the potential of ligands **L6-L20a-i**. **S1** was chosen as the substrate because it has been hydrogenated by a wide range of catalysts, which enabled the efficiency of the various ligand systems to be compared directly.[2] The results are summarized in Table 3.3.2. We found 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.

The results indicate a cooperative effect between the position of the thioether group and the configuration of carbon atom C-3 of the furanoside backbone (Table 3.3.2, entries 1, 10, 23 and 25). The results indicate that the matched combination is achieved with 5-deoxy-ribofuranoside derived ligands **L13**–**L16**, which have the thioether moiety attached to C-5 and an (*R*)-configuration of carbon atom C-3 (entries 10, 18-20).

Results also showed that enantioselectivity is mainly dependent on the steric properties of the substituents in the thioether moiety. Enantioselectivity increases by increasing the steric bulk of the thioether substituent (2,6-Me_2-C_6H_3>^{t}Bu≈^{i}Pr>Ph≈4-X-

C_6H_4≈Me; Table 3.3.2, entries 1 and 4-9). Bulky aryl substituents are therefore needed if enantioselectivities are to be high.

Table 3.3.2. Selected results for the Ir-catalyzed hydrogenation of **S1** using the furanoside P,S-ligand library **L6-L20a-i**.[a]



Entry	Ligand	% Conv[b]	% ee[b]	Entry	Ligand	% Conv[b]	% ee[b]
1	**L6a**	100	13 (*R*)	21	**L16e**	100	99 (*R*)
2	**L6g**	100	50 (*R*)	22	**L16f**	100	50 (*S*)
3	**L6h**	100	48 (*R*)	23	**L17a**	100	68 (*R*)
4	**L7a**	100	15 (*R*)	24	**L18a**	100	21 (*R*)
5	**L8a**	100	23 (*R*)	25	**L19a**	100	68 (*S*)
6	**L9a**	100	24 (*R*)	26	**L20a**	100	24 (*S*)
7	**L10a**	100	14 (*R*)	27	**L6i**	100	17 (*R*)
8	**L11a**	100	13 (*R*)	28	**L7i**	100	8 (*R*)
9	**L12a**	100	30 (*R*)	29	**L8i**	100	14 (*R*)
10	**L13a**	100	87 (*R*)	30	**L9i**	100	10 (*R*)
11	**L13b**	100	85 (*R*)	31	**L10i**	100	16 (*R*)
12	**L13c**	100	87 (*R*)	32	**L11i**	100	17(*R*)
13	**L13d**	100	21 (*R*)	33	**L12i**	100	45 (*R*)
14	**L13e**	100	82 (*R*)	34	**L13i**	100	69 (*R*)
15	**L13f**	100	27 (*S*)	35	**L16i**	100	77 (*R*)
16	**L13g**	100	26 (*R*)	36	**L17i**	100	76 (*R*)
17	**L13h**	100	24 (*R*)	37[c]	**L16a**	82	99 (*R*)
18	**L14a**	100	45 (*R*)	38[c]	**L16e**	81	99 (*R*)
19	**L15a**	100	72 (*R*)	39	**L27a**	100	19 (*R*)
20	**L16a**	100	99 (*R*)	40	**L27c**	100	18 (*R*)

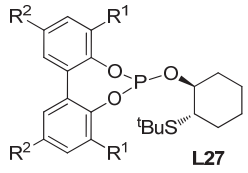
[a] Reactions carried out using 1 mmol of **S1** and 2 mol% of Ir-catalyst precursor.[b] Conversion and enantiomeric excesses determined by chiral GC. [c] Reaction carried out at 0.5 mol% of Ir-catalyst precursor.

We also found that bulky substituents need to be present in the biaryl phosphite moieties if enantioselectivities are to be high (i.e. Table 3.3.2, entries 10-12 *vs* 13). The results also show a cooperative effect between the configuration of the bulky biphenyl moiety and the configuration of the ligand backbone on enantioselectivity. This led to a matched combination for ligand **L13e**, which contains an (*R*)-biaryl moiety (Table 3.3.2, entry 14). In addition, a comparison of the absolute stereochemistry obtained by using ligands with bulky tropoisomeric biphenyl moieties (**L13a-c**; entries 10-12) with those obtained upon using the related enantiopure biphenyl ligands **L13e** and **L13f** (entries 14-15) shows that the tropoisomeric biphenyl moiety in ligands **L13a**–**c** adopts an (*R*)-configuration upon forming a complex with iridium. In contrast, the biaryl-configuration of ligands containing less sterically hindered binaphthyl substituents (**g**-**h**) has little effect on the enantioselectivity (entries 16 and 17).

Finally, we studied the effect of introducing a phosphinite moiety in catalytic performance. In general, the results of using ligands **L6-L20i** indicated that the replacing the phosphite moiety by a phosphinite group in the ligands had a negative effect on enantioselectivity (Table 3.3.2, entry 27-36).

In summary, excellent enantioselectivities (ee's up to 99%) were obtained with ligands **L16a** and **L16e** (Table 3.3.2, entries 20 and 21), which contain the optimal combination of ligand parameters. We also performed the reaction at low catalyst loading (0.5 mol%) using ligand Ir-**L16a** and Ir-**L16e** catalysts (Table 3.3.2, entries 37 and 38). The excellent enantioselectivities (99% (*R*) ee) were maintained.

For comparison purposes, we also screened cyclohexane-based phosphite-thioether ligands **L27a-c**, which are based on one of the most successful ligand backbones developed for this process (Figure 3.3.4).[15] The results indicate that the cyclohexane-backbone is much less effective in transferring the chiral information than the ribofuranoside backbone (Table 3.3.2; entries 19 *vs* 39-40).

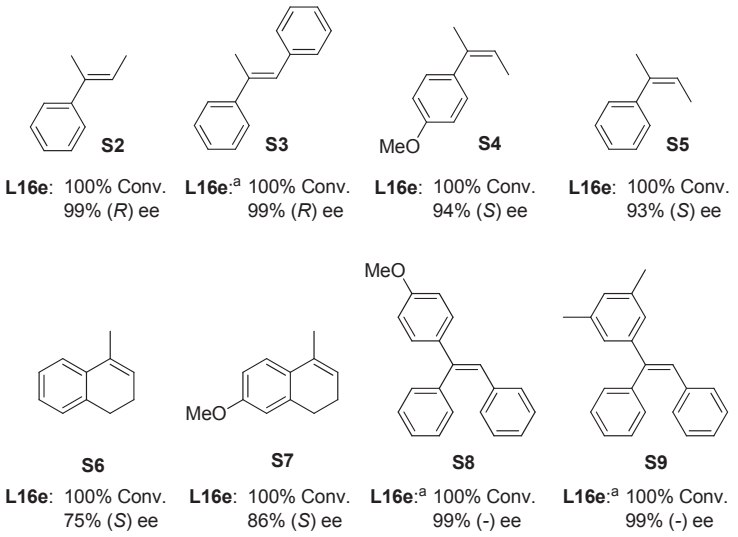


L27

a $R^1 = R^2 = {}^t$Bu
b $R^1 = {}^t$Bu; R^2 = OMe
c $R^1 = SiMe_3$; R^2 = H

Figure 3.3.4. Thioether-phosphite ligand **L27a-c** based on Evan's cyclohexane backbone.

We then studied the asymmetric hydrogenation of other *E*- and *Z*-trisubstituted olefins (**S2**-**S9**) by using the thioether-phosphite/phosphinite ligand library **L6**–**L20a**–**i**. The most noteworthy results are shown in Scheme 3.3.4 (for a full set of results, see Tables 3.3.5-3.3.7 in supporting information).



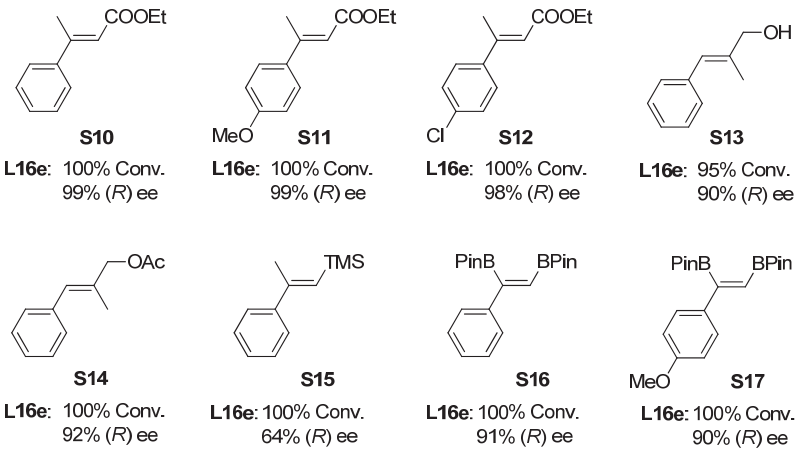
Scheme 3.3.4. Selected hydrogenation results of trisubstituted olefins using [Ir(cod)(**L6-L20a-i**)]BAr_F catalyst precursors. Reaction conditions: 2 mol % catalyst precursor, CH_2Cl_2 as solvent, 100 bar H_2, 4 h.[a] 8 h.

The enantioselectivities are among the best observed for these substrates.[2,5] The hydrogenation of both *E*- and *Z*-trisubstituted olefins followed the same trends as the reduction of **S1**. The best enantioselectivities (ee's up to 99%) were therefore obtained using Ir-**L16a** and Ir-**L16e** catalytic systems. Interestingly, *Z*-trisubstituted isomers, which are usually hydrogenated less enantioselectively than the corresponding *E*-isomers, were also hydrogenated in high enantioselectivities using the [Ir(cod)(P-S)]BAr_F catalyst precursors. Our results also indicated that for acyclic olefins enantioselectivity (ee values up to 99%) is relatively insensitive to the electronic nature of the substrate phenyl ring (substrates **S1** and **S4** *vs* **S2** and **S5**, respectively). This contrast with the positive effect on enantioselectivity observed for cyclic substrates when introducing a methoxy substituent in the phenyl ring (Scheme 3.3.4, substrate **S6** *vs* **S7**). It should be pointed out the excellent enantioselectivities obtained in the reduction of triarylsubstituted substrates **S8** and **S9** (ee's up to 99%). This latter

substrate class provides an easy entry point to diarylmethine chiral centers, which are present in several important drugs and natural products.[16] Despite this, only two catalytic systems have recently able to hydrogenate this type of substrate with high enantioselectivities.[17]

3.3.2.4.2. Asymmetric hydrogenation of trisubstituted olefins containing a neighboring polar group

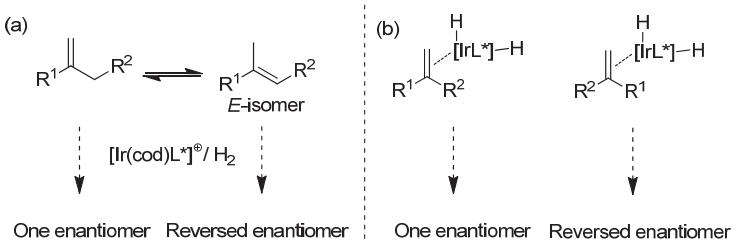
To further study the potential of the furanoside thioether-phosphite/phosphinite ligand library **L6-L20a-i** in the reduction of minimally functionalized trisubstituted olefins, we screened it in the Ir-catalyzed hydrogenation of trisubstituted alkenes containing a neighboring polar group. These substrates are interesting because they allow for further functionalization and they therefore are important synthons for the synthesis of more complex chiral molecules. The results are summarized in Scheme 3.3.5 (for a full set of results, see Table 3.3.8 in supporting information). The reduction of substrates **S10-S17** followed the same trends as those observed for the previous *E*- and *Z*-trisubstituted substrates. Again, high-to-excellent enantioselectivities (ee values up to 99%) for a range of substrates were obtained using [Ir(cod)(**L16a**)]BAr_F and [Ir(cod)(**L16e**)]BAr_F catalyst precursors. The reduction of several α,β-unsaturated esters (**S10-S12**) is highly independent of the electronic nature of the substrate phenyl ring (ee's ranging from 98% to 99%). High enantioselectivities were also obtained in the asymmetric reduction of allylic alcohol **S13** and allylic acetate **S14**. On the other hand, the presence of trimethylsilyl groups in the substrate has a negative effect on enantioselectivity. The reduction of enol silane **S15** therefore proceeds with moderate enantiocontrol. Finally, high enantioselectivities (up to 90%) were obtained in the hydrogenation of vinylboronates **S16** and **S17.** The hydrogenation of vinylboronates provides an easy access to chiral borane compounds, which are useful building blocks in organic synthesis because the C-B bond can be readily converted to C-O, C-N and C-C bonds with retention of the chirality.[18]



Scheme 3.3.5. Selected hydrogenation results of trisubstituted olefins containing a neighboring polar group using [Ir(cod)(**L6-L20a-i**)]BAr_F catalyst precursors. Reaction conditions: 2 mol % catalyst precursor, CH_2Cl_2 as solvent, 100 bar H_2, 4 h.

3.3.2.5. Asymmetric hydrogenation of 1,1-disubstituted terminal olefins

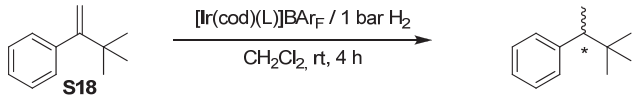
We next applied thioether-phosphite/phoshinite ligands **L6-L20a-i** in the asymmetric hydrogenation of more demanding class of substrates: 1,1-disubstituted terminal olefins. Enantioselectivity is more difficult to control in these substrates than in trisubstituted olefins.[2d-f] There are two main reasons for this: a) the terminal double bond can isomerize to form the more stable internal alkene, which usually leads to the predominant formation of the opposite enantiomer of the hydrogenated product (Scheme 3.3.6 (a)) and b) face selectivity is more difficult to control due to the presence of only two substituents in the substrate (Scheme 3.3.6 (b)).[2e] Few known catalytic systems provide high enantioselectivities for these substrates, and those that do are usually limited in substrate scope.[2e,19,20] 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.[19a]



Scheme 3.3.6

In a first set of experiments we used the Ir-catalyzed asymmetric hydrogenation of 3,3-dimethyl-2-phenyl-1-butene **S18**. The results obtained using the ligand library **L6-L20a-i** are summarized in Table 3.3.3. We were again 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). Enantioselectivities were again 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. In general the effect of these ligand parameters on enantioselectivity followed the same trend as for the reduction of trisubstituted olefins. However, the effect of the configuration of the biaryl phosphite moiety is different. Therefore, in contrast to the previous cooperative effect observed for trisubstituted olefins that lead to higher ee's with ligands containing enantiopure bulky (*R*)-biaryl moieties (**e**), in the reduction of **S18** ligands containing enantiopure bulky (*R*)- and (*S*)-biaryl moieties (**e** and **f**) acted as pseudo-enantiomers (Table 3.3.3, entries 19 and 20). Both enantiomers of the hydrogenation product can be therefore obtained in high enantioselectivities (ee's up to 98%) using Ir-**L16e** and Ir-**L16f** catalytic systems. In summary, enantioselectivities were best using the Ir-catalysts precursors containing thioether-phosphite ligands **L16a**, **L16e** and **L16f**. These results, which again clearly show the efficiency of using modular scaffolds in the ligand design among the best that have been reported for this demanding substrate.substrate.[2e]

Table 3.3.3. Selected results for the Ir-catalyzed hydrogenation of **S18** using the furanoside P,S-ligand library **L6-L20a-i**.[a]



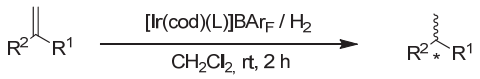
Entry	Ligand	% Conv[b]	% ee[b]	Entry	Ligand	% Conv[b]	% ee[b]
1	**L6a**	100	28 (*R*)	17	**L15a**	100	42 (*S*)
2	**L7a**	100	4 (*R*)	18	**L16a**	100	98 (*S*)
3	**L8a**	100	31(*R*)	19	**L16e**	100	98 (*S*)
4	**L9a**	100	35 (*R*)	20	**L16f**	100	97 (*R*)
5	**L10a**	100	27 (*R*)	21	**L17a**	100	45 (*S*)
6	**L11a**	100	25 (*R*)	22	**L18a**	100	13 (*S*)
7	**L12a**	100	42 (*R*)	23	**L19a**	100	6 (*R*)
8	**L13a**	100	63 (*S*)	24	**L20a**	100	3 (*R*)
9	**L13b**	100	62 (*S*)	25	**L6i**	100	4 (*S*)
10	**L13c**	100	62 (*S*)	26	**L7i**	100	6 (*S*)
11	**L13d**	100	3 (*S*)	27	**L8i**	100	2 (*S*)
12	**L13e**	100	64 (*S*)	28	**L9i**	100	4 (*S*)
13	**L13f**	100	61 (*R*)	29	**L12i**	100	60 (*S*)
14	**L13g**	100	49 (*S*)	30	**L13i**	100	20 (*S*)
15	**L13h**	100	11 (*R*)	31	**L16i**	100	42 (*S*)
16	**L14a**	100	8 (*S*)	32	**L17i**	100	17 (*S*)

[a] Reactions carried out using 1 mmol of **S18** and 2 mol% of Ir-catalyst precursor.[b] Conversion and enantiomeric excesses determined by chiral GC.

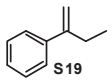
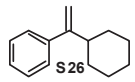
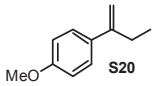
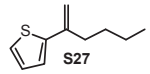
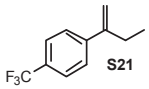
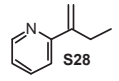
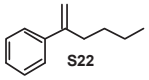
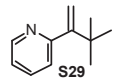
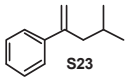
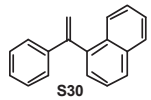
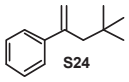
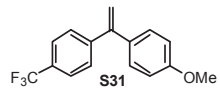
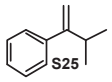
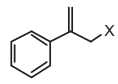
We then studied the asymmetric hydrogenation of other 1,1-disubstituted aryl–alkyl substrates (**S19-S26**), 1,1-disubstituted heteroaryl–alkyl olefins (**S27-S29**), 1,1-diaryl terminal alkenes (**S30-S31**) and 1,1-allylic alcohol and acetate (**S32** and **S33**) by using the thioether-phosphite/phosphinite ligand library **L6-L20a-i**. The most noteworthy results are shown in Table 3.3.4 (See also supporting information). The results follow the same trends as the hydrogenation of **S18**. Again, catalyst precursors

containing the thioether-phosphite ligands **L16a** and **L16e-f** provided the best enantioselectivities (ee's up to 99%).

Table 3.3.4. Selected results for the Ir-catalyzed hydrogenation of minimally functionalized 1,1-disubstituted terminal olefins using ligands **L6-L20a-i**.[a]



R^2 = aryl, 2-thiophene, 2-pyridine
R^1 = alkyl, aryl, CH_2OH, CH_2OAc

Entry	Substrate	Ligand	% ee[b]	Entry	Substrate	Ligand	% ee[b]
1	 S19	**L16a**	78 (*S*)	10	 S26	**L16a**	40 (*S*)
2		**L16e**	79 (*S*)				
3		**L16f**	77 (*R*)				
4	 MeO S20	**L16a**	73 (*S*)	11	 S S27	**L16a**	55 (-)
5	 F_3C S21	**L16a**	81 (*S*)	12	 N S28	**L16a**	61 (+)
6	 S22	**L16a**	62 (*S*)	13	 N S29	**L16a**	99 (+)
				14		**L16e**	99 (+)
				15		**L16f**	98 (-)
7	 S23	**L16a**	65 (*S*)	16[c]	 S30	**L16a**	43 (+)
8	 S24	**L16a**	43 (*S*)	17[c]	 F_3C S31 OMe	**L16a**	18 (+)
9	 S25	**L16a**	28 (*S*)	18[c]	 X **S32**; X = OH	**L16a**	83 (*S*)
				19[c]	**S33**; X = OAc	**L16a**	81 (*S*)

[a] Reactions carried out using 1 mmol of substrate and 0.2 mol% of Ir-catalyst precursor at 1 bar of H_2. Full conversions were obtained in all cases. [b] Enantiomeric excesses determined by chiral GC (except for entry 16 that were measured by HPLC). [c] Reaction carried out at 50 bar of H_2.

Our results with several 1,1-disubstituted aryl–alkyl substrates (**S18-S26**) indicated that enantioselectivity is highly affected by the nature of the alkyl chain (ee's ranging from 28% to 98%, Table 3.3.4, entry 18 and Table 3.3.4, entries 1 and 6-10) and less affected by the electronic nature of the aryl ring (ee's ranging from 79% to

81%, Table 3.3.4, entries 1 and 4-5). One plausible explanation can be found in the competition between direct hydrogenation *vs* isomerization for the different substrates. This is supported by the fact that the hydrogenation of substrate **S18** bearing a *tert*-butyl group, for which isomerization cannot occur, provides high levels of enantioselectivity (ee's up to 98%; Table 3.3.3, entry 18), while the lowest enantioselectivities of the series (Table 3.3.4, entries 9-10) are found for substrates **S25-S26** which form the most stable isomerized tetrasubstituted olefins.

We then decided to apply this ligand library in the asymmetric hydrogenation of 1,1-heteroaromatic alkenes (**S27**–**S29**) because heterocycles are used in industry and because the heterocyclic part can be modified posthydrogenation. Under standard conditions, our catalyst systems were also able to hydrogenate this type of substrate with excellent activities and moderate-to-excellent enantioselectivities (ee's up to 99%; Table 3.3.4, entries 11-15). The results again suggest that isomerization is a key factor to achieve high ee's for this substrate class. Therefore, the highest enantioselectivity was obtained in the hydrogenation of **S29** bearing a *tert*-butyl group (Table 3.3.4, entries 13-15).

Next, we studied the hydrogenation of several diaryl terminal alkenes (**S30-S31**; Table 3.3.4, entries 16-17). Enantiopure diarylalkanes are important intermediates for the preparation of drugs and research materials.[21] They have traditionally been prepared using rather laborious approaches.[21,22] Recently, it has been shown that they can be prepared more efficiently using enantioselective hydrogenation.[5h] Substrates differing sterically (**S30**) and electronically (**S31**) were hydrogenated with low-to-moderate enantioselectivities (ee's up to 40%) using Ir-**L16a** catalytic system.

Finally, we tested the ligand library in the hydrogenation of the allylic alcohol **S32** and allylic acetate **S33**. Derivatives of the hydrogenation of these products are important intermediates for the synthesis of high-value cosmetics, natural products and drugs.[23] Good enantioselectivities up to 83% were obtained using ligand **L16a** (Table 3.3.4, entries 18 and 19). These results again indicate that the new Ir-P,S catalytic systems are also able to efficiently hydrogenate substrates containing a neighboring polar group in terminal olefins.

3.3.3. Conclusions

A thioether-phosphite/phosphinite ligand library, which contains a furanoside as a simple but effective backbone, was tested in the asymmetric Ir-catalyzed hydrogenation of several minimally functionalized alkenes. We found that their effectiveness at transferring the chiral information in the product can be tuned by correctly choosing the ligand components. Enantioselectivities were therefore excellent (ee's up to 99%) in a wide range of *E*- and *Z*-trisubstituted alkenes. It should be pointed out that these catalysts are also very tolerant to the presence of neighboring polar group. Thus, a range of allylic alcohols, acetates, α,β-unsaturated esters and vinylboronates were hydrogenated in high enantioselectivities. The good performance extends to the very challenging class of terminal disubstituted aryl/alkyl olefins. For this substrate class, our results indicated that enantioselectivity is dependent on the nature of the alkyl substrate substituent, which has been attributed to the presence of an isomerisation process under hydrogenation conditions. Enantioselectivities were therefore best in the asymmetric reduction of aryl and heteroaryl/*tert*-butyl substrates (ee's up to 99%). Interestingly, for 1,1-disubstitued substrates, both enantiomers of the hydrogenation product can be obtained in high enantioselectivity, simply by changing the configuration of the biaryl phosphite moiety. These results provide a new class of ligands for the highly enantioselective Ir-catalyzed hydrogenation of a wide range of substrates and open up the enantioselective Ir-catalyzed hydrogenation of minimally functionalized olefins to a type of ligand other than N-donor heterodonor ligands.

3.3.4. Experimental section

3.3.4.1. General considerations

All reactions were carried out using standard Schlenk techniques under an atmosphere of argon. Solvents were purified and dried by standard procedures. Phosphorochloridites are easily prepared in one step from the corresponding biaryls.[24] Phosphite-thioether ligands **L6-L8a**,[10] phosphinite-thioether ligands **L6-L12i**,[12a,25] thioether-hydroxyl compounds **5-11**[10,12a] and (1*R*,2*R*)-2-(*tert*-butylthio)cyclohexanol[26] were prepared as previously described. ^{1}H, $^{13}C\{^{1}H\}$, $^{31}P\{1H\}$ NMR spectra and NOESY experiments were recorded using a 400 MHz spectrometer. Chemical shifts are

relative to that of $SiMe_4$ (^1H and ^{13}C) as internal standard or H_3PO_4 (^{31}P) as external standard. ^1H and ^{13}C assignments were done based on ^1H-^1H gCOSY and ^1H-^{13}C gHSQC experiments.

3.3.4.2. Typical procedure for the preparation of thioether-phosphite ligands L6-L20a-h and L27a-c

The corresponding phosphorochloridite (1.1 mmol) produced *in situ* was dissolved in toluene (5 mL) and pyridine (0.3 mL, 3.9 mmol) was added. The corresponding thioether-hydroxyl compound (1 mmol) was azeotropically dried with toluene (3 x 2 mL) and then dissolved in toluene (5 mL) to which pyridine (0.3 mL, 3.9 mmol) was added. The alcohol solution was transferred slowly to 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.

L6g: Yield: 435 mg, 73 %. ^{31}P NMR (400 MHz, C_6D_6) δ: 148.6 (s). ^1H NMR (400 MHz, C_6D_6) δ: 0.97 (s, 3H, CH_3), 1.18 (s, 3H, CH_3), 3.27 (m, 2H, H-5' and H-5), 4.49 (m, 1H, H-4), 4.68 (d, 1H, H-2, $^2J_{2\text{-}1}$= 4.0 Hz), 4.97 (dd, 1H, H-3, $J_{3\text{-}P}$= 5.6 Hz, $^3J_{3\text{-}4}$= 2.0 Hz), 5.82 (d, 1H, H-1, $^3J_{1\text{-}2}$= 4.0 Hz), 6.8-7.6 (m, 17H, CH=). ^{13}C NMR (400 MHz, C_6D_6) δ: 26.0 (CH_3), 26.5 (CH_3), 30.9 (C-5), 78.0 (d, C-3, $J_{C\text{-}P}$= 16 Hz), 78.7 (C-4), 84.5 (C-2), 105.0 (C-1), 111.7 (CMe_2), 121.4 (CH=), 121.7 (CH=), 123.0 (C), 124.4 (C), 124.9 (d, CH=, $J_{C\text{-}P}$= 7.1 Hz), 126.0 (CH=), 126.3 (CH=), 127.1 (CH=), 128.3 (CH=), 128.4 (CH=), 19.3 (CH=), 130.0 (CH=), 130.5 (CH=), 131.2 (C), 131.7 (C), 132.8 (C), 132.9 (C), 135.6 (C), 147.3 (C), 148.2 (d, C, $J_{C\text{-}P}$= 5.3 Hz). Anal. calcd (%) for $C_{34}H_{29}O_6PS$: C 68.45, H 4.90, S 5.37; found: C 68.54, H 4.86, S 5.24.

L6h: Yield: 393 mg, 66%. ^{31}P NMR (400 MHz, C_6D_6) δ: 145.7 (s). ^1H NMR (400 MHz, C_6D_6) δ: 0.89 (s, 3H, CH_3), 1.16 (s, 3H, CH_3), 3.03 (dd, 1H, H-5', $^2J_{5'\text{-}5}$= 13.2 Hz, $^3J_{5'\text{-}4}$= 5.6 Hz), 3.90 (dd, 1H, H-5, $^2J_{5\text{-}5'}$= 13.2 Hz, $^3J_{5\text{-}4}$= 4.6 Hz), 4.39 (d, 1H, H-2, $^2J_{2\text{-}1}$= 3.6 Hz), 4.41 (m, 1H, H-4), 4.89 (dd, 1H, H-3, $J_{3\text{-}P}$= 9.2 Hz, $^3J_{3\text{-}4}$= 2.8 Hz), 5.68 (d, 1H, H-1, $^3J_{1\text{-}2}$= 3.6 Hz), 6.8-7.6 (m, 17H, CH=). ^{13}C NMR (400 MHz, C_6D_6) δ: 24.4 (CH_3), 27.0 (CH_3), 32.4 (C-5), 76.6 (d, C-3, $J_{C\text{-}P}$= 10.5 Hz), 79.4 (d, C-4, $J_{C\text{-}P}$= 5.3 Hz), 85.1 (C-2), 105.6 (C-1), 112.1 (CMe_2), 122.2 (CH=), 122.3 (CH=), 123.5 (C),

125.1 (C), 125.6 (CH=), 125.7 (CH=), 126.7 (CH=), 127.0 (d, CH=, $J_{C\text{-}P}$= 3.5 Hz), 127.7 (d, CH=, $J_{C\text{-}P}$= 14.7 Hz), 129.0 (d, CH=, $J_{C\text{-}P}$= 4.0 Hz), 129.6 (CH=), 130.3 (CH=), 130.9 (C), 131.3 (C), 131.8 (C), 132.4 (C), 133.4 (C), 133.7 (C), 135.1 (C), 147.9 (d, C, $J_{C\text{-}P}$= 4.0 Hz) , 148.9 (d, C, $J_{C\text{-}P}$= 6.0 Hz). Anal. calcd (%) for $C_{34}H_{29}O_6PS$: C 68.45, H 4.90, S 5.37; found: C 68.51, H 4.92, S 5.44.

L9a: Yield: 442 mg, 63 %. ^{31}P NMR (400 MHz, C_6D_6) δ: 142.4 (s). ^{1}H NMR (400 MHz, C_6D_6) δ: 1.15 (s, 3H, CH_3), 1.25 (s, 9H, CH_3, ^{t}Bu), 1.29 (s, 18H, CH_3, ^{t}Bu), 1.45 (s, 3H, CH_3), 1.63 (s, 9H, CH_3, ^{t}Bu), 1.69 (s, 9H, CH_3, ^{t}Bu), 2.68 (dd, 1H, H-5', $^2J_{5'\text{-}5}$= 13.6 Hz, $^3J_{5'\text{-}4}$= 6.8 Hz), 3.16 (dd, 1H, H-5, $^2J_{5\text{-}5'}$= 13.6 Hz, $^3J_{5\text{-}4}$= 2.8 Hz), 3.99 (m, 1H, H-2), 4.11 (m, 1H, H-4), 4.17 (m, 1H, H-3), 5.52 (d, 1H, H-1, $^3J_{1\text{-}2}$= 3.6 Hz), 6.8-7.6 (m, 4H, CH=). ^{13}C NMR (400 MHz, C_6D_6) δ: 26.9 (CH_3), 27.2 (CH_3), 31.8 (CH_3, ^{t}Bu), 32.0 (CH_3, ^{t}Bu), 32.1 (CH_3, ^{t}Bu), 32.2 (CH_3, ^{t}Bu), 32.3 (CH_3, ^{t}Bu), 35.0 (C, ^{t}Bu), 35.2 (C, ^{t}Bu), 36.4 (C-5), 75.3 (C-3), 76.9 (C-4), 77.9 (C-2), 103.4 (C-1), 113.4 (CMe_2), 124.6 (CH=), 125.3 (CH=), 127.2 (CH=), 127.5 (CH=), 134.2 (C), 134.4 (C), 134.5 (C), 141.5 (C), 141.6 (C) 141.7 (C), 147.0 (C), 147.2 (C), 147.6 (C). Anal. calcd (%) for $C_{40}H_{61}O_6PS$: C 68.54, H 8.77, S 4.57; found: C 68.49, H 8.75, S 4.53.

L10a: Yield: 595 mg, 81 %. ^{31}P NMR (400 MHz, C_6D_6) δ: 143.2 (bs). ^{1}H NMR (400 MHz, C_6D_6) δ: 1.14 (s, 3H, CH_3), 1.29 (s, 18H, CH_3, ^{t}Bu), 1.33 (s, 3H, CH_3), 1.59 (s, 9H, CH_3, ^{t}Bu), 1.63 (s, 9H, CH_3, ^{t}Bu), 2.23 (s, 3H, CH_3-Ph), 2.98 (dd, 1H, H-5', $^2J_{5'\text{-}5}$= 14.0 Hz, $^3J_{5'\text{-}4}$= 6.4 Hz), 3.48 (dd, 1H, H-5, $^2J_{5\text{-}5'}$= 14.0 Hz, $^3J_{5\text{-}4}$= 3.2 Hz), 4.41 (d, 1H, H-2, $^2J_{2\text{-}1}$= 3.6 Hz), 4.53 (m, 1H, H-4), 4.76 (m, 1H, H-3), 5.64 (d, 1H, H-1, $^3J_{1\text{-}2}$= 4.0 Hz), 6.8-7.5 (m, 8H, CH=). ^{13}C NMR (400MHz, C_6D_6), δ: 21.3 (CH_3-Ph), 25.4 (CH_3), 26.0 (CH_3), 31.8 (CH_3, ^{t}Bu), 32.0 (CH_3, ^{t}Bu), 32.1 (CH_3, ^{t}Bu), 32.2 (CH_3, ^{t}Bu), 34.7 (C, ^{t}Bu), 35.0 (C, ^{t}Bu), 36.0 (C-5), 75.1 (C-3), 76.5 (C-4), 78.3 (C-2), 102.9 (C-1), 113.1 (CMe_2), 124.9 (CH=), 125.1 (CH=), 125.8 (CH=), 126.9 (CH=), 127.0 (CH=), 127.2 (CH=), 131.8 (C). 133.8 (C), 134.0 (C), 134.2 (C), 141.1 (C), 141.4 (C) 141.5 (C), 145.8 (C), 146.2 (C), 146.3 (C). Anal. calcd (%) for $C_{43}H_{59}O_6PS$: C 70.27, H 8.09, S 4.36; found: C 70.25, H 8.10, S 4.38.

L11a: Yield: 623 mg, 79%. ^{31}P NMR (400 MHz, C_6D_6) δ: 143.4 (bs). ^{1}H NMR (400 MHz, C_6D_6) δ: 1.17 (s, 3H, CH_3), 1.29 (s, 9H, CH_3, ^{t}Bu), 1.31 (s, 9H, CH_3, ^{t}Bu), 1.38 (s, 3H, CH_3), 1.51 (s, 9H, CH_3, ^{t}Bu), 1.60 (s, 9H, CH_3, ^{t}Bu), 2.87 (dd, 1H, H-5', $^2J_{5'\text{-}5}$= 14.0 Hz, $^3J_{5'\text{-}4}$= 6.4 Hz), 3.48 (dd, 1H, H-5, $^2J_{5\text{-}5'}$= 14.0 Hz, $^3J_{5\text{-}4}$= 3.2 Hz), 4.52 (d, 1H, H-2, $^2J_{2\text{-}1}$= 4.0 Hz), 4.64 (m, 1H, H-4), 4.69 (m, 1H, H-3), 5.59 (d, 1H, H-1, $^3J_{1\text{-}}$

$_2$= 4.0 Hz), 6.8-7.5 (m, 8H, CH=). ^{13}C NMR (400MHz, C_6D_6), δ: 26.0 (CH_3), 26.3 (CH_3), 31.9 (CH_3, ^{t}Bu), 32.0 (CH_3, ^{t}Bu), 32.2 (CH_3, ^{t}Bu), 34.7 (C, ^{t}Bu), 34.8 (C, ^{t}Bu), 35.0 (C, ^{t}Bu), 35.8 (C-5), 74.3 (C-3), 76.9 (C-4), 78.2 (C-2), 102.8 (C-1), 113.4 (CMe_2), 124.8 (CH=), 125.6 (CH=), 125.9 (CH=), 126.8 (CH=), 126.9 (CH=), 127.2 (CH=), 131.4 (C). 132.8 (C), 133.4 (C), 133.6 (C), 141.4 (C), 141.8 (C), 145.9 (C), 146.1 (C), 146.2 (C), 146.4 (C). Anal. calcd (%) for $C_{43}H_{56}F_3O_6PS$: C 65.46, H 7.15, S 4.06; found: C 65.43, H 7.13, S 4.04.

L12a: Yield: 520 mg, 69 %. ^{31}P NMR (400 MHz, C_6D_6) δ: 142.7 (bs). ^{1}H NMR (400 MHz, C_6D_6) δ: 1.15 (s, 3H, CH_3), 1.25 (s, 9H, CH_3, ^{t}Bu), 1.31 (s, 9H, CH_3, ^{t}Bu), 1.43 (s, 3H, CH_3), 1.52 (s, 9H, CH_3, ^{t}Bu), 1.60 (s, 9H, CH_3, ^{t}Bu), 2.59 (s, 6H, CH_3-Ar), 2.72 (dd, 1H, H-5', $^2J_{5'-5}$= 14 Hz, $^3J_{5'-4}$= 7.2 Hz), 3.13 (dd, 1H, H-5, $^2J_{5-5'}$= 14 Hz, $^3J_{5-4}$= 3.2 Hz), 3.98 (m, 1H, H-2), 4.03 (m, 1H, H-4), 4.19 (m, 1H, H-3), 5.43 (d, 1H, H-1, $^3J_{1-2}$= 3.6 Hz), 6.8-7.6 (m, 7H, CH=). ^{13}C NMR (400 MHz, C_6D_6) δ: 22.1 (CH_3-Ar), 26.4 (CH_3), 27.0 (CH_3), 31.0 (CH_3, ^{t}Bu) 31.2 (CH_3, ^{t}Bu), 34.3 (C, ^{t}Bu), 35.2 (C, ^{t}Bu), 35.4 (C-5), 75.4 (C-3), 76.5 (C-4), 78.3 (C-2), 104.0 (C-1), 112.8 (CMe_2), 124.0 (d, CH=, J_{C-P}= 12 Hz), 126.7 (CH=), 126.8 (CH=), 128.1 (CH=), 128.2 (CH=), 129.2 (CH=), 133.6 (C), 137.8 (C), 140.4 (C), 141.3 (C), 143.2 (C), 146.8 (C). Anal. calcd (%) for $C_{44}H_{61}O_6PS$: C 70.56, H 8.21, S 4.28; found: C 70.62, H 8.25, S 4.21.

L13a: Yield: 532 mg, 73 %. ^{31}P NMR (400 MHz, C_6D_6) δ: 143.1 (s). ^{1}H NMR (400 MHz, C_6D_6) δ: 1.12 (s, 3H, CH_3), 1.25 (s, 9H, CH_3, ^{t}Bu), 1.27 (s, 9H, CH_3, ^{t}Bu), 1.44 (s, 3H, CH_3), 1.57 (s, 9H, CH_3, ^{t}Bu), 1.59 (s, 9H, CH_3, ^{t}Bu), 2.90 (dd, 1H, H-5', $^2J_{5'-5}$= 13.6 Hz, $^3J_{5'-4}$= 5.2 Hz), 3.23 (dd, 1H, H-5, $^2J_{5-5'}$= 13.6 Hz, $^3J_{5-4}$= 3.2 Hz), 3.96 (m, 1H, H-2), 4.41 (m, 1H, H-3), 4.48 (m, 1H, H-4), 5.41 (d, 1H, H-1, $^3J_{1-2}$= 3.2 Hz), 6.8-7.6 (m, 9H, CH=). ^{13}C NMR (400 MHz, C_6D_6) δ: 26.4 (CH_3), 26.6 (CH_3), 31.0 (CH_3, ^{t}Bu), 31.1 (CH_3, ^{t}Bu), 31.2 (CH_3, ^{t}Bu), 34.3 (C, ^{t}Bu), 35.2 (C, ^{t}Bu), 35.3 (C-5), 76.2 (C-3), 77.5 (d, C-4, J_{C-P}= 3.1 Hz), 78.3 (C-2), 103.8 (C-1), 112.6 (CMe_2), 123.9 (d, CH=, J_{C-P}= 25.9 Hz), 125.6 (CH=), 126.7 (CH=), 126.9 (CH=), 128.6 (CH=), 128.9 (CH=), 129.4 (CH=), 133.1 (C), 133.4 (C), 137.0 (C), 140.4 (C), 140.6 (C), 146.1 (C), 146.2 (C), 146.7 (C). Anal. calcd (%) for $C_{42}H_{57}O_6PS$: C 69.97, H 7.97, S 4.45; found: C 69.95, H 8.01, S 4.41.

L13b: Yield: 408 mg, 61 %. ^{31}P NMR (400 MHz, C_6D_6) δ: 141.8 (s). ^{1}H NMR (400 MHz, C_6D_6) δ: 1.18 (s, 3H, CH_3), 1.27 (s, 9H, CH_3, ^{t}Bu), 1.29 (s, 9H, CH_3, ^{t}Bu), 1.40 (s, 3H, CH_3), 1.59 (s, 9H, CH_3, ^{t}Bu), 1.62 (s, 9H, CH_3, ^{t}Bu), 2.97 (dd, 1H, H-5',

$^2J_{5'-5}$= 13.2 Hz, $^3J_{5'-4}$= 6.4 Hz), 3.23 (dd, 1H, H-5, $^2J_{5-5'}$= 13.2 Hz, $^3J_{5-4}$= 2.4 Hz), 3.28 (s, 3H, CH_3-O), 3.29 (s, 3H, CH_3-O), 3.92 (m, 1H, H-2), 4.39 (m, 1H, H-3), 4.42 (m, 1H, H-4), 5.39 (d, 1H, H-1, $^3J_{1-2}$= 3.6 Hz), 6.8-7.6 (m, 9H, CH=). ^{13}C NMR (400 MHz, C_6D_6) δ: 26.2 (CH_3), 26.5 (CH_3), 31.2 (CH_3, ^{t}Bu), 31.3 (CH_3, ^{t}Bu), 31.5 (CH_3, ^{t}Bu), 34.2 (C, ^{t}Bu), 34.9 (C, ^{t}Bu), 35.6 (C-5), 54.8 (CH_3-O), 76.3 (C-3), 77.4 (b, C-4), 78.5 (C-2), 103.4 (C-1), 112.4 (CMe_2), 123.8 (d, CH=, J_{C-P}= 24.2 Hz), 125.3 (CH=), 126.4 (CH=), 126.9 (CH=), 128.2 (CH=), 128.5 (CH=), 129.0 (CH=), 133.4 (C), 133.4 (C), 137.0 (C), 140.4 (C), 140.6 (C), 146.1 (C), 151.3 (C), 151.6 (C). Anal. calcd (%) for $C_{36}H_{45}O_8PS$: C 64.65, H 6.78, S 4.79; found: C 64.64, H 6.77, S 4.77.

L13c: Yield: 397 mg, 62 %. ^{31}P NMR (400 MHz, C_6D_6) δ: 141.7 (s). ^{1}H NMR (400 MHz, C_6D_6) δ: 0.37 (s, 9H, CH_3-Si), 0.42 (s, 9H, CH_3-Si) 1.09 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 2.84 (dd, 1H, H-5', $^2J_{5'-5}$= 14.0 Hz, $^3J_{5'-4}$= 6.4 Hz), 3.20 (dd, 1H, H-5, $^2J_{5-5'}$= 14.0 Hz, $^3J_{5-4}$= 3.2 Hz), 3.91 (m, 1H, H-2), 4.29 (m, 1H, H-3), 4.46 (m, 1H, H-4), 5.32 (d, 1H, H-1, $^3J_{1-2}$= 4.0 Hz), 6.8-7.6 (m, 11H, CH=). ^{13}C NMR (400 MHz, C_6D_6) δ: 0 (CH_3-Si), 0.1 (CH_3-Si), 26.6 (CH_3), 26.7 (CH_3), 35.9 (C-5), 76.3 (C-3), 77.8 (C-4), 78.5 (C-2), 104.0 (C-1), 112.7 (CMe_2), 125.1 (CH=), 125.3 (CH=), 125.8 (C), 126.0 (CH=), 126.9 (C), 128.2 (CH=), 128.8 (CH=), 129.8 (CH=), 130.9 (C), 132.5 (CH=), 132.7 (CH=), 133.1 (C), 135.2 (CH=), 135.7 (CH=), 145.9 (C), 146.6 (C). Anal. calcd (%) for $C_{32}H_{41}O_6PS$: C 59.97, H 6.45, S 5.00; found: C 60.02, H 6.49, S 4.98.

L13d: Yield: 243 mg, 49 %. ^{31}P NMR (400 MHz, C_6D_6) δ: 141.8 (s). ^{1}H NMR (400 MHz, C_6D_6) δ: 1.11 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 2.92 (dd, 1H, H-5', $^2J_{5'-5}$= 14.0 Hz, $^3J_{5'-4}$= 6.4 Hz), 3.22 (dd, 1H, H-5, $^2J_{5-5'}$= 14.0 Hz, $^3J_{5-4}$= 4.4 Hz), 4.06 (m, 1H, H-2), 4.32 (m, 1H, H-3), 4.36 (m, 1H, H-4), 5.25 (d, 1H, H-1, $^3J_{1-2}$= 3.6 Hz), 6.8-7.6 (m, 13H, CH=). ^{13}C NMR (400 MHz, C_6D_6) δ: 26.1 (CH_3), 26.4 (CH_3), 34.8 (C-5), 76.2 (C-3), 77.9 (C-4), 79.1 (C-2), 103.2 (C-1), 113.1 (CMe_2), 121.5 (CH=), 121.8 (CH=), 124.6 (CH=), 125.3 (CH=), 125.9 (CH=), 126.8 (CH=), 127.9 (CH=), 128.2 (CH=), 129.1 (CH=), 129.5 (CH=), 129.4 (CH=), 131.0 (C), 131.3 (C), 132.4 (C), 132.9 (C), 141.7 (C). Anal. calcd (%) for $C_{26}H_{25}O_6PS$: C 62.89, H 5.08, S 6.46; found: C 62.85, H 5.06, S 6.43.

L13e: Yield: 471 mg, 72 %. ^{31}P NMR (400 MHz, C_6D_6) δ: 136.6 (s). ^{1}H NMR (400 MHz, C_6D_6) δ: 1.11 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 1.58 (s, 9H, CH_3, ^{t}Bu), 1.60 (s, 9H, CH_3, ^{t}Bu), 1.67 (s, 3H, CH_3-Ph), 1.74 (s, 3H, CH_3-Ph), 2.04 (s, 3H, CH_3-Ph), 2.11 (s, 3H, CH_3-Ph), 3.05 (dd, 1H, H-5', $^2J_{5'-5}$= 14.0 Hz, $^3J_{5'-4}$= 4.8 Hz), 3.29 (dd, 1H,

H-5, $^{2}J_{5\text{-}5'}$= 14.0 Hz, $^{3}J_{5\text{-}4}$= 3.6 Hz), 4.06 (m, 1H, H-2), 4.37 (m, 1H, H-3), 4.44 (m, 1H, H-4), 5.38 (d, 1H, H-1, $^{3}J_{1\text{-}2}$= 3.6 Hz), 6.8-7.5 (m, 7H, CH=). ^{13}C NMR (400 MHz, C_6D_6) δ: 16.1 (CH_3-Ph), 16.4 (CH_3-Ph), 19.9 (CH_3-Ph), 20.0 (CH_3-Ph), 26.2 (CH_3), 26.6 (CH_3), 31.2 (CH_3, ^{t}Bu), 31.5 (CH_3, ^{t}Bu), 34.5 (C, ^{t}Bu), 34.7 (C, ^{t}Bu), 35.0 (C-5), 75.5 (d, C-3, $J_{C\text{-}P}$= 4.7 Hz), 77.6 (d, C-4, $J_{C\text{-}P}$= 3.8 Hz), 78.7 (d, C-2, $J_{C\text{-}P}$= 3.1 Hz), 103.6 (C-1), 112.7 (CMe_2), 125.3 (CH=), 125.6 (CH=), 128.1 (CH=), 128.6 (CH=), 128.9 (CH=), 129.2 (CH=), 129.4 (C), 131.6 (C), 132.5 (C), 134.6 (C), 135.1 (C), 137.4 (C), 137.5 (C), 137.6 (C) 138.0 (C), 145.5 (C). Anal. calcd (%) for $C_{38}H_{49}O_6PS$: C 68.65, H 7.43, S 4.82; found: C 68.61, H 7.36, S 4.77.

L13f: Yield: 458 mg, 69 %. ^{31}P NMR (400 MHz, C_6D_6) δ: 136.5 (s). ^{1}H NMR (400 MHz, C_6D_6) δ: 1.11 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 1.57 (s, 9H, CH_3, ^{t}Bu), 1.61 (s, 9H, CH_3, ^{t}Bu), 1.69 (s, 3H, CH_3-Ph), 1.80 (s, 3H, CH_3-Ph), 2.06 (s, 3H, CH_3-Ph), 2.09 (s, 3H, CH_3-Ph), 2.74 (dd, 1H, H-5', $^{2}J_{5'\text{-}5}$= 14.0 Hz, $^{3}J_{5'\text{-}4}$= 6.0 Hz), 3.15 (dd, 1H, H-5, $^{2}J_{5\text{-}5'}$= 14.0 Hz, $^{3}J_{5\text{-}4}$= 2.8 Hz), 4.18 (m, 1H, H-3), 4.36 (m, 1H, H-3), 4.43 (m, 1H, H-4), 5.35 (d, 1H, H-1, $^{3}J_{1\text{-}2}$= 3.6 Hz), 6.8-7.5 (m, 7H, CH=). ^{13}C NMR (400 MHz, C_6D_6) δ: 16.1 (CH_3-Ph), 16.4 (CH_3-Ph), 20.0 (CH_3-Ph), 20.1 (CH_3-Ph), 26.4 (CH_3), 26.5 (CH_3), 31.2 (CH_3, ^{t}Bu), 31.5 (CH_3, ^{t}Bu), 34.5 (C, ^{t}Bu), 34.7 (C, ^{t}Bu), 35.0 (C-5), 76.2 (d, C-3, $J_{C\text{-}P}$= 1.6 Hz), 77.9 (d, C-4, $J_{C\text{-}P}$= 1.8 Hz), 78.2 (d, C-2, $J_{C\text{-}P}$= 2.3 Hz), 104.1 (C-1), 112.5 (CMe_2), 125.5 (CH=), 127.8 (CH=), 128.1 (CH=), 128.3 (CH=), 128.5 (CH=), 128.9 (CH=), 129.2 (CH=), 130.9 (C), 131.0 (C), 131.8 (C), 132.1 (C), 132.2 (C), 132.5 (C), 134.4 (C), 135.2 (C) 137.3 (C), 137.6 (C), 138.0 (C), 138.1 (C), 144.6 (C), 145.3 (C). Anal. calcd (%) for $C_{38}H_{49}O_6PS$: C 68.65, H 7.43, S 4.82; found: C 68.63, H 7.41, S 4.81.

L13g: Yield: 322 mg, 54 %. ^{31}P NMR (400 MHz, C_6D_6) δ: 141.8 (s). ^{1}H NMR (400 MHz, C_6D_6) δ: 1.10 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 2.89 (dd, 1H, H-5', $^{2}J_{5'\text{-}5}$= 14.0 Hz, $^{3}J_{5'\text{-}4}$= 4.4 Hz), 3.20 (dd, 1H, H-5, $^{2}J_{5\text{-}5'}$= 14.0 Hz, $^{3}J_{5\text{-}4}$= 3.2 Hz), 4.04 (m, 1H, H-2), 4.38 (m, 2H, H-3 and H-4), 5.24 (d, 1H, H-1, $^{3}J_{1\text{-}2}$= 3.2 Hz), 6.8-7.6 (m, 17H, CH=). ^{13}C NMR (400 MHz, C_6D_6) δ: 26.4 (CH_3), 26.5 (CH_3), 34.5 (C-5), 76.3 (C-3), 77.8 (C-4), 78.5 (C-2), 104.0 (C-1), 112.8 (CMe_2), 121.6 (CH=), 121.9 (CH=), 123.1 (C), 124.9 (d, CH=, $J_{C\text{-}P}$= 7.8 Hz), 125.6 (CH=), 126.3 (d, CH=, $J_{C\text{-}P}$= 3.1 Hz), 127.0 (d, CH=, $J_{C\text{-}P}$= 8.9 Hz), 127.8 (CH=), 128.2 (CH=), 128.6 (CH=), 129.0 (CH=), 129.7 (CH=), 130.5 (CH=), 131.2 (C), 131.7 (C), 132.9 (C), 133.0 (C), 137.0 (C), 147.4 (d, C,

$J_{C\text{-}P}$= 2.3 Hz), 148.0 (d, C, $J_{C\text{-}P}$= 4.6 Hz). Anal. calcd (%) for $C_{34}H_{29}O_6PS$: C 68.45, H 4.90, S 5.37; found: C 68.52, H 4.89, S 5.34.

L13h: Yield: 364 mg, 61 %. ^{31}P NMR (400 MHz, C_6D_6) δ: 140.9 (s). ^{1}H NMR (400 MHz, C_6D_6) δ: 1.11 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 3.00 (dd, 1H, H-5', $^2J_{5'\text{-}5}$= 14.0 Hz, $^3J_{5'\text{-}4}$= 6.6 Hz), 3.31 (dd, 1H, H-5, $^2J_{5\text{-}5'}$= 14.0 Hz, $^3J_{5\text{-}4}$= 3.6 Hz), 4.12 (m, 1H, H-2), 4.19 (m, 1H, H-3), 4.47 (m, 1H, H-4), 5.17 (d, 1H, H-1, $^3J_{1\text{-}2}$= 3.2 Hz), 6.8-7.6 (m, 17H, CH=). ^{13}C NMR (400 MHz, C_6D_6) δ: 27.1 (CH_3), 35.7 (C-5), 77.4 (d, C-3, $J_{C\text{-}P}$= 4.6 Hz), 77.8 (d, C-4, $J_{C\text{-}P}$= 3.9 Hz), 79.2 (C-2), 104.6 (C-1), 113.2 (CMe_2), 122.4 (CH=), 122.8 (CH=), 123.4 (C), 125.2 (C), 125.6 (d, CH=, $J_{C\text{-}P}$= 12.2 Hz), 126.5 (CH=), 127.2 (CH=), 127.0 (d, CH=, $J_{C\text{-}P}$= 17.0 Hz), 129.0 (CH=), 129.5 (CH=), 129.9 (CH=), 130.6 (CH=), 131.3 (CH=), 131.9 (C), 132.4 (C), 133.4 (C), 133.7 (d, C, $J_{C\text{-}P}$= 1.5 Hz), 137.6 (C), 148.2, 149.4 (d, C, $J_{C\text{-}P}$= 4.5 Hz). Anal. calcd (%) for $C_{34}H_{29}O_6PS$: C 68.45, H 4.90, S 5.37; found: C 68.48, H 4.82, S 5.35.

L14a: Yield: 382 mg, 58 %. ^{31}P NMR (400 MHz, C_6D_6) δ: 143.4 (s). ^{1}H NMR (400 MHz, C_6D_6) δ: 1.14 (s, 3H, CH_3), 1.25 (s, 9H, CH_3, ^{t}Bu), 1.27 (s, 9H, CH_3, ^{t}Bu), 1.48 (s, 3H, CH_3), 1.59 (s, 9H, CH_3, ^{t}Bu), 1.61 (s, 9H, CH_3, ^{t}Bu), 1.92 (s, 3H, CH_3-S), 2.46 (dd, 1H, H-5', $^2J_{5'\text{-}5}$= 14.4 Hz, $^3J_{5'\text{-}4}$= 5.6 Hz), 2.71 (dd, 1H, H-5, $^2J_{5\text{-}5'}$= 14.4 Hz, $^3J_{5\text{-}4}$= 3.2 Hz), 3.99 (m, 1H, H-2), 4.38 (m, 1H, H-4), 4.42 (m, 1H, H-3), 5.42 (d, 1H, H-1, $^3J_{1\text{-}2}$= 3.6 Hz), 7.2-7.7 (m, 4H, CH=). ^{13}C NMR (400 MHz, C_6D_6) δ: 17.7 (CH_3-S), 27.3 (CH_3), 27.5 (CH_3), 32.1 (CH_3, ^{t}Bu), 35.2 (C, ^{t}Bu), 35.9 (C, ^{t}Bu), 36.2 (C-5), 76.9 (C-3), 79.1 (C-2), 80.4 (C-4), 104.7 (C-1), 113.5 (CMe_2), 124.9 (CH=), 125.2 (CH=), 127.6 (CH=), 127.8 (CH=), 129.8 (C), 134.4 (C), 134.8 (C), 141.5 (C), 147.2 (C), 147.3 (C), 147.5 (C). Anal. calcd (%) for $C_{37}H_{55}O_6PS$: C 67.45, H 8.41, S 4.87; found: C 67.51, H 8.45, S 4.81.

L15a: Yield: 588 mg, 84 %. ^{31}P NMR (400 MHz, C_6D_6) δ: 143.1 (s). ^{1}H NMR (400 MHz, C_6D_6) δ: 1.13 (s, 3H, CH_3), 1.21 (s, 9H, CH_3, ^{t}Bu), 1.25 (s, 9H, CH_3, ^{t}Bu), 1.28 (s, 9H, CH_3, ^{t}Bu), 1.47 (s, 3H, CH_3), 1.61 (s, 9H, CH_3, ^{t}Bu), 1.62 (s, 9H, CH_3, ^{t}Bu), 2.66 (dd, 1H, H-5', $^2J_{5'\text{-}5}$= 14.0 Hz, $^3J_{5'\text{-}4}$= 7.2 Hz), 2.95 (dd, 1H, H-5, $^2J_{5\text{-}5'}$= 14.0 Hz, $^3J_{5\text{-}4}$= 2.8 Hz), 3.95 (m, 1H, H-2), 4.35 (m, 1H, H-3), 4.49 (m, 1H, H-4), 5.46 (d, 1H, H-1, $^3J_{1\text{-}2}$= 4.0 Hz), 7.0-7.7 (m, 4H, CH=). ^{13}C NMR (400 MHz, C_6D_6) δ: 27.3 (CH_3), 27.5 (CH_3), 31.7 (CH_3, ^{t}Bu), 32.0 (CH_3, ^{t}Bu), 32.1 (CH_3, ^{t}Bu), 32.2 (CH_3, ^{t}Bu), 32.3 (CH_3, ^{t}Bu), 35.2 (C, ^{t}Bu), 36.3 (C, ^{t}Bu), 42.4 (C-5), 77.5 (C-3), 79.2 (C-2), 79.6 (C-4), 104.7 (C-1), 113.5 (CMe_2), 124.9 (CH=), 125.1 (CH=), 127.5 (CH=), 127.9 (CH=),

134.1 (C), 134.2 (C), 134.3 (C), 134.4 (C), 141.4 (C), 141.6 (C) 141.7 (C), 147.1 (C), 147.2 (C), 147.5 (C). Anal. calcd (%) for $C_{40}H_{61}O_6PS$: C 68.54, H 8.77, S 4.57; found: C 68.52, H 8.75, S 4.53.

L16a: Yield: 452 mg, 60 %. ^{31}P NMR (400 MHz, C_6D_6) δ: 142.7 (bs). ^{1}H NMR (400 MHz, C_6D_6) δ: 1.11(s, 3H, CH_3), 1.24 (s, 9H, CH_3, ^{t}Bu), 1.26 (s, 9H, CH_3, ^{t}Bu), 1.41 (s, 3H, CH_3), 1.52 (s, 9H, CH_3, ^{t}Bu), 1.56 (s, 9H, CH_3, ^{t}Bu), 2.58 (s, 6H, CH_3-Ar), 2.62 (dd, 1H, H-5', $^2J_{5'-5}$= 14 Hz, $^3J_{5'-4}$= 8.8 Hz), 3.06 (dd, 1H, H-5, $^2J_{5-5'}$= 14 Hz, $^3J_{5-4}$= 2.4 Hz), 3.93 (m, 1H, H-2), 4.16 (m, 1H, H-4), 4.28 (m, 1H, H-3), 5.40 (d, 1H, H-1, $^3J_{1-2}$= 3.2 Hz), 6.8-7.6 (m, 7H, CH=). ^{13}C NMR (400 MHz, C_6D_6) δ: 21.9 (CH_3-Ar), 26.4 (CH_3), 31.0 (CH_3, ^{t}Bu), 31.2 (CH_3, ^{t}Bu), 34.3 (C, ^{t}Bu), 35.2 (C, ^{t}Bu), 35.3 (C-5), 76.6 (C-4), 77.5 (C-3), 78.2 (C-2), 103.6 (C-1), 112.5 (CMe_2), 123.9 (d, CH=, J_{C-P}= 15.3 Hz), 126.6 (CH=), 126.9 (CH=), 128.1 (CH=), 128.2 (CH=), 128.9 (CH=), 133.5 (C), 137.5 (C), 140.4 (C), 140.7 (C), 143.3 (C), 146.6 (C), 146.7 (C). Anal. calcd (%) for $C_{44}H_{61}O_6PS$: C 70.56, H 8.21, S 4.28; found: C 70.53, H 8.23, S 4.30.

L16e: Yield: 374 mg, 54 %. ^{31}P NMR (400 MHz, C_6D_6) δ: 135.9 (s). ^{1}H NMR (400 MHz, C_6D_6) δ: 1.08 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 1.54 (s, 9H, CH_3, ^{t}Bu), 1.58 (s, 9H, CH_3, ^{t}Bu), 1.67 (s, 3H, CH_3-Ph), 1.69 (s, 3H, CH_3-Ph), 2.03 (s, 3H, CH_3-Ph), 2.05 (s, 3H, CH_3-Ph), 2.79 (dd, 1H, H-5', $^2J_{5'-5}$= 13.6 Hz, $^3J_{5'-4}$= 7.2 Hz), 3.11 (dd, 1H, H-5, $^2J_{5-5'}$= 13.6 Hz, $^3J_{5-4}$= 2.8 Hz), 4.05 (m, 1H, H-2), 4.22 (m, 1H, H-3), 4.27 (m, 1H, H-4), 5.39 (d, 1H, H-1, $^3J_{1-2}$= 3.6 Hz), 6.9-7.3 (m, 5H, CH=). ^{13}C NMR (400 MHz, C_6D_6) δ: 16.5 (CH_3-Ph), 16.7 (CH_3-Ph), 20.2 (CH_3-Ph), 20.4 (CH_3-Ph), 26.6 (CH_3), 26.8 (CH_3), 31.5 (CH_3, ^{t}Bu), 31.8 (CH_3, ^{t}Bu), 34.8 (C, ^{t}Bu), 35.1 (C, ^{t}Bu), 37.2 (C-5), 76.3 (C-4), 77.8 (C-3), 79.2 (C-2), 103.8 (C-1), 113.0 (CMe_2), 127.8 (CH=), 128.4 (CH=), 128.5 (CH=), 128.6 (CH=), 129.5 (C), 132.9 (C), 134.7 (C), 134.9 (C), 135.5 (C), 137.9 (C), 143.5 (C). Anal. calcd (%) for $C_{40}H_{53}O_6PS$: C 69.34, H 7.71, S 4.63; found: C 69.31, H 7.70, S 4.65.

L16f: Yield: 436 mg, 63 %. ^{31}P NMR (400 MHz, C_6D_6) δ: 136.7 (s). ^{1}H NMR (400 MHz, C_6D_6) δ: 1.20 (s, 3H, CH_3), 1.52 (s, 3H, CH_3), 1.58 (s, 9H, CH_3, ^{t}Bu), 1.67 (s, 9H, CH_3, ^{t}Bu), 1.77 (s, 3H, CH_3-Ph), 1.87 (s, 3H, CH_3-Ph), 2.14 (s, 3H, CH_3-Ph), 2.20 (s, 3H, CH_3-Ph), 2.56 (dd, 1H, H-5', $^2J_{5'-5}$= 13.6 Hz, $^3J_{5'-4}$= 7.6 Hz), 2.99 (dd, 1H, H-5, $^2J_{5-5'}$= 13.6 Hz, $^3J_{5-4}$= 2.0 Hz), 3.98 (m, 1H, H-3), 4.32 (m, 1H, H-4), 4.48 (m, 1H, H-2), 5.47 (d, 1H, H-1, $^3J_{1-2}$= 4.0 Hz), 6.9-7.3 (m, 5H, CH=). ^{13}C NMR (400 MHz, C_6D_6) δ: 16.3 (CH_3-Ph), 16.5 (CH_3-Ph), 20.1 (CH_3-Ph), 22.0 (CH_3-Ph), 26.5 (CH_3), 26.6

(CH_3), 31.4 (CH_3, ^{t}Bu), 31.6 (CH_3, ^{t}Bu), 34.6 (C, ^{t}Bu), 34.8 (C, ^{t}Bu), 36.8 (C-5), 76.8 (C-4), 78.0 (C-3), 78.3 (C-2), 104.1 (C-1), 112.6 (CMe_2), 128.0 (CH=), 128.1 (CH=), 128.3 (CH=), 129.0 (CH=), 131.0 (C), 131.8 (C), 132.6 (C), 133.7 (C), 134.4 (C), 135.4 (C), 137.9 (C), 138.0 (C), 143.4 (C). Anal. calcd (%) for $C_{40}H_{53}O_6PS$: C 69.34, H 7.71, S 4.63; found: C 69.37, H 7.74, S 4.61.

L17a: Yield: 536 mg, 72 %. ^{31}P NMR (400 MHz, C_6D_6) δ: 136.4 (s). ^{1}H NMR (400 MHz, C_6D_6) δ: 0.95 (s, 3H, CH_3), 1.26 (s, 9H, CH_3, ^{t}Bu), 1.28 (s, 9H, CH_3, ^{t}Bu), 1.38 (s, 3H, CH_3), 1.59 (s, 9H, CH_3, ^{t}Bu), 1.60 (s, 9H, CH_3, ^{t}Bu), 3.68 (d, 1H, H-3, $^3J_{3\text{-}4}$= 3.6 Hz), 4.38 (m, 2H, H-5' and H-5), 4.47 (d, 1H, H-2, $^3J_{1\text{-}2}$= 3.6 Hz), 4.82 (m, 1H, H-4), 5.78 (d, 1H, H-1, $^3J_{1\text{-}2}$= 3.6 Hz), 6.8-7.6 (m, 9H, CH=). ^{13}C NMR (400 MHz, C_6D_6) δ: 26.7 (CH_3), 27.2 (CH_3), 31.5 (CH_3, ^{t}Bu), 31.6 (CH_3, ^{t}Bu), 31.9 (CH_3, ^{t}Bu), 32.0 (CH_3, ^{t}Bu), 35.0 (C, ^{t}Bu), 36.0 (C, ^{t}Bu), 53.8 (C-3), 64.4 (C-5), 78.9 (C-4), 86.2 (C-2), 105.8 (C-1), 112.3 (CMe_2), 124.1 (d, CH=, $J_{C\text{-}P}$= 13.0 Hz), 125.3 (CH=), 126.3 (CH=), 126.7 (d, CH=, $J_{C\text{-}P}$= 20 Hz), 128.1 (CH=), 128.9 (CH=), 129.0 (CH=), 129.6 (CH=), 133.1 (C), 133.3 (C), 134.3 (C), 137.5 (C), 140.1 (C), 140.3 (C), 146.5 (C), 146.6 (C). Anal. calcd (%) for $C_{42}H_{57}O_6PS$: C 69.97, H 7.97, S 4.45; found: C 69.99, H 8.01, S 4.47.

L18a: Yield: 500 mg, 76 %. ^{31}P NMR (400 MHz, C_6D_6) δ: 136.7 (s). ^{1}H NMR (400 MHz, C_6D_6) δ: 1.07 (s, 3H, CH_3), 1.25 (s, 9H, CH_3, ^{t}Bu), 1.28 (s, 9H, CH_3, ^{t}Bu), 1.38 (s, 3H, CH_3), 1.58 (s, 9H, CH_3, ^{t}Bu), 1.59 (s, 9H, CH_3, ^{t}Bu), 2.10 (s, 3H, CH_3), 2.94 (d, 1H, H-3, $^3J_{3\text{-}4}$= 4.4 Hz), 4.29 (m, 2H, H-5' and H-5), 4.38 (d, 1H, H-2, $^3J_{1\text{-}2}$= 3.6 Hz), 4.69 (m, 1H, H-4), 5.72 (d, 1H, H-1, $^3J_{1\text{-}2}$= 3.6 Hz), 7.2-7.6 (m, 4H, CH=). ^{13}C NMR (400 MHz, C_6D_6) δ: 15.3 (CH_3-S), 27.0 (CH_3), 27.5 (CH_3), 31.8 (CH_3, ^{t}Bu), 32.1 (CH_3, ^{t}Bu), 35.2 (C, ^{t}Bu), 36.2 (C, ^{t}Bu), 54.0 (C-3), 64.7 (C-5), 79.4 (C-4), 86.4 (C-2), 105.9 (C-1), 112.2 (CMe_2), 125.0 (CH=), 125.1 (CH=), 127.5 (CH=), 127.7 (CH=), 134.0 (C), 134.3 (C), 141.1 (C), 147.3 (C), 147.5 (C), 147.7 (C). Anal. calcd (%) for $C_{37}H_{55}O_6PS$: C 67.45, H 8.41, S 4.87; found: C 67.40, H 8.38, S 4.86.

L19a: Yield: 415 mg, 57 %. ^{31}P NMR (400 MHz, C_6D_6) δ: 142.5 (bs). ^{1}H NMR (400 MHz, C_6D_6) δ: 1.09 (s, 3H, CH_3), 1.23 (s, 9H, CH_3, ^{t}Bu), 1.27 (s, 9H, CH_3, ^{t}Bu), 1.39 (s, 3H, CH_3), 1.50 (s, 9H, CH_3, ^{t}Bu), 1.52 (s, 9H, CH_3, ^{t}Bu), 3.39 (dd, 1H, H-3, $^3J_{3\text{-}2}$= 4 Hz, $^3J_{3\text{-}4}$= 10 Hz), 3.87 (m, 1H, H-5'), 4.03 (m, 1H, H-4), 4.19 (m, 1H, H-2), 4.31 (m, 1H, H-5), 5.71 (d, 1H, H-1, $^3J_{1\text{-}2}$= 3.6 Hz), 6.8-7.6 (m, 9H, CH=). ^{13}C NMR (400 MHz, C_6D_6) δ: 26.2 (CH_3), 26.6 (CH_3), 30.7 (CH_3, ^{t}Bu), 30.9 (CH_3, ^{t}Bu), 31.2 (CH_3, ^{t}Bu), 31.1 (CH_3, ^{t}Bu), 34.3 (C, ^{t}Bu), 35.3 (C, ^{t}Bu), 49.6 (C-3), 61.9 (d, C-5, $J_{C\text{-}P}$= 8 Hz),

80.7 (C-4), 81.1 (C-2), 104.4 (C-1), 111.7 (CMe_2), 123.9 (d, CH=, J_{C-P}= 7.6 Hz), 125.3 (CH=), 126.4 (CH=), 126.6 (d, CH=, J_{C-P}= 13 Hz), 128.1 (CH=), 128.8 (CH=), 128.9 (CH=), 130.8 (CH=), 133.2 (C), 133.5 (C), 135.1 (C), 140.3 (C), 146.2 (C), 146.5 (C). Anal. calcd (%) for $C_{42}H_{57}O_6PS$: C 69.97, H 7.97, S 4.45; found: C 70.01, H 8.02, S 4.43.

L20a: Yield: 395 mg, 60 %. ^{31}P NMR (400 MHz, C_6D_6) δ: 139.6 (s). ^{1}H NMR (400 MHz, C_6D_6) δ: 1.12 (s, 3H, CH_3), 1.26 (s, 9H, CH_3, ^{t}Bu), 1.27 (s, 9H, CH_3, ^{t}Bu), 1.38 (s, 3H, CH_3), 1.60 (s, 9H, CH_3, ^{t}Bu), 1.62 (s, 9H, CH_3, ^{t}Bu), 1.76 (s, 3H, CH_3-S), 2.63 (dd, 1H, H-3, $^3J_{3-2}$= 4 Hz, $^3J_{3-4}$= 12 Hz), 3.97 (m, 1H, H-4), 4.06 (m, 1H, H-5'), 4.19 (m, 1H, H-2), 4.32 (m, 1H, H-5), 5.65 (d, 1H, H-1, $^3J_{1-2}$= 3.6 Hz), 7.3-7.6 (m, 4H, CH=). ^{13}C NMR (400 MHz, C_6D_6) δ: 14.9 (CH_3-S), 26.6 (CH_3), 26.9 (CH_3), 31.5 (CH_3, ^{t}Bu), 31.3 (CH_3, ^{t}Bu), 31.4 (CH_3, ^{t}Bu), 31.6 (CH_3, ^{t}Bu), 34.7 (C, ^{t}Bu), 35.7 (C, ^{t}Bu), 48.6 (C-3), 62.9 (d, C-5, J_{C-P}= 6.2 Hz), 80.7 (C-4), 82.0 (C-2), 104.7 (C-1), 111.9 (CMe_2), 124.4 (CH=), 124.5 (CH=), 127.0 (CH=), 127.2 (CH=), 133.5 (C), 133.6 (C), 133.9 (C), 137.8 (C), 140.6 (C), 140.7 (C), 146.7 (C), 146.9 (C). Anal. calcd (%) for $C_{37}H_{55}O_6PS$: C 67.45, H 8.41, S 4.87; found: C 67.38, H 8.37, S 4.89.

L27a: Yield: 367 mg, 57 %. ^{31}P NMR (400 MHz, C_6D_6) δ: 144.3 (s). ^{1}H NMR (400 MHz, C_6D_6) δ: 1.27 (s, 9H, CH_3, ^{t}Bu), 1.33 (s, 9H, CH_3, ^{t}Bu), 1.35 (b, 1H, CH_2), 1.38 (s, 9H, CH_3, ^{t}Bu), 1.59 (b, 4H, CH_2), 1.71 (s, 18H, CH_3, ^{t}Bu), 1.85 (b, 2H, CH_2), 2.32 (b, 1H, CH_2), 3.18 (b, 1H, CH-S), 4.75 (b, 1H, CH-O), 7.4-7.7 (m, 4H, CH=). ^{13}C NMR (400 MHz, C_6D_6) δ: 20.2 (CH_2), 21.0 (CH_2), 22.1 (CH_2), 30.9 (CH_3, ^{t}Bu), 31.1 (CH_3, ^{t}Bu), 31.2 (CH_3, ^{t}Bu), 31.3 (CH_3, ^{t}Bu), 34.2 (C, ^{t}Bu), 34.3 (C, ^{t}Bu), 34.3 (C, ^{t}Bu), 34.4 (C, ^{t}Bu), 43.0 (CH-S), 44.2 (C-S), 76.6 (d, CH-O, J_{C-P}= 7.7Hz), 123.9 (CH=), 126.6 (CH=), 126.8 (CH=), 133.6 (C), 133.8 (C), 139.9 (C), 140.3 (C), 146.1 (C), 146.2 (C). Anal. calcd (%) for $C_{38}H_{59}O_3PS$: C 72.80, H 9.49, S 5.11; found: C 72.77, H 9.42, S 5.09.

L27b: Yield: 367 mg, 64 %. ^{31}P NMR (400 MHz, C_6D_6) δ: 145.0 (s). ^{1}H NMR (400 MHz, C_6D_6) δ: 1.21 (s, 9H, CH_3, ^{t}Bu), 1.33 (b, 1H, CH_2), 1.55 (s, 18H, CH_3, ^{t}Bu), 1.63 (b, 4H, CH_2), 1.83 (b, 1H, CH_2), 1.90 (b, 1H, CH_2), 2.31 (b, 1H, CH_2), 3.14 (b, 1H, CH-S), 3.31 (s, 3H, CH_3-O), 3.34 (s, 3H, CH_3-O), 4.73 (b, 1H, CH-O), 6.71 (m, 2H, CH=), 7.11 (m, 2H, CH=). ^{13}C NMR (400 MHz, C_6D_6) δ: 20.1 (CH_2), 21.9 (CH_2), 29.4 (CH_2), 30.8 (CH_3, ^{t}Bu), 30.9 (CH_3, ^{t}Bu), 35.1 (C, ^{t}Bu), 35.3 (C, ^{t}Bu), 43.0 (CH-S), 44.1 (C-S), 54.6 (CH_3-O), 54.7 (CH_3-O), 76.5 (d, CH-O, J_{C-P}= 9.1 Hz), 113.0 (CH=), 114.4

(CH=), 127.6 (CH=), 127.8 (CH=), 134.0 (C), 134.2 (C), 142.0 (C), 142.4 (C), 155.9 (C), 156.0 (C). Anal. calcd (%) for $C_{32}H_{47}O_5PS$: C 66.87, H 8.24, S 5.58; found: C 66.82, H 8.19, S 5.57.

L27c: Yield: 289 mg, 53 %. ^{31}P NMR (400 MHz, C_6D_6) δ: 142.4 (s). ^{1}H NMR (400 MHz, C_6D_6) δ: 0.43 (s, 9H, CH_3-Si), 0.47 (s, 9H, CH_3-Si), 1.16 (s, 9H, CH_3, ^{t}Bu), 1.25 (b, 2H, CH_2), 1.62 (b, 4H, CH_2), 2.24 (b, 2H, CH_2), 2.98 (b, 1H, CH-S), 4.51 (b, 1H, CH-O), 7.0-7.5 (m, 6H, CH=). ^{13}C NMR (400 MHz, C_6D_6) δ: 0.0 (CH_3-Si), 0.1 (CH_3-Si), 20.8 (CH_2), 22.5 (CH_2), 29.7 (CH_2), 31.0 (CH_3, ^{t}Bu), 43.1 (CH-S), 44.5 (C-S), 76.9 (d, CH-O, $J_{C\text{-}P}$= 3.1 Hz), 124.5 (CH=), 124.6 (CH=), 131.2 (C), 131.6 (C), 131.7 (C), 132.1 (CH=), 132.5 (CH=), 135.1 (CH=), 154.5 (C), 155.1 (C). Anal. calcd (%) for $C_{28}H_{43}O_3PS$: C 61.50, H 7.93, S 5.86; found: C 61.43, H 7.91, S 5.84.

3.3.4.3. Typical procedure for the preparation of thioether-phosphinite ligands L6-L20i

A solution of chlorodiphenylphosphine (0.2 mL, 1.1 mmol) in THF (4 mL) was slowly added at 0 °C to a solution of the corresponding thioether-alcohol (1 mmol) and DMAP (5.7 mg, 0.05 mmol) in pyridine (1 mL). The reaction mixture was stirred during 90 minutes at room temperature. Diethyl ether was then added and the pyridine salts were removed by filtration. The residue was purified by flash chromatography (eluent: Toluene/NEt_3= 100/1).

L13i: Yield: 317 mg, 68 %. ^{31}P NMR (400 MHz, C_6D_6) δ: 117.6 (s). ^{1}H NMR (400 MHz, C_6D_6) δ: 1.08 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 2.92 (dd, 1H, H-5', $^2J_{5'\text{-}5}$= 14.0 Hz, $^3J_{5'\text{-}4}$= 5.2 Hz), 3.28 (dd, 1H, H-5, $^2J_{5\text{-}5'}$= 14.0 Hz, $^3J_{5\text{-}4}$= 3.6 Hz), 4.10 (m, 1H, H-3), 4.15 (m, 1H, H-2), 4.54 (m, 1H, H-4), 5.43 (d, 1H, H-1, $^3J_{1\text{-}2}$= 3.6 Hz), 6.8-7.7 (m, 15H, CH=). ^{13}C NMR (400 MHz, C_6D_6) δ: 26.3 (CH_3), 26.5 (CH_3), 36.3 (C-5), 77.5 (d, C-4, $J_{C\text{-}P}$= 6.1 Hz), 78.3 (d, C-2, $J_{C\text{-}P}$= 3.1 Hz), 80.8 (d, C-3, $J_{C\text{-}P}$= 18.2 Hz), 103.9 (C-1), 112.5 (CMe_2), 125.6 (CH=), 128.0 (CH=), 128.1 (CH=), 128.3 (CH=), 128.4 (CH=), 128.7 (CH=), 128.9 (CH=), 129.2 (CH=), 129.6 (CH=), 130.0 (CH=), 130.2(CH=), 130.9 (CH=), 131.1 (CH=), 137.2 (C), 141.9 (C), 142.0 (C), 142.1 (C), 142.2 (C). Anal. calcd (%) for $C_{26}H_{27}O_4PS$: C 66.94, H 5.83, S 6.87; found: C 66.91, H 5.82, S 6.89.

L16i: Yield: 286 mg, 56 %. ^{31}P NMR (400 MHz, C_6D_6) δ: 117.5 (s). ^{1}H NMR (400 MHz, C_6D_6) δ: 1.04 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 2.49 (s, 6H, CH_3-Ph), 2.57

(dd, 1H, H-5', $^{2}J_{5'-5}$= 13.2 Hz, $^{3}J_{5'-4}$= 7.2 Hz), 2.99 (dd, 1H, H-5, $^{2}J_{5-5'}$= 13.2 Hz, $^{3}J_{5-4}$= 2.8 Hz), 3.87 (m, 1H, H-3), 4.08 (m, 1H, H-2), 4.29 (m, 1H, H-4), 5.40 (d, 1H, H-1, $^{3}J_{1-2}$= 4.0 Hz), 7.0-7.7 (m, 13H, CH=). ^{13}C NMR (400 MHz, C_6D_6) δ: 26.3 (CH_3), 26.4 (CH_3), 36.5 (C-5), 77.3 (d, C-4, J_{C-P}= 6.2 Hz), 78.4 (d, C-2, J_{C-P}= 3.8 Hz), 81.4 (d, C-3, J_{C-P}= 19.4 Hz), 103.8 (C-1), 112.4 (CMe_2), 128.0 (CH=), 128.1 (CH=), 128.2 (CH=), 128.3 (CH=), 128.4 (CH=), 128.9 (CH=), 129.5 (CH=), 129.9 (CH=), 130.1 (CH=), 130.6 (CH=), 130.8 (CH=), 133.5 (C), 141.9 (C), 142.1 (C), 142.2 (C), 142.3 (C), 132.3 (C). Anal. calcd (%) for $C_{28}H_{31}O_4PS$: C 68.00, H 6.32, S 6.48; found: C 68.02, H 6.35, S 6.49.

L17i: Yield: 340 mg, 73 %. ^{31}P NMR (400 MHz, C_6D_6) δ: 117.3 (s). ^{1}H NMR (400 MHz, C_6D_6) δ: 0.93 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 2.07 (s, 3H, CH_3-S), 3.64 (d, 1H, H-3, $^{3}J_{3-4}$= 4.0 Hz), 4.25 (m, 1H, H-5'), 4.37 (m, 1H, H-5), 4.49 (d, 1H, H-2, $^{3}J_{1-2}$= 4.0 Hz), 4.84 (m, 1H, H-4), 5.81 (d, 1H, H-1, $^{3}J_{1-2}$= 4.0 Hz), 6.9-7.6 (m, 15H, CH=). ^{13}C NMR (400 MHz, C_6D_6) δ: 25.9 (CH_3), 26.5 (CH_3), 53.5 (C-3), 69.2 (d, C-5, J_{C-P}= 20.1 Hz), 78.6 (d, C-4, J_{C-P}= 8.5 Hz), 85.6 (C-2), 105.2 (C-1), 111.5 (CMe_2), 126.3 (CH=), 128.1 (CH=), 128.2 (CH=), 128.3 (CH=), 128.9 (CH=), 129.0 (CH=), 129.1 (CH=), 129.2 (CH=), 129.7 (CH=), 130.4 (CH=), 130.5 (CH=), 130.6 (CH=), 130.7 (CH=), 134.6 (C), 137.4 (C), 142.0 (C), 142.1 (C), 142.2 (C), 142.3 (C). Anal. calcd (%) for $C_{26}H_{27}O_4PS$: C 66.94, H 5.83, S 6.87; found: C 66.88, H 5.79, S 6.86.

3.3.4.4. Typical procedure for the preparation of [Ir(cod)(L)]BAr_F (L = L6-L20a-i and L27a-c)

The corresponding ligand (0.037 mmol) was dissolved in CH_2Cl_2 (2 mL) and [Ir(μ-Cl)(cod)]$_2$ (12.5 mg, 0.0185 mmol) was added. The reaction was refluxed at 50 °C for 1 hour. After 5 min at room temperature, $NaBAr_F$ (38.6 mg, 0.041 mmol) and water (2 mL) were added and the reaction mixture was stirred vigorously for 30 min at room temperature. The phases were separated and the aqueous phase was extracted twice with CH_2Cl_2. The combined organic phases were dried with $MgSO_4$, filtered through a plug of celite and the solvent was evaporated to give the product as red-orange solids.

[Ir(cod)(**L6a**)]BAr_F. Yield 64 mg (91 %). ^{31}P NMR ($CDCl_3$, 298 K), δ: 112.9 (b). Anal. calc (%) for $C_{82}H_{81}BF_{24}IrO_6PS$: C 52.26, H 4.33, S 1.70; found: C 52.32, H 4.41, S 1.65. Major isomer (60%): ^{31}P NMR ($CDCl_3$, 213 K), δ: 117.3 (s). ^{1}H NMR

($CDCl_3$, 213 K), δ: 1.19 (s, 3H, CH_3), 1.33 (s, 18H, CH_3, ^{t}Bu), 1.37 (s, 3H, CH_3), 1.64 (s, 18H, CH_3, ^{t}Bu), 1.8-2.4 (b, 8H, CH_2, cod), 3.48 (m, 2H, H-5' and H-2), 3.87 (m, 2H, CH=, cod and H-5), 4.10 (m, 1H, CH=, cod), 4.34 (m, 1H, CH=, cod), 4.54 (m, 1H, H-4), 4.71 (m, 1H, H-3), 5.01 (m, 1H, CH=, cod), 5.58 (b, 1H, H-1), 7.0-8.0 (m, 21H, CH= aromatics). ^{13}C NMR ($CDCl_3$, 213 K), δ: 25.5 (CH_3), 26.2 (CH_3), 30.2 (b, CH_2, cod), 30.7 (b, CH_2, cod), 31.2-31.8 (CH_3, ^{t}Bu), 33.9 (b, CH_2, cod), 34.7-35.5 (C, tBu), 46.5 (C-5), 71.1 (b, CH=, cod), 75.5 (C-3), 78.0 (b, CH=, cod), 78.7 (b, C-4), 83.3 (C-2), 104.3 (b, CH=, cod), 104.6 (C-1), 105.9 (d, CH=, cod, $J_{C\text{-}P}$= 15 Hz), 112.6 (CMe_2), 117.5-162.3 (aromatic carbons). Minor isomer (40%): ^{31}P NMR ($CDCl_3$, 213 K), δ: 109.9 (s). ^{1}H NMR ($CDCl_3$, 213 K), δ: 1.14 (s, 3H, CH_3), 1.33 (s, 3H, CH_3), 1.41 (s, 9H, CH_3, ^{t}Bu), 1.47 (s, 9H, CH_3, ^{t}Bu), 1.69 (s, 18H, CH_3, ^{t}Bu), 1.8-2.4 (b, 8H, CH_2, cod), 3.97 (m, 1H, H-5'), 4.10 (m, 1H, H-5), 4.18 (m, 1H, CH=, cod), 4.45 (m, 2H, H-4 and H-2), 4.54 (m, 1H, CH=, cod), 4.71 (m, 1H, H-3), 4.92 (m, 1H, CH=, cod), 5.01 (m, 1H, CH=, cod), 5.92 (b, 1H, H-1), 7.0-8.0 (m, 21H, CH= aromatics). ^{13}C NMR ($CDCl_3$, 213 K), δ: 26.2 (CH_3), 26.6 (b, CH_2, cod), 27.2 (b, CH_2, cod), 28.7 (b, CH_2, cod), 29.8 (b, CH_2, cod), 31.2-31.8 (CH_3, ^{t}Bu), 34.7-35.5 (C, tBu), 41.4 (C-5), 69.1 (b, CH=, cod), 74.3 (C-3), 76.8 (b, C-4), 82.0 (b, CH=, cod), 84.7 (C-2), 104.3 (b, CH=, cod), 104.6 (C-1), 106.4 (b, CH=, cod), 113.2 (CMe_2), 117.5-162.3 (aromatic carbons).

[Ir(cod)(**L6g**)]BAr_F. Yield 65 mg (96 %). Anal. calc (%) for $C_{74}H_{53}BF_{24}IrO_6PS$: C 50.49, H 3.03, S 1.82; found: C 50.53, H 3.11, S 1.77. Major isomer (65%): ^{31}P NMR ($CDCl_3$), δ: 119.6 (s). ^{1}H NMR ($CDCl_3$), δ: 1.27 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 1.8-2.4 (b, 8H, CH_2, cod), 2.98 (m, 1H, CH=, cod), 3.66 (dd, 1H, H-5', $^2J_{5'\text{-}5}$= 13.6 Hz, $^3J_{5'\text{-}4}$= 10.2 Hz), 3.93 (m, 1H, H-5), 4.38 (m, 1H, CH=, cod), 4.48 (m, 1H, H-4), 4.62 (d, 1H, H-2, $^3J_{2\text{-}1}$ = 4.0 Hz), 4.88 (m, 1H, CH= cod), 5.24 (m, 1H, CH=, cod), 5.48 (m, 1H, H-3), 5.77 (d, 1H, H-1, $^3J_{1\text{-}2}$ = 4.0 Hz), 7.0-8.1 (m, 29H, CH= aromatics). ^{13}C NMR ($CDCl_3$), δ: 26.1 (CH_3), 26.5 (CH_3), 27.4 (b, CH_2, cod), 29.3 (b, CH_2, cod), 31.3 (b, CH_2, cod), 33.5 (b, CH_2, cod), 40.8 (C-5), 74.3 (b, CH=, cod), 75.9 (C-4), 77.8 (b, CH=, cod), 79.0 (C-3), 83.7 (C-2), 100.9 (b, CH=, cod), 105.1 (C-1), 107.2 (b, CH=, cod), 113.2 (CMe_2), 117.4-162.4 (aromatic carbons). Minor isomer (35%): ^{31}P NMR ($CDCl_3$), δ: 114.6 (s). ^{1}H NMR ($CDCl_3$), δ: 1.31 (s, 3H, CH_3), 1.39 (s, 3H, CH_3), 1.8-2.4 (b, 8H, CH_2, cod), 2.81 (m, 1H, CH=, cod), 3.33 (m, 1H, H-5'), 3.49 (m, 1H, H-5), 4.04 (m, 1H, H-4), 4.18 (d, 1H, H-2, $^3J_{2\text{-}1}$ = 3.6 Hz), 4.88 (m, 3H, CH= cod), 5.44 (m, 1H, H-3), 5.57 (d, 1H, H-1, $^3J_{1\text{-}2}$ = 3.6 Hz), 7.0-8.1 (m, 29H, CH= aromatics). ^{13}C NMR

($CDCl_3$), δ: 26.3 (CH_3), 26.7 (CH_3), 28.1 (b, CH_2, cod), 29.6 (b, CH_2, cod), 31.0 (b, CH_2, cod), 31.8 (b, CH_2, cod), 40.8 (C-5), 75.3 (b, CH=, cod), 75.9 (C-4), 78.3 (b, CH=, cod), 79.2 (C-3), 83.8 (C-2), 100.9 (b, CH=, cod), 105.1 (C-1), 108.1 (b, CH=, cod), 112.9 (CMe_2), 117.4-162.4 (aromatic carbons).

[Ir(cod)(**L6h**)]BAr_F. Yield 62 mg (93 %). Anal. calc (%) for $C_{74}H_{53}BF_{24}IrO_6PS$: C 50.49, H 3.03, S 1.82; found: C 50.55, H 3.12, S 1.75. Major isomer (90%): ^{31}P NMR ($CDCl_3$), δ: 115.0 (s). ^{1}H NMR ($CDCl_3$), δ: 1.15 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 1.8-2.4 (b, 8H, CH_2, cod), 3.64 (m, 1H, CH=, cod), 4.18 (dd, 1H, H-5', $^2J_{5'-5}$= 12.4 Hz, $^3J_{5'-4}$= 9.2 Hz), 4.30 (m, 2H, CH=, cod and H-5), 4.39 (d, 1H, H-2, $^3J_{2-1}$ = 3.6 Hz), 4.52 (m, 2H, CH= cod and H-4), 4.89 (m, 2H, CH=, cod), 5.14 (m, 1H, H-3), 5.82 (d, 1H, H-1, $^3J_{1-2}$ = 3.6 Hz), 7.0-8.1 (m, 29H, CH= aromatics). ^{13}C NMR ($CDCl_3$), δ: 26.0 (CH_3), 26.5 (CH_3), 29.7 (b, CH_2, cod), 30.3 (b, CH_2, cod), 30.9 (b, CH_2, cod), 44.0 (C-5), 74.9 (b, CH=, cod), 77.3 (C-4), 82.2 (C-3), 83.3 (b, CH=, cod), 83.5 (C-2), 100.9 (b, CH=, cod), 104.8 (C-1), 113.2 (CMe_2), 117.4 (b, CH=, BAr_F), 119-132 (aromatic carbons), 134.7 (b, CH=, BAr_F), 138-150 (aromatic carbons), 161.8 (q, C-B, BAr_F, $^1J_{C-B}$ = 49 Hz). Minor isomer (10%): ^{31}P NMR ($CDCl_3$), δ: 107.6 (s). ^{1}H NMR ($CDCl_3$), δ: 1.22 (s, 3H, CH_3), 1.33 (s, 3H, CH_3), 1.8-2.4 (b, 8H, CH_2, cod), 4.01 (m, 1H, CH=, cod), 4.33 (m, 2H, CH=, cod and H-5'), 4.52 (m, 2H, H-5 and H-4), 4.77 (m, 2H, CH= cod and H-2), 4.89 (m, 1H, CH=, cod), 5.21 (m, 1H, H-3), 5.75 (d, 1H, H-1, $^3J_{1-2}$ = 3.2 Hz), 7.0-8.1 (m, 29H, CH= aromatics).

[Ir(cod)(**L6i**)]BAr_F. Yield 54 mg (90 %). ^{31}P NMR ($CDCl_3$), δ: 112.1 (s). ^{1}H NMR ($CDCl_3$), δ: 1.17 (s, 3H, CH_3), 1.30 (s, 9H, CH_3, ^{t}Bu), 1.34 (s, 9H, CH_3, ^{t}Bu), 1.42 (s, 3H, CH_3), 1.62 (s, 18H, CH_3, ^{t}Bu), 1.8-2.4 (b, 8H, CH_2, cod), 3.43 (m, 1H, H-5'), 3.47 (m, 1H, H-2), 3.83 (m, 2H, CH=, cod and H-5), 4.06 (m, 1H, CH=, cod), 4.43 (m, 2H, CH=, cod and H-4), 4.75 (m, 1H, H-3), 5.12 (m, 1H, CH=, cod), 5.54 (d, 1H, H-1, $^3J_{1-2}$= 3.2 Hz), 6.8-8.0 (m, 27H, CH= aromatics). ^{13}C NMR ($CDCl_3$), δ: 26.0 (CH_3), 26.4 (CH_3), 30.1 (b, CH_2, cod), 30.5 (b, CH_2, cod), 32.5 (b, CH_2, cod), 33.9 (b, CH_2, cod), 46.6 (C-5), 71.0 (b, CH=, cod), 75.3 (C-3), 77.6 (b, CH=, cod), 79.2 (b, C-4), 82.1 (C-2), 103.6 (b, CH=, cod), 104.2 (C-1), 106.1 (b, CH=, cod), 113.3 (CMe_2), 117.4 (b, CH=, BAr_F), 119-132 (aromatic carbons), 134.7 (b, CH=, BAr_F), 138-150 (aromatic carbons), 161.8 (q, C-B, BAr_F, $^1J_{C-B}$ = 49 Hz). Anal. calc (%) for $C_{66}H_{51}BF_{24}IrO_4PS$: C 48.63, H 3.15, S 1.97; found: C 48.58, H 3.13, S 1.95.

[Ir(cod)(**L7a**)]BAr_F. Yield 62 mg (92 %). ^{31}P NMR ($CDCl_3$, 298 K), δ: 115.1 (b). Anal. calc (%) for $C_{77}H_{79}BF_{24}IrO_6PS$: C 50.75, H 4.37, S 1.76; found: C 50.81, H 4.40, S 1.74. Major isomer (95%): ^{31}P NMR ($CDCl_3$, 213 K), δ: 120.4 (s). ^{1}H NMR ($CDCl_3$, 213 K), δ: 1.22 (s, 3H, CH_3), 1.28 (s, 9H, CH_3, ^{t}Bu), 1.32 (s, 9H, CH_3, ^{t}Bu), 1.41 (s, 9H, CH_3, ^{t}Bu), 1.46 (s, 3H, CH_3), 1.65 (s, 9H, CH_3, ^{t}Bu), 2.15 (b, 4H, CH_2, cod), 2.28 (b, 2H, CH_2, cod), 2.37 (b, 2H, CH_2, cod), 3.30 (m, 1H, H-5'), 3.89 (m, 1H, H-5), 4.02 (d, 1H, H-2, $^3J_{2\text{-}1}$= 3.6 Hz), 4.41 (m, 1H, CH=, cod), 4.55 (m, 2H, CH=, cod and H-4), 5.14 (m, 1H, CH=, cod), 5.36 (m, 2H, CH=, cod and H-3), 5.71 (d, 1H, H-1, $^3J_{1\text{-}2}$= 3.6 Hz), 7.0-7.8 (m, 16H, CH= aromatics). ^{13}C NMR ($CDCl_3$, 213 K), δ: 25.7 (CH_3), 26.4 (CH_3), 28.0 (b, CH_2, cod), 29.9 (b, CH_2, cod), 30.7 (CH_3, ^{t}Bu), 30.9 (CH_3, ^{t}Bu), 31.3 (CH_3, ^{t}Bu), 31.5 (b, CH_2, cod), 32.9 (b, CH_2, cod), 34.7 (C, tBu), 34.8 (C, tBu), 35.4 (C, tBu), 53.4 (C-5), 74.0 (C-4), 75.0 (b, CH=, cod), 75.8 (C-3), 79.9 (b, CH=, cod), 83.7 (C-2), 100.5 (d, CH=, cod, $J_{C\text{-}P}$= 15.5 Hz), 104.4 (d, CH=, cod, $J_{C\text{-}P}$= 13.2 Hz), 104.9 (C-1), 113.0 (CMe_2), 117.4 (b, CH=, BAr_F), 120-131 (aromatic carbons), 134.7 (b, CH=, BAr_F), 138-149 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^1J_{C\text{-}B}$ = 49 Hz). Minor isomer (5%): ^{31}P NMR ($CDCl_3$, 213 K), δ: 109.0 (s).

[Ir(cod)(**L7i**)]BAr_F. Yield 56 mg (96 %). ^{31}P NMR ($CDCl_3$), δ: 110.5 (s). ^{1}H NMR ($CDCl_3$), δ: 1.25 (b, 2H, CH_2, cod), 1.38 (s, 3H, CH_3), 1.54 (s, 3H, CH_3), 1.82 (b, 2H, CH_2, cod), 2.24 (b, 4H, CH_2, cod), 2.48 (s, 1H, CH_3-S), 2.66 (m, 1H, H-5'), 3.30 (m, 1H, CH=, cod), 3.43 (m, 1H, H-5), 3.55 (m, 1H, CH=, cod), 4.48 (m, 1H, CH=, cod), 4.96 (d, 1H, H-2, $^3J_{2\text{-}1}$= 3.6 Hz), 4.99 (m, 1H, CH=, cod), 5.15 (m, 1H, CH=, cod), 5.49 (m, 1H, H-3), 6.02 (d, 1H, H-1, $^3J_{1\text{-}2}$= 3.6 Hz), 7.0-7.9 (m, 22H, CH= aromatics). ^{13}C NMR ($CDCl_3$), δ: 21.2 (CH_3-S), 26.2 (CH_3), 26.8 (CH_3), 29.5 (CH_2, cod), 30.0 (CH_2, cod), 30.5 (CH_2, cod), 31.2 (CH_2, cod), 36.5 (C-5), 72.5 (CH=, cod), 74.7 (CH=, cod), 76.2 (C-4), 83.9 (d, C-2, $J_{C\text{-}P}$= 4.2 Hz), 84.7 (C-3), 97.5 (b, CH=, cod), 101.2 (b, CH=, cod), 105.5 (C-1), 113.5 (CMe_2), 117.7 (b, CH=, BAr_F), 120-134 (aromatic carbons), 134.9 (b, CH=, BAr_F), 161.8 (q, C-B, BAr_F, $^1J_{C\text{-}B}$ = 49 Hz). Anal. calc (%) for $C_{61}H_{49}BF_{24}IrO_4PS$: C 46.72, H 3.15, S 2.04; found: C 46.77, H 3.18, S 2.02.

[Ir(cod)(**L8a**)]BAr_F. Yield 62 mg (91 %). ^{31}P NMR ($CDCl_3$, 298 K), δ: 112.5 (b). Anal. calc (%) for $C_{79}H_{83}BF_{24}IrO_6PS$: C 51.27, H 4.52, S 1.73; found: C 51.33, H 4.55, S 1.70. Major isomer (70%): ^{31}P NMR ($CDCl_3$, 213 K), δ: 114.9 (s). ^{1}H NMR ($CDCl_3$, 213 K), δ: 1.31-1.36 (b, 30H, CH_3 and CH_3 ^{t}Bu), 1.39 (s, 3H, CH_3), 1.46 (b, 6H, CH_3, ^{i}Pr), 1.55 (s, 9H, CH_3, ^{t}Bu), 1.9-2.4 (b, 2H, CH_2, cod), 3.26 (m, 2H, H-5' and

CH ^{i}Pr), 3.46 (d, 1H, H-2, $^{3}J_{2\text{-}1}$= 3.2 Hz), 3.75 (m, 1H, H-5), 4.35 (m, 1H, CH=, cod), 4.41 (m, 1H, H-4), 4.55 (m, 2H, CH=, cod), 4.84 (m, 1H, H-3), 5.35 (m, 1H, CH=, cod), 5.46 (d, 1H, H-1, $^{3}J_{1\text{-}2}$= 3.2 Hz), 7.1-7.8 (m, 16H, CH= aromatics). ^{13}C NMR ($CDCl_3$, 213 K), δ: 22.0 (CH_3, ^{i}Pr), 23.6 (CH_3, ^{i}Pr), 25.3 (CH_3), 26.0 (CH_3), 27-35 (CH_3 ^{t}Bu, C ^{t}Bu, CH_2 cod and C-5), 43.6 (b, CH ^{i}Pr), 70.2 (b, CH=, cod), 75.3 (b, CH=, cod), 77.2 (C-4), 77.9 (C-3), 82.3 (b, C-2), 104.1 (b, CH=, cod), 104.9 (C-1), 112.7 (CMe_2), 117.5 (b, CH=, BAr_F), 120-130 (aromatic carbons), 134.6 (b, CH=, BAr_F), 138-149 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^{1}J_{C\text{-}B}$ = 49 Hz). Minor isomer (30%): ^{31}P NMR ($CDCl_3$, 213 K), δ: 109.2 (s). ^{1}H NMR ($CDCl_3$, 213 K), δ: 1.15 (s, 3H, CH_3), 1.31-1.36 (b, 27H, CH_3 ^{t}Bu), 1.37 (s, 3H, CH_3), 1.46 (b, 6H, CH_3, ^{i}Pr), 1.55 (s, 9H, CH_3, ^{t}Bu), 1.9-2.4 (b, 2H, CH_2, cod), 3.26 (m, 1H, CH ^{i}Pr), 3.44 (d, 1H, H-2, $^{3}J_{2\text{-}1}$= 3.2 Hz), 3.75 (m, 1H, H-5'), 3.84 (m, 1H, H-3), 3.96 (m, 1H, H-5), 4.25 (m, 1H, CH=, cod), 4.41 (m, 1H, H-4), 4.55 (m, 1H, CH=, cod), 4.92 (m, 1H, CH=, cod), 5.62 (m, 1H, CH=, cod), 5.85 (d, 1H, H-1, $^{3}J_{1\text{-}2}$= 3.2 Hz), 7.1-7.8 (m, 16H, CH= aromatics). ^{13}C NMR ($CDCl_3$, 213 K); δ: 21.7 (CH_3, ^{i}Pr), 22.9 (CH_3, ^{i}Pr), 25.8 (CH_3), 26.5 (CH_3), 27-35 (CH_3 ^{t}Bu, C ^{t}Bu, CH_2 cod and C-5), 43.6 (b, CH ^{i}Pr), 69.8 (b, CH=, cod), 73.5 (C-4), 77.5 (b, CH=, cod), 78.2 (C-3), 82.3 (b, C-2), 103.2 (b, CH=, cod), 104.3 (b, CH=, cod), 104.9 (C-1), 113.2 (CMe_2), 117.5 (b, CH=, BAr_F), 120-130 (aromatic carbons), 134.6 (b, CH=, BAr_F), 138-149 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^{1}J_{C\text{-}B}$ = 49 Hz).

[Ir(cod)(**L8i**)]BAr_F. Yield 54 mg (92 %). ^{31}P NMR ($CDCl_3$), δ: 111.5 (s). ^{1}H NMR ($CDCl_3$), δ: 1.12 (d, 3H, CH_3, ^{i}Pr, $^{3}J_{H\text{-}H}$= 7.2 Hz), 1.32 (b, 2H, CH_2, cod), 1.38 (s, 3H, CH_3), 1.42 (d, 3H, CH_3, ^{i}Pr, $^{3}J_{H\text{-}H}$= 7.2 Hz), 1.57 (s, 3H, CH_3), 1.85 (b, 2H, CH_2, cod), 2.07 (b, 2H, CH_2, cod), 2.31 (b, 2H, CH_2, cod), 2.79 (m, 1H, H-5'), 3.17 (sp, 1H, CH, ^{i}Pr, $^{3}J_{H\text{-}H}$= 7.2 Hz), 3.36 (m, 1H, CH=, cod), 3.44 (m, 1H, CH=, cod), 3.55 (m, 1H, H-5), 4.49 (m, 1H, H-4), 4.91 (d, 1H, H-2, $^{3}J_{2\text{-}1}$= 3.6 Hz), 5.13(m, 1H, CH=, cod), 5.28 (m, 2H, H-3 and CH=, cod), 6.03 (d, 1H, H-1, $^{3}J_{1\text{-}2}$= 3.6 Hz), 7.1-7.9 (m, 22H, CH= aromatics). ^{13}C NMR ($CDCl_3$), δ: 22.6 (CH_3, ^{i}Pr), 23.4 (CH_3, ^{i}Pr), 26.3 (CH_3), 26.8 (CH_3), 28.8 (CH_2, cod), 29.9 (CH_2, cod), 31.1 (C-5), 31.9 (CH_2, cod), 32.9 (CH_2, cod), 44.9 (CH-S), 71.0 (CH=, cod), 73.8 (CH=, cod), 77.4 (C-4), 84.0 (C-3 and C-2), 98.9 (b, CH=, cod), 100.2 (b, CH=, cod), 105.1 (C-1), 113.4 (CMe_2), 117.7 (b, CH=, BAr_F), 120-134 (aromatic carbons), 134.9 (b, CH=, BAr_F), 161.8 (q, C-B, BAr_F, $^{1}J_{C\text{-}B}$ = 49 Hz). Anal. calc (%) for $C_{63}H_{53}BF_{24}IrO_4PS$: C 47.41, H 3.35, S 2.01; found: C 47.52, H 3.39, S 1.97.

[Ir(cod)(**L9a**)]BAr_F. Yield 65 mg (94 %). Anal. calc (%) for $C_{80}H_{85}BF_{24}IrO_6PS$: C 51.53, H 4.59, S 1.72; found: C 51.49, H 4.58, S 1.69. ^{31}P NMR ($CDCl_3$, 298 K), δ: 114.5 (bs). Major isomer (80%): ^{31}P NMR ($CDCl_3$, 213 K), δ: 114.8 (s). ^{1}H NMR ($CDCl_3$, 213 K), δ: 1.28-1.36 (b, 30H, CH_3 and CH_3 ^{t}Bu), 1.41 (s, 3H, CH_3), 1.55 (s, 9H, CH_3, ^{t}Bu), 1.68 (s, 9H, CH_3, ^{t}Bu), 1.9-2.4 (b, 8H, CH_2, cod), 3.21 (m, 1H, H-5'), 3.44 (d, 1H, H-2, $^3J_{2\text{-}1}$= 3.6 Hz), 3.51 (m, 1H, H-5), 4.12 (m, 1H, CH=, cod), 4.26 (m, 1H, H-4), 4.35 (m, 1H, CH=, cod), 4.56 (m, 1H, CH=, cod), 4.77 (m, 1H, H-3), 5.31 (m, 1H, CH=, cod), 5.48 (d, 1H, H-1, $^3J_{1\text{-}2}$= 3.6 Hz), 7.1-7.8 (m, 16H, CH= aromatics). ^{13}C NMR ($CDCl_3$, 213 K), δ: 26.0 (CH_3), 26.3 (CH_3), 27-36 (CH_3 ^{t}Bu, C ^{t}Bu, CH_2 cod and C-5), 69.2 (b, CH=, cod), 73.8 (b, CH=, cod), 77.5 (C-4), 78.4 (C-3), 81.9 (b, C-2), 99.8 (b, CH=, cod), 103.6 (b, CH=, cod), 104.1 (C-1), 113.4 (CMe_2), 117.5 (b, CH=, BAr_F), 120-130 (aromatic carbons), 134.6 (b, CH=, BAr_F), 138-149 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^1J_{C\text{-}B}$ = 49 Hz). Minor isomer (20%): ^{31}P NMR ($CDCl_3$, 213 K), δ: 110.8 (s). ^{1}H NMR ($CDCl_3$, 213 K), δ: 1.14 (s, 3H, CH_3), 1.31-1.36 (b, 27H, CH_3 ^{t}Bu), 1.44 (s, 3H, CH_3), 1.56 (s, 9H, CH_3, ^{t}Bu), 1.66 (s, 9H, CH_3, ^{t}Bu), 1.9-2.4 (b, 2H, CH_2, cod), 3.40 (d, 1H, H-2, $^3J_{2\text{-}1}$= 3.2 Hz), 3.81 (m, 1H, H-5'), 3.86 (m, 1H, H-3), 4.02 (m, 1H, H-5), 4.26 (m, 1H, CH=, cod), 4.46 (m, 1H, H-4), 4.61 (m, 1H, CH=, cod), 4.99 (m, 1H, CH=, cod), 5.57 (m, 1H, CH=, cod), 5.86 (d, 1H, H-1, $^3J_{1\text{-}2}$= 3.2 Hz), 7.1-7.8 (m, 16H, CH= aromatics). ^{13}C NMR ($CDCl_3$, 213 K); δ: 25.8 (CH_3), 26.4 (CH_3), 27-36 (CH_3 ^{t}Bu, C ^{t}Bu, CH_2 cod and C-5), 69.7 (b, CH=, cod), 73.1 (C-4), 78.6 (b, CH=, cod), 79.2 (C-3), 82.6 (b, C-2), 103.6 (b, CH=, cod), 104.5 (b, CH=, cod), 104.9 (C-1), 113.4 (CMe_2), 117.5 (b, CH=, BAr_F), 120-130 (aromatic carbons), 134.6 (b, CH=, BAr_F), 138-149 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^1J_{C\text{-}B}$ = 49 Hz).

[Ir(cod)(**L9i**)]BAr_F. Yield 56 mg (94 %). ^{31}P NMR ($CDCl_3$), δ: 108.1 (s). ^{1}H NMR ($CDCl_3$), δ: 1.23 (s, 9H, CH_3, ^{t}Bu), 1.36 (s, 3H, CH_3), 1.56 (s, 3H, CH_3), 1.70 (b, 2H, CH_2, cod), 2.05 (b, 4H, CH_2, cod), 2.31 (b, 2H, CH_2, cod), 3.03 (m, 1H, H-5'), 3.31 (m, 1H, CH=, cod), 3.51 (m, 1H, H-5), 3.67 (m, 1H, CH=, cod), 4.45 (m, 1H, H-4), 4.97 (d, 1H, H-2, $^3J_{2\text{-}1}$= 3.2 Hz), 5.24 (m, 1H, CH=, cod), 5.49 (m, 1H, H-3), 5.65 (m, 1H, CH=, cod), 6.06 (d, 1H, H-1, $^3J_{1\text{-}2}$= 3.2 Hz), 7.1-7.9 (m, 22H, CH= aromatics). ^{13}C NMR ($CDCl_3$), δ: 25.8 (C-S), 26.3 (CH_3), 26.9 (CH_3), 28.1 (CH_2, cod), 29.9 (CH_2, cod), 30.6 (CH_2, cod), 31.1 (CH_3, ^{t}Bu), 31.6 (C-5), 31.7 (CH_2, cod), 72.2 (CH=, cod), 72.4 (CH=, cod), 76.9 (C-4), 84.0 (C-3), 84.3 (d, C-2, $J_{C\text{-}P}$= 10.1 Hz), 96.8 (b, CH=, cod), 103.9 (b, CH=, cod), 104.9 (C-1), 113.4 (CMe_2), 117.6 (b, CH=, BAr_F), 120-133 (aromatic

carbons), 134.9 (b, CH=, BAr_F), 161.8 (q, C-B, BAr_F, $^1J_{C-B}$ = 49 Hz). Anal. calc (%) for $C_{64}H_{55}BF_{24}IrO_4PS$: C 47.74, H 3.44, S 1.99; found: C 47.76, H 3.49, S 1.98.

[Ir(cod)(**L10a**)]BAr_F. Yield 65 mg (93 %). ^{31}P NMR ($CDCl_3$, 298 K), δ: 113.7 (b). Anal. calc (%) for $C_{83}H_{83}BF_{24}IrO_6PS$: C 52.51, H 4.41, S 1.69; found: C 52.48, H 4.39, S 1.66. Major isomer (75%): ^{31}P NMR ($CDCl_3$, 213 K), δ: 116.4 (s). ^{1}H NMR ($CDCl_3$, 213 K), δ: 1.21 (s, 3H, CH_3), 1.36 (s, 18H, CH_3, ^{t}Bu), 1.43 (s, 3H, CH_3), 1.64 (s, 18H, CH_3, ^{t}Bu), 1.8-2.3 (b, 8H, CH_2, cod), 2.38 (s, 3H, CH_3-Ph), 3.41 (m, 1H, H-5'), 3.45 (m, 1H, H-2), 3.72 (m, 2H, CH=, cod and H-5), 3.99 (m, 1H, CH=, cod), 4.27 (m, 1H, CH=, cod), 4.47 (m, 1H, H-4), 4.67 (m, 1H, H-3), 5.00 (m, 1H, CH=, cod), 5.51 (d, 1H, H-1, $^3J_{1-2}$= 3.2 Hz), 7.0-8.0 (m, 20H, CH= aromatics). ^{13}C NMR ($CDCl_3$, 213 K), δ: 21.3 (CH_3-Ph), 25.8 (CH_3), 26.1 (CH_3), 30.3 (b, CH_2, cod), 30.9 (b, CH_2, cod), 31.2-31.8 (CH_3, ^{t}Bu), 32.9 (b, CH_2, cod), 35-36 (C, tBu), 46.6 (C-5), 70.8 (b, CH=, cod), 75.2 (C-3), 77.8 (b, CH=, cod), 78.6 (b, C-4), 82.9 (C-2), 104.1 (b, CH=, cod), 104.3 (C-1), 105.4 (b, CH=, cod), 113.1 (CMe_2), 117.5-162.3 (aromatic carbons). Minor isomer (25%): ^{31}P NMR ($CDCl_3$, 213 K), δ: 110.1 (s). ^{1}H NMR ($CDCl_3$, 213 K), δ: 1.16 (s, 3H, CH_3), 1.31 (s, 3H, CH_3), 1.44 (s, 9H, CH_3, ^{t}Bu), 1.48 (s, 9H, CH_3, ^{t}Bu), 1.69 (s, 18H, CH_3, ^{t}Bu), 1.8-2.3 (b, 8H, CH_2, cod), 2.36 (s, 3H, CH_3), 4.01 (m, 1H, H-5'), 4.12 (m, 1H, H-5), 4.17 (m, 1H, CH=, cod), 4.39 (m, 2H, H-4 and H-2), 4.46 (m, 1H, CH=, cod), 4.74 (m, 1H, H-3), 4.96 (m, 1H, CH=, cod), 5.04 (m, 1H, CH=, cod), 5.90 (b, 1H, H-1), 7.0-8.0 (m, 20H, CH= aromatics). ^{13}C NMR ($CDCl_3$, 213 K), δ: 20.9 (CH_3-Ph), 26.2 (CH_3), 26.5 (b, CH_2, cod), 27.1 (b, CH_2, cod), 28.9 (b, CH_2, cod), 30.3 (b, CH_2, cod), 31.2-31.8 (CH_3, ^{t}Bu), 34-36 (C, tBu), 41.7 (C-5), 69.7 (b, CH=, cod), 73.8 (C-3), 77.3 (b, C-4), 80.2 (b, CH=, cod), 84.5 (C-2), 102.2 (b, CH=, cod), 104.1 (C-1), 105.6 (b, CH=, cod), 113.3 (CMe_2), 117.5-162.3 (aromatic carbons).

[Ir(cod)(**L10i**)]BAr_F. Yield 60 mg (98 %). ^{31}P NMR ($CDCl_3$), δ: 112.2 (s). ^{1}H NMR ($CDCl_3$), δ: 1.18 (b, 2H, CH_2, cod), 1.32 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 1.83 (b, 1H, CH_2, cod), 1.97 (b, 1H, CH_2, cod), 2.12 (b, 2H, CH_2, cod), 2.21 (b, 2H, CH_2, cod), 2.28 (s, 3H, CH_3-Ph), 2.96 (m, 1H, H-5'), 3.24 (m, 1H, CH=, cod), 3.36 (m, 1H, CH=, cod), 3.50 (m, 1H, H-5), 4.49 (m, 1H, H-4), 4.68 (m, 1H, CH=, cod), 4.73 (m, 1H, CH=, cod), 4.86 (d, 1H, H-2, $^3J_{2-1}$= 3.6 Hz), 5.40 (m, 1H, H-3), 5.93 (d, 1H, H-1, $^3J_{1-2}$= 3.6 Hz), 7.1-8.1 (m, 26H, CH= aromatics). ^{13}C NMR ($CDCl_3$), δ: 21.4 (CH_3-Ph), 26.3 (CH_3), 26.8 (CH_3), 28.2 (CH_2, cod), 29.9 (CH_2, cod), 31.7 (CH_2, cod), 33.6 (CH_2, cod), 39.6 (C-5), 70.5 (CH=, cod), 74.5 (CH=, cod), 76.6 (C-4), 83.9 (d, C-2, J_{C-P}=6.2 Hz),

84.2 (C-3), 101.3 (d, CH=, cod, $J_{C\text{-}P}$=13.9 Hz), 101.9 (d, CH=, cod, $J_{C\text{-}P}$=7.3 Hz), 105.4 (C-1), 113.3 (CMe_2), 117.7 (b, CH=, BAr_F), 120-133 (aromatic carbons), 134.9 (b, CH=, BAr_F), 144.2 (C), 161.7 (q, C-B, BAr_F, $^1J_{C\text{-}B}$ = 49 Hz). Anal. calc (%) for $C_{67}H_{53}BF_{24}IrO_4PS$: C 48.94, H 3.25, S 1.95; found: C 49.00, H 3.31, S 1.91.

[Ir(cod)(**L11a**)]BAr_F. Yield 66 mg (92 %). ^{31}P NMR ($CDCl_3$, 298 K), δ: 112.4 (b). Anal. calc (%) for $C_{83}H_{80}BF_{27}IrO_6PS$: C 51.06, H 4.13, S 1.64; found: C 51.08, H 4.16, S 1.66. Major isomer (85%): ^{31}P NMR ($CDCl_3$, 213 K), δ: 114.3 (s). ^{1}H NMR ($CDCl_3$, 213 K), δ: 1.19 (s, 3H, CH_3), 1.32 (s, 9H, CH_3, ^{t}Bu), 1.34 (s, 9H, CH_3, ^{t}Bu), 1.38 (s, 3H, CH_3), 1.54 (s, 9H, CH_3, ^{t}Bu), 1.61 (s, 9H, CH_3, ^{t}Bu), 1.8-2.3 (b, 8H, CH_2, cod), 3.38 (m, 1H, H-5'), 3.42 (m, 1H, H-2), 3.68 (m, 1H, H-5), 3.72 (m, 1H, CH=, cod), 4.02 (m, 1H, CH=, cod), 4.32 (m, 1H, CH=, cod), 4.52 (m, 1H, H-4), 4.66 (m, 1H, H-3), 5.04 (m, 1H, CH=, cod), 5.48 (d, 1H, H-1, $^3J_{1\text{-}2}$= 3.6 Hz), 7.0-8.0 (m, 20H, CH= aromatics). ^{13}C NMR ($CDCl_3$, 213 K), δ: 26.0 (CH_3), 26.2 (CH_3), 29.9 (b, CH_2, cod), 30.1 (b, CH_2, cod), 31-33 (CH_3, ^{t}Bu), 33.1 (b, CH_2, cod), 33.4 (b, CH_2, cod), 35-36 (C, tBu), 46.9 (C-5), 70.4 (b, CH=, cod), 75.1 (C-3), 77.9 (b, CH=, cod), 78.8 (b, C-4), 84.1 (C-2), 100.3 (b, CH=, cod), 103.7 (b, CH=, cod), 104.1 (C-1), 113.0 (CMe_2), 117.5-162.3 (aromatic carbons). Minor isomer (15%): ^{31}P NMR ($CDCl_3$, 213 K), δ: 110.0 (s). ^{1}H NMR ($CDCl_3$, 213 K), δ: 1.11 (s, 3H, CH_3), 1.29 (s, 9H, CH_3, ^{t}Bu), 1.36 (s, 9H, CH_3, ^{t}Bu), 1.45 (s, 3H, CH_3), 1.50 (s, 9H, CH_3, ^{t}Bu), 1.58 (s, 9H, CH_3, ^{t}Bu), 1.8-2.3 (b, 8H, CH_2, cod), 3.21 (m, 1H, H-5'), 3.54 (m, 1H, H-5), 3.58 (m, 1H, H-2), 3.69 (m, 1H, CH=, cod), 3.88 (m, 1H, CH=, cod), 4.26 (m, 1H, CH=, cod), 4.47 (m, 1H, H-4), 4.62 (m, 1H, H-3), 5.11 (m, 1H, CH=, cod), 5.39 (d, 1H, H-1, $^3J_{1\text{-}2}$= 3.2 Hz), 7.0-8.0 (m, 20H, CH= aromatics).

[Ir(cod)(**L11i**)]BAr_F. Yield 60 mg (96 %). ^{31}P NMR ($CDCl_3$), δ: 112.1 (s). ^{1}H NMR ($CDCl_3$), δ: 1.18 (b, 2H, CH_2, cod), 1.29 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 1.96 (b, 2H, CH_2, cod), 2.15 (b, 4H, CH_2, cod), 3.11 (m, 1H, H-5'), 3.32 (m, 1H, CH=, cod), 3.46 (m, 1H, CH=, cod), 3.59 (m, 1H, H-5), 4.46 (m, 1H, H-4), 4.53 (m, 1H, CH=, cod), 4.77 (m, 1H, CH=, cod), 4.86 (d, 1H, H-2, $^3J_{2\text{-}1}$= 3.2 Hz), 5.37 (m, 1H, H-3), 5.95 (d, 1H, H-1, $^3J_{1\text{-}2}$= 3.2 Hz), 7.0-7.9 (m, 26H, CH= aromatics). ^{13}C NMR ($CDCl_3$), δ: 26.0 (CH_3), 26.5 (CH_3), 28.2 (CH_2, cod), 29.5 (CH_2, cod), 31.6 (CH_2, cod), 33.2 (CH_2, cod), 39.0 (C-5), 71.8 (CH=, cod), 75.7 (CH=, cod), 76.1 (C-4), 83.5 (d, C-2, $J_{C\text{-}P}$=8.7 Hz), 83.8 (C-3), 100.8 (d, CH=, cod, $J_{C\text{-}P}$=10.4 Hz), 101.5 (d, CH=, cod, $J_{C\text{-}P}$=9.2 Hz), 105.1 (C-1), 113.4 (CMe_2), 117.7 (b, CH=, BAr_F), 120-133 (aromatic carbons), 134.9 (b, CH=,

BAr_F), 144.2 (C), 161.7 (q, C-B, BAr_F, $^1J_{C-B}$ = 49 Hz). Anal. calc (%) for $C_{67}H_{50}BF_{27}IrO_4PS$: C 47.39, H 2.97, S 1.89; found: C 47.43, H 3.02, S 1.87.

[Ir(cod)(**L12a**)]BAr_F. Yield 59 mg (90 %). ^{31}P NMR ($CDCl_3$, 298 K), δ: 111.9 (s). Anal. calc (%) for $C_{84}H_{85}BF_{24}IrO_6PS$: C 52.75, H 4.48, S 1.68; found: C 52.77, H 4.52, S 1.65. Major isomer (65%): ^{31}P NMR ($CDCl_3$, 213 K), δ: 105.8 (s). ^{1}H NMR ($CDCl_3$, 213 K), δ: 1.19 (s, 3H, CH_3), 1.39 (s, 18H, CH_3, ^{t}Bu), 1.43 (s, 3H, CH_3), 1.57 (s, 9H, CH_3, ^{t}Bu), 1.67 (s, 9H, CH_3, ^{t}Bu), 1.8-2.4 (b, 8H, CH_2, cod), 2.83 (b, 6H, CH_3-Ar), 2.91 (b, 3H, CH_3-Ar), 3.65 (m, 1H, H-5'), 3.91 (m, 1H, H-5), 4.02 (d, 1H, H-2, $^3J_{2-1}$= 3.6 Hz), 4.03 (m, 2H, CH=, cod and H-3), 4.39 (m, 2H, H-4 and CH=, cod), 4.54 (m, 1H, CH=, cod), 4.71 (b, 1H, CH= cod), 5.42 (d, 1H, H-1, $^3J_{1-2}$ = 3.6 Hz), 7.2-7.8 (m, 19H, CH= aromatics). ^{13}C NMR ($CDCl_3$), δ: 22.9 (CH_3-Ar), 23.5 (CH_3-Ar), 25.3 (CH_3), 26.9 (CH_3), 27.9 (b, CH_2, cod), 31-32.5 (CH_3, ^{t}Bu), 33.1 (CH_2, cod), 33.4 (CH_2, cod), 34.5-35.5 (C, tBu), 46.3 (C-5), 70.4 (CH=, cod), 72.1 (CH=, cod), 72.5 (C-4), 75.3 (C-3), 79.4 (C-2), 102.3 (d, CH= cod, J_{C-P}= 16.0 Hz), 103.8 (b, CH= cod), 104.3 (C-1), 112.8 (CMe_2), 117.4 (b, CH=, BAr_F), 120-132 (aromatic carbons), 134.7 (b, CH=, BAr_F), 138-149 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^1J_{C-B}$ = 49 Hz). Minor isomer (35%): ^{31}P NMR ($CDCl_3$, 213 K), δ: 117.2 (s). ^{1}H NMR ($CDCl_3$, 213 K), δ: 1.24 (s, 3H, CH_3), 1.39 (s, 18H, CH_3, ^{t}Bu), 1.43 (s, 3H, CH_3), 1.54 (s, 9H, CH_3, ^{t}Bu), 1.67 (s, 9H, CH_3, ^{t}Bu), 1.8-2.4 (b, 8H, CH_2, cod), 2.83 (b, 6H, CH_3-Ar), 2.91 (b, 3H, CH_3-Ar), 3.85 (m, 1H, H-5'), 3.91 (m, 1H, H-5), 4.05 (m, 1H, CH=, cod), 4.13 (d, 1H, H-2, $^3J_{2-1}$= 3.6 Hz), 4.49 (m, 2H, H-4 and CH=, cod), 4.76 (m, 1H, CH=, cod), 4.84 (b, 2H, CH= cod and H-3), 5.67 (d, 1H, H-1, $^3J_{1-2}$ = 3.6 Hz), 7.2-7.8 (m, 19H, CH= aromatics). ^{13}C NMR ($CDCl_3$), δ: 23.2 (CH_3-Ar), 23.7 (CH_3-Ar), 25.7 (CH_3), 26.7 (CH_3), 28.3 (b, CH_2, cod), 28.9 (b, CH_2, cod), 31-32.5 (CH_3, ^{t}Bu), 33.3 (CH_2, cod), 33.7 (CH_2, cod), 34.5-35.5 (C, tBu), 46.3 (C-5), 69.8 (CH=, cod), 70.3 (CH=, cod), 71.2 (C-4), 75.5 (C-3), 79.6 (C-2), 102.5 (b, CH= cod), 103.9 (b, CH= cod), 104.3 (C-1), 113.3 (CMe_2), 117.4 (b, CH=, BAr_F), 120-132 (aromatic carbons), 134.7 (b, CH=, BAr_F), 138-149 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^1J_{C-B}$ = 49 Hz).

[Ir(cod)(**L12i**)]BAr_F. Yield 60 mg (97 %). ^{31}P NMR ($CDCl_3$), δ: 112.9 (s). ^{1}H NMR ($CDCl_3$), δ: 1.27 (b, 2H, CH_2, cod), 1.35 (s, 3H, CH_3), 1.56 (s, 3H, CH_3), 1.96 (b, 4H, CH_2, cod), 2.27 (b, 5H, CH_2, cod and CH_3-Ph), 2.68 (s, 3H, CH_3-Ph), 3.20 (m, 1H, CH=, cod), 3.35 (m, 1H, H-5'), 3.50 (m, 1H, CH=, cod), 3.60 (m, 1H, H-5), 4.32 (m, 1H, CH=, cod), 4.49 (m, 1H, CH=, cod), 4.65 (m, 1H, H-4), 4.78 (d, 1H, H-2, $^3J_{2-1}$= 3.2

Hz), 5.26 (m, 1H, H-3), 6.03 (d, 1H, H-1, $^{3}J_{1\text{-}2}{}^{=}$ 3.2 Hz), 7.1-8.1 (m, 25H, CH= aromatics). ^{13}C NMR ($CDCl_3$), δ: 22.6 (CH_3-Ph), 22.9 (CH_3-Ph), 26.0 (CH_3), 26.5 (CH_3), 28.3 (CH_2, cod), 29.6 (CH_2, cod), 31.6 (CH_2, cod), 33.2 (CH_2, cod), 40.7 (C-5), 68.6 (CH=, cod), 73.6 (CH=, cod), 77.2 (C-4), 82.0 (C-3), 83.6 (d, C-2, $J_{C\text{-}P}$=7.0 Hz), 97.5 (d, CH=, cod, $J_{C\text{-}P}$=12.8 Hz), 100.2 (d, CH=, cod, $J_{C\text{-}P}$=10.0 Hz), 105.1 (C-1), 113.2 (CMe_2), 117.5 (b, CH=, BAr_F), 120-133 (aromatic carbons), 134.8 (b, CH=, BAr_F), 140.8 (C), 141.3 (C), 161.7 (q, C-B, BAr_F, $^{1}J_{C\text{-}B}$ = 49 Hz). Anal. calc (%) for $C_{68}H_{55}BF_{24}IrO_4PS$: C 49.25, H 3.34, S 1.93; found: C 49.31, H 3.37, S 1.92.

[Ir(cod)(**L13a**)]BAr_F. Yield 64 mg (91 %). ^{31}P NMR ($CDCl_3$), δ: 109.5 (s). ^{1}H NMR ($CDCl_3$), δ: 1.19 (s, 3H, CH_3), 1.36 (s, 9H, CH_3, ^{t}Bu), 1.38 (s, 9H, CH_3, ^{t}Bu), 1.41 (s, 3H, CH_3), 1.57 (s, 9H, CH_3, ^{t}Bu), 1.65 (s, 9H, CH_3, ^{t}Bu), 1.90-2.18 (b, 8H, CH_2, cod), 3.64 (dd, 1H, H-5', $^{2}J_{5'\text{-}5}$= 13.2 Hz, $^{3}J_{5'\text{-}4}$= 8.8 Hz), 3.96 (m, 1H, CH=, cod), 4.19 (m, 1H, H-2), 4.22 (m, 1H, H-5), 4.31 (m, 1H, H-4), 4.54 (b, 2H, CH= cod and H-3), 4.61 (m, 1H, CH=, cod), 4.92 (b, 1H, CH=, cod), 5.66 (d, 1H, H-1, $^{3}J_{1\text{-}2}$ = 4.4 Hz), 7.1-7.8 (m, 21H, CH= aromatics). ^{13}C NMR ($CDCl_3$), δ: 26.2 (CH_3), 26.4 (CH_3), 28.4 (b, CH_2, cod), 28.6 (b, CH_2, cod), 31.5 (CH_3, ^{t}Bu), 31.7 (CH_3, ^{t}Bu), 32.1 (CH_3, ^{t}Bu), 32.5 (b, CH_2, cod), 33.3 (b, CH_2, cod), 34.9 (C, tBu), 35.0 (C, tBu), 35.7 (C, tBu), 45.1 (C-5), 71.4 (b, CH=, cod), 72.6 (C-3), 76.2 (b, CH=, cod), 78.3 (d, C-4, $J_{C\text{-}P}$= 5.2 Hz), 78.8 (C-2), 103.7 (b, CH=, cod), 104.5 (C-1), 105.2 (b, CH=, cod), 114.3 (CMe_2), 117.6 (b, CH=, BAr_F), 120.6-133 (aromatic carbons), 135.0 (b, CH=, BAr_F), 139-150 (aromatic carbons), 161.9 (q, C-B, BAr_F, $^{1}J_{C\text{-}B}$ = 49 Hz). Anal. calc (%) for $C_{82}H_{81}BF_{24}IrO_6PS$: C 52.26, H 4.33, S 1.70; found: C 52.21, H 4.28, S 1.68.

[Ir(cod)(**L13b**)]BAr_F. Yield 62 mg (91 %). ^{31}P NMR ($CDCl_3$), δ: 108.7 (s). ^{1}H NMR ($CDCl_3$), δ: 1.21 (s, 3H, CH_3), 1.35 (s, 9H, CH_3, ^{t}Bu), 1.39 (s, 3H, CH_3), 1.54 (s, 9H, CH_3, ^{t}Bu), 1.85-2.20 (b, 8H, CH_2, cod), 3.24 (s, 3H, CH_3-O), 3.26 (s, 3H, CH_3-O), 3.55 (dd, 1H, H-5', $^{2}J_{5'\text{-}5}$= 14.0 Hz, $^{3}J_{5'\text{-}4}$= 9.2 Hz), 3.87 (m, 1H, CH=, cod), 4.21 (m, 1H, H-2), 4.26 (m, 1H, H-5), 4.36 (m, 1H, H-4), 4.51 (b, 1H, CH= cod), 4.56 (m, 1H, H-3), 4.65 (m, 1H, CH=, cod), 4.99 (b, 1H, CH=, cod), 5.69 (d, 1H, H-1, $^{3}J_{1\text{-}2}$ = 3.2 Hz), 6.8-7.8 (m, 21H, CH= aromatics). ^{13}C NMR ($CDCl_3$), δ: 25.9 (CH_3), 26.1 (CH_3), 28.6 (b, CH_2, cod), 29.2 (b, CH_2, cod), 31.6 (CH_3, ^{t}Bu), 32.1 (CH_3, ^{t}Bu), 32.8 (b, CH_2, cod), 33.1 (b, CH_2, cod), 34.9 (C, tBu), 35.2 (C, tBu), 44.9 (C-5), 55.3 (CH_3-O), 70.9 (b, CH=, cod), 72.4 (C-3), 76.0 (b, CH=, cod), 78.7 (d, C-4, $J_{C\text{-}P}$= 8.2 Hz), 78.7 (C-2), 103.1 (b, CH=, cod), 104.3 (C-1), 104.9 (b, CH=, cod), 114.1 (CMe_2), 117.6 (b, CH=,

BAr_F), 120.6-133 (aromatic carbons), 135.0 (b, CH=, BAr_F), 139-150 (aromatic carbons), 161.9 (q, C-B, BAr_F, $^1J_{C\text{-}B}$ = 49 Hz). Anal. calc (%) for $C_{76}H_{69}BF_{24}IrO_8PS$: C 49.82, H 3.80, S 1.75; found: C 49.80, H 3.77, S 1.73.

[Ir(cod)(**L13c**)]BAr_F. Yield 60 mg (89 %). ^{31}P NMR ($CDCl_3$), δ: 109.0 (s). ^{1}H NMR ($CDCl_3$), δ: 0.51 (m, 9H, CH_3-Si), 0.61 (m, 9H, CH_3-Si), 1.19 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 2.0-2.3 (b, 8H, CH_2, cod), 3.56 (dd, 1H, H-5', $^2J_{5'\text{-}5}$= 14.4 Hz, $^3J_{5'\text{-}4}$= 10.8 Hz), 3.82 (m, 1H, CH=, cod), 4.28 (m, 3H, H-2, H-4, H-5), 4.50 (m, 1H, H-3), 4.66 (m, 2H, CH=, cod), 5.08 (b, 1H, CH=, cod), 5.66 (d, 1H, H-1, $^3J_{1\text{-}2}$ = 3.6 Hz), 7.3-7.9 (m, 23H, CH= aromatics). ^{13}C NMR ($CDCl_3$), δ: 0.50 (CH_3-Si), 1.60 (CH_3-Si), 26.5 (CH_3), 26.6 (CH_3), 28.2 (CH_2, cod), 29.9 (CH_2, cod), 30.2 (CH_2, cod), 34.6 (CH_2, cod), 45.2 (C-5), 71.8 (CH=, cod), 72.8 (C-4), 78.2 (CH=, cod), 79.0 (C-2), 79.2 (C-3), 104.4 (CH=, cod), 104.8 (C-1), 106.5 (d, CH=, cod, $J_{C\text{-}P}$= 12 Hz), 114.7 (CMe_2), 117.9 (b, CH=, BAr_F), 123-134 (aromatic carbons), 135.3 (b, CH=, BAr_F), 137-155 (aromatic carbons), 162.3 (q, C-B, BAr_F, $^1J_{C\text{-}B}$ = 49 Hz). Anal. calc (%) for $C_{72}H_{65}BF_{24}IrO_6PSSi_2$: C 47.52, H 3.63, S 1.78; found: C 47.54, H 3.65, S 1.77.

[Ir(cod)(**L13d**)]BAr_F. Yield 58 mg (95 %). ^{31}P NMR ($CDCl_3$), δ: 117.4 (s). ^{1}H NMR ($CDCl_3$), δ: 1.22 (s, 3H, CH_3), 1.39 (s, 3H, CH_3), 1.8-2.4 (b, 8H, CH_2, cod), 2.99 (m, 1H, CH=, cod), 3.84 (dd, 1H, H-5', $^2J_{5'\text{-}5}$= 13.2 Hz, $^3J_{5'\text{-}4}$= 8.8 Hz), 4.09 (dd, 1H, H-5, $^2J_{5\text{-}5'}$= 13.2 Hz, $^3J_{5\text{-}4}$= 3.2 Hz), 4.29 (m, 1H, CH=, cod), 4.53 (m, 1H, H-4), 4.59 (m, 1H, CH= cod), 4.86 (m, 1H, H-2), 5.11 (m, 1H, H-3), 5.19 (m, 1H, CH=, cod), 5.88 (d, 1H, H-1, $^3J_{1\text{-}2}$ = 3.6 Hz), 6.9-8.0 (m, 25H, CH= aromatics). ^{13}C NMR ($CDCl_3$), δ: 25.9 (CH_3), 26.2 (CH_3), 28.4 (CH_2, cod), 29.0 (CH_2, cod), 30.4 (CH_2, cod), 32.2 (CH_2, cod), 43.7 (C-5), 75.0 (C-4), 76.3 (CH=, cod), 76.9 (CH=, cod), 79.1 (C-3), 80.4 (C-2), 102.5 (CH=, cod), 103.1 (C-1), 104.8 (CH=, cod), 114.6 (CMe_2), 117.4 (b, CH=, BAr_F), 120-132 (aromatic carbons), 134.7 (b, CH=, BAr_F), 138-148 (aromatic carbons), 161.9 (q, C-B, BAr_F, $^1J_{C\text{-}B}$ = 49 Hz). Anal. calc (%) for $C_{66}H_{49}BF_{24}IrO_6PS$: C 47.75, H 2.98, S 1.93; found: C 47.71, H 2.96, S 1.88.

[Ir(cod)(**L13e**)]BAr_F. Yield 65 mg (96 %). ^{31}P NMR ($CDCl_3$), δ: 102.5 (s). ^{1}H NMR ($CDCl_3$), δ: 1.20 (s, 3H, CH_3), 1.26 (b, CH_2, cod), 1.33 (s, 3H, CH_3), 1.48 (s, 9H, CH_3, ^{t}Bu), 1.68 (s, 9H, CH_3, ^{t}Bu), 1.76 (s, 3H, CH_3-Ph), 1.82 (s, 3H, CH_3-Ph), 1.85-2.20 (b, 6H, CH_2, cod), 2.26 (s, 3H, CH_3-Ph), 2.31 (s, 3H, CH_3-Ph), 3.13 (m, 1H, CH=, cod), 3.49 (m, 1H, H-5'), 4.21 (m, 2H, H-2 and CH= cod), 4.29 (m, 1H, H-5), 4.52 (m, 2H, H-4 and CH= cod), 4.71 (m, 1H, CH= cod), 4.89 (m, 1H, CH=, cod), 5.62 (d, 1H, H-1,

$^{3}J_{1\text{-}2}$ = 3.6 Hz), 7.1-7.8 (m, 19H, CH= aromatics). ^{13}C NMR ($CDCl_3$), δ: 16.2 (CH_3-Ph), 16.3 (CH_3-Ph), 19.9 (CH_3-Ph), 20.1 (CH_3-Ph), 25.8 (CH_3), 26.1 (CH_3), 27.7 (b, CH_2, cod), 29.0 (b, CH_2, cod), 30.7 (b, CH_2, cod), 31.4 (CH_3, ^{t}Bu), 31.9 (b, CH_2, cod), 32.4 (CH_3, ^{t}Bu), 33.9 (C, tBu), 34.9 (C, tBu), 44.7 (C-5), 69.5 (CH=, cod), 72.3 (CH=, cod), 77.7 (C-2), 78.5 (C-2), 79.0 (d, C-4, $J_{C\text{-}P}$= 7.8 Hz), 102.4 (d, CH=, cod, $J_{C\text{-}P}$=15.5 Hz), 104.5 (C-1), 105.2 (d, CH=, cod, $J_{C\text{-}P}$=13.5 Hz), 113.9 (CMe_2), 117.5 (b, CH=, BAr_F), 120.4-133 (aromatic carbons), 134.7 (b, CH=, BAr_F), 135-144 (aromatic carbons), 161.9 (q, C-B, BAr_F, $^{1}J_{C\text{-}B}$ = 49 Hz). Anal. calc (%) for $C_{78}H_{73}BF_{24}IrO_6PS$: C 51.24, H 4.02, S 1.75; found: C 51.26, H 4.06, S 1.73.

[Ir(cod)(**L13f**)]BAr_F. Yield 63 mg (95 %). ^{31}P NMR ($CDCl_3$), δ: 115.5 (s). ^{1}H NMR ($CDCl_3$), δ: 1.31 (s, 3H, CH_3), 1.45 (s, 9H, CH_3, ^{t}Bu), 1.52 (s, 3H, CH_3), 1.74 (s, 9H, CH_3, ^{t}Bu), 1.80 (s, 3H, CH_3-Ph), 1.81 (s, 3H, CH_3-Ph), 1.85-2.20 (b, 8H, CH_2, cod), 2.30 (s, 3H, CH_3-Ph), 2.32 (s, 3H, CH_3-Ph), 3.24 (m, 1H, CH=, cod), 4.14 (dd, 1H, H-5', $^{2}J_{5'\text{-}5}$= 13.6 Hz, $^{3}J_{5'\text{-}4}$= 1.2 Hz), 4.23 (dd, 1H, H-5, $^{2}J_{5'\text{-}5}$= 13.6 Hz, $^{3}J_{5'\text{-}4}$= 4.4 Hz), 4.44 (m, 1H, CH= cod), 4.55 (m, 2H, H-4 and CH= cod), 4.79 (m, 1H, H-2), 4.92 (m, 1H, CH=, cod), 5.06 (m, 1H, H-3), 5.62 (d, 1H, H-1, $^{3}J_{1\text{-}2}$ = 3.6 Hz), 7.1-7.8 (m, 19H, CH= aromatics). ^{13}C NMR ($CDCl_3$), δ: 16.5 (CH_3-Ph), 16.7 (CH_3-Ph), 20.4 (CH_3-Ph), 20.6 (CH_3-Ph), 26.0 (CH_3), 26.4 (CH_3), 27.9 (b, CH_2, cod), 30.2 (b, CH_2, cod), 32.0 (b, CH_2, cod), 32.4 (CH_3, ^{t}Bu), 33.0 (CH_3, ^{t}Bu), 34.3 (C, tBu), 35.5 (C, tBu), 44.4 (C-5), 71.5 (CH=, cod), 73.4 (CH=, cod), 75.7 (C-3), 77.3 (C-2), 77.5 (C-4), 102.2 (d, CH=, cod, $J_{C\text{-}P}$=15.1 Hz), 104.1 (C-1), 104.8 (d, CH=, cod, $J_{C\text{-}P}$=10.2 Hz), 115.1 (CMe_2), 117.6 (b, CH=, BAr_F), 120-132 (aromatic carbons), 134.8 (b, CH=, BAr_F), 135-144 (aromatic carbons), 161.9 (q, C-B, BAr_F, $^{1}J_{C\text{-}B}$ = 49 Hz). Anal. calc (%) for $C_{78}H_{73}BF_{24}IrO_6PS$: C 51.24, H 4.02, S 1.75; found: C 51.28, H 4.08, S 1.72.

[Ir(cod)(**L13g**)]BAr_F. Yield 62 mg (95 %). ^{31}P NMR ($CDCl_3$), δ: 111.1 (s). ^{1}H NMR ($CDCl_3$), δ: 1.30 (s, 3H, CH_3), 1.52 (s, 3H, CH_3), 1.8-2.4 (b, 8H, CH_2, cod), 3.09 (m, 1H, CH=, cod), 3.80 (dd, 1H, H-5', $^{2}J_{5'\text{-}5}$= 13.6 Hz, $^{3}J_{5'\text{-}4}$= 10.0 Hz), 4.15 (m, 1H, H-5), 4.36 (m, 2H, CH=, cod and H-4), 4.46 (m, 1H, H-2), 4.68 (m, 1H, CH= cod), 4.86 (m, 1H, H-3), 4.97 (m, 1H, CH=, cod), 5.59 (d, 1H, H-1, $^{3}J_{1\text{-}2}$ = 3.2 Hz), 7.2-8.1 (m, 29H, CH= aromatics). ^{13}C NMR ($CDCl_3$), δ: 26.1 (CH_3), 26.3 (CH_3), 26.9 (b, CH_2, cod), 31.9 (CH_2, cod), 33.0 (CH_2, cod), 44.4 (C-5), 78.4 (C-4), 75.7 (b, CH=, cod), 78.4 (C-2), 80.6 (C-3), 103.4 (b, CH=, cod and C-1), 107.1 (b, CH=, cod), 114.3 (CMe_2), 123.2 (b, CH=, BAr_F), 125-133 (aromatic carbons), 134.8 (b, CH=, BAr_F), 137-148

(aromatic carbons), 161.7 (q, C-B, BAr_F, $^1J_{C-B}$ = 49 Hz). Anal. calc (%) for $C_{74}H_{53}BF_{24}IrO_6PS$: C 50.49, H 3.03, S 1.82; found: C 50.58, H 3.13, S 1.78.

[Ir(cod)(**L13h**)]BAr_F. Yield 62 mg (95 %). ^{31}P NMR ($CDCl_3$), δ: 117.4 (s). ^{1}H NMR ($CDCl_3$), δ: 1.24 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 1.8-2.4 (b, 8H, CH_2, cod), 3.03 (m, 1H, CH=, cod), 4.03 (dd, 1H, H-5', $^2J_{5'-5}$= 12.0 Hz, $^3J_{5'-4}$= 9.2 Hz), 4.18 (dd, 1H, H-5, $^2J_{5-5'}$= 12.0 Hz, $^3J_{5-4}$= 3.6 Hz), 4.45 (m, 1H, CH=, cod), 4.56 (m, 1H, H-4), 4.62 (m, 1H, CH= cod), 4.88 (m, 1H, H-2), 5.03 (m, 1H, H-3), 5.16 (m, 1H, CH=, cod), 5.92 (d, 1H, H-1, $^3J_{1-2}$ = 3.6 Hz), 7.2-8.2 (m, 29H, CH= aromatics). ^{13}C NMR ($CDCl_3$), δ: 26.1 (CH_3), 28.5 (CH_2, cod), 29.2 (CH_2, cod), 30.4 (CH_2, cod), 30.9 (CH_2, cod), 43.8 (C-5), 75.2 (C-4), 76.4 (CH=, cod), 77.2 (CH=, cod), 78.5 (C-3), 78.9 (C-2), 103.9 (C-1), 105.8 (CH=, cod), 107.3 (CH=, cod), 114.7 (CMe_2), 117.4 (b, CH=, BAr_F), 120-132 (aromatic carbons), 134.7 (b, CH=, BAr_F), 138-148 (aromatic carbons), 161.9 (q, C-B, BAr_F, $^1J_{C-B}$ = 49 Hz). Anal. calc (%) for $C_{74}H_{53}BF_{24}IrO_6PS$: C 50.49, H 3.03, S 1.82; found: C 50.57, H 3.18, S 1.75.

[Ir(cod)(**L13i**)]BAr_F. Yield 58 mg (97 %). ^{31}P NMR ($CDCl_3$), δ: 111.4 (s). ^{1}H NMR ($CDCl_3$), δ: 1.39 (s, 3H, CH_3), 1.56 (s, 3H, CH_3), 1.83 (b, 4H, CH_2, cod), 2.04 (b, 4H, CH_2, cod), 2.29 (b, 4H, CH_2, cod), 3.30 (dd, 1H, H-5', $^2J_{5'-5}$= 14.0 Hz, $^3J_{5'-4}$= 4.8 Hz), 3.36 (m, 1H, CH=, cod), 3.51 (m, 1H, CH=, cod), 3.55 (m, 1H, H-5, $^2J_{5'-5}$= 14.0 Hz, $^3J_{5-4}$= 2.0 Hz), 4.23 (m, 1H, H-4), 4.29 (m, 1H, CH=, cod), 4.75 (m, 1H, H-3), 4.94 (m, 2H, H-2 and CH=, cod), 5.86 (d, 1H, H-1, $^3J_{1-2}$= 3.6 Hz), 7.1-8.2 (m, 27H, CH= aromatics). ^{13}C NMR ($CDCl_3$), δ: 26.4 (CH_3), 26.5 (CH_3), 28.5 (CH_2, cod), 29.6 (CH_2, cod), 32.2 (CH_2, cod), 33.4 (CH_2, cod), 41.9 (C-5), 71.6 (CH=, cod), 72.2 (C-4), 73.2 (CH=, cod), 78.2 (d, C-2, J_{C-P}=9.9 Hz), 79.3 (C-3), 99.1 (d, CH=, cod, J_{C-P}=12.4 Hz), 102.2 (d, CH=, cod, J_{C-P}=10.1 Hz), 103.6 (C-1), 114.6 (CMe_2), 117.7 (b, CH=, BAr_F), 120-134 (aromatic carbons), 134.9 (b, CH=, BAr_F), 161.7 (q, C-B, BAr_F, $^1J_{C-B}$ = 49 Hz). Anal. calc (%) for $C_{66}H_{51}BF_{24}IrO_4PS$: C 48.63, H 3.15, S 1.97; found: C 48.68, H 3.18, S 1.95.

[Ir(cod)(**L14a**)]BAr_F. Yield 67 mg (93 %). ^{31}P NMR ($CDCl_3$), δ: 114.8 (s). ^{1}H NMR ($CDCl_3$), δ: 1.25 (s, 3H, CH_3), 1.34 (s, 18H, CH_3, ^{t}Bu), 1.48 (s, 12H, CH_3 and CH_3, ^{t}Bu), 1.54 (s, 9H, CH_3, ^{t}Bu), 1.90 (b, 4H, CH_2, cod), 2.14 (b, 4H, CH_2, cod), 2.49 (s, 3H, CH_3-S), 3.63 (m, 1H, H-5'), 3.85 (m, 1H, H-5), 4.14 (m, 1H, CH=, cod), 4.20 (m, 1H, CH=, cod), 4.45 (m, 1H, H-4), 4.53 (m, 1H, H-2), 4.72 (m, 1H, H-3), 4.97 (m, 2H, CH=, cod), 5.75 (d, 1H, H-1, $^3J_{1-2}$ = 3.2 Hz), 7.1-7.8 (m, 16H, CH= aromatics). ^{13}C

NMR ($CDCl_3$), δ: 21.4 (CH_3-S), 26.1 (CH_3), 26.4 (CH_3), 29.9 (b, CH_2, cod), 31.1 (b, CH_2, cod), 31.5 (CH_3, ^{t}Bu), 31.7 (CH_3, ^{t}Bu), 31.8 (CH_3, ^{t}Bu), 33.0 (b, CH_2, cod), 34.9 (C, tBu), 35.6 (C, tBu), 42.6 (C-5), 65.4 (b, CH=, cod), 73.0 (C-3), 73.9 (b, CH=, cod), 77.2 (C-4), 77.8 (C-2), 101.3 (b, CH=, cod), 104.0 (C-1), 114.6 (CMe_2), 117.6 (b, CH=, BAr_F), 120-131 (aromatic carbons), 135.0 (b, CH=, BAr_F), 139-150 (aromatic carbons), 161.9 (q, C-B, BAr_F, $^1J_{C\text{-}B}$ = 49 Hz). Anal. calc (%) for $C_{77}H_{79}BF_{24}IrO_6PS$: C 50.75, H 4.37, S 1.76; found: C 50.69, H 4.29, S 1.74.

[Ir(cod)(**L15a**)]BAr_F. Yield 67 mg (97 %). ^{31}P NMR ($CDCl_3$), δ: 108.0 (s). ^{1}H NMR ($CDCl_3$), δ: 1.20 (s, 3H, CH_3), 1.34 (s, 9H, CH_3, ^{t}Bu), 1.36 (s, 9H, CH_3, ^{t}Bu), 1.44 (s, 3H, CH_3), 1.50 (s, 9H, CH_3, ^{t}Bu), 1.55 (s, 9H, CH_3, ^{t}Bu), 1.62 (s, 9H, CH_3, ^{t}Bu), 1.67 (b, 2H, CH_2, cod), 1.71 (b, 2H, CH_2, cod), 1.87 (b, 2H, CH_2, cod), 2.15 (b, 2H, CH_2, cod), 2.99 (m, 1H, H-5'), 3.79 (m, 2H, H-5 and CH=, cod), 4.36 (m, 1H, H-2), 4.43 (m, 1H, H-4), 4.61 (m, 1H, H-3), 4.93 (m, 1H, CH=, cod), 5.25 (m, 1H, CH= cod), 5.73 (d, 1H, H-1, $^3J_{1\text{-}2}$ = 3.6 Hz), 5.94 (m, 1H, CH=, cod), 7.0-7.8 (m, 25H, CH= aromatics). ^{13}C NMR ($CDCl_3$), δ: 26.5 (CH_3), 26.6 (CH_3), 29.4 (b, CH_2, cod), 29.9 (b, CH_2, cod), 31.1 (CH_3, ^{t}Bu), 31.2 (CH_3, ^{t}Bu), 31.3 (CH_3, ^{t}Bu), 31.5 (CH_3, ^{t}Bu), 31.6 (CH_3, ^{t}Bu), 33.2 (b, CH_2, cod), 36.9 (C-5), 70.8 (CH=, cod), 73.3 (C-4), 77.3 (CH=, cod), 78.3 (C-3), 78.7 (d, C-2, $J_{C\text{-}P}$= 4.2 Hz), 98.3 (d, CH=, cod, $J_{C\text{-}P}$= 9.6 Hz), 103.8 (C-1), 104.7 (d, CH=, cod, $J_{C\text{-}P}$= 10.4 Hz), 114.3 (CMe_2), 117.7 (b, CH=, BAr_F), 120-132 (aromatic carbons), 135.0 (b, CH=, BAr_F), 138-150 (aromatic carbons), 161.9 (q, C-B, BAr_F, $^1J_{C\text{-}B}$ = 49 Hz). Anal. calc (%) for $C_{80}H_{85}BF_{24}IrO_6PS$: C 51.53, H 4.59, S 1.72; found: C 51.55, H 4.60, S 1.70.

[Ir(cod)(**L16a**)]BAr_F. Yield 66 mg (93 %). ^{31}P NMR ($CDCl_3$), δ: 107.6 (s). ^{1}H NMR ($CDCl_3$), δ: 1.18 (s, 3H, CH_3), 1.37 (s, 9H, CH_3, ^{t}Bu), 1.38 (s, 9H, CH_3, ^{t}Bu), 1.46 (s, 3H, CH_3), 1.54 (s, 9H, CH_3, ^{t}Bu), 1.71 (s, 9H, CH_3, ^{t}Bu), 1.8-2.4 (b, 8H, CH_2, cod), 2.76 (s, 3H, CH_3-Ar), 2.90 (s, 3H, CH_3-Ar), 3.74 (dd, 1H, H-5', $^2J_{5'\text{-}5}$= 13.2 Hz, $^3J_{5'\text{-}4}$= 9.2 Hz), 3.92 (m, 2H, H-5, H-2), 4.05 (m, 1H, CH=, cod), 4.40 (m, 3H, H-4, H-3 and CH=, cod), 4.71 (b, 2H, CH= cod), 5.62 (d, 1H, H-1, $^3J_{1\text{-}2}$ = 3.2 Hz), 7.2-7.8 (m, 19H, CH= aromatics). ^{13}C NMR ($CDCl_3$), δ: 22.7 (CH_3-Ar), 24.3 (CH_3-Ar), 25.9 (CH_3), 27.9 (CH_2, cod), 28.9 (CH_2, cod), 30.8 (CH_3, ^{t}Bu), 31.0 (CH_3, ^{t}Bu), 31.1 (CH_3, ^{t}Bu), 31.9 (CH_2, cod), 33.5 (CH_2, cod), 34.6 (C, tBu), 35.3 (C, tBu), 35.5 (C, tBu), 45.9 (C-5), 68.5 (CH=, cod), 73.2 (CH=, cod), 73.6 (C-4), 78.1 (d, C-2, $J_{C\text{-}P}$= 4.5 Hz), 79.0 (d, C-3, $J_{C\text{-}P}$= 7.2 Hz), 102.5 (d, CH= cod, $J_{C\text{-}P}$= 16.0 Hz), 104.7 (C-1), 105.8 (d, CH= cod, $J_{C\text{-}P}$= 15.9

Hz), 114.0 (CMe_2), 117.4 (b, CH=, BAr_F), 120-132 (aromatic carbons), 134.7 (b, CH=, BAr_F), 138-149 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^1J_{C\text{-}B}$ = 49 Hz). Anal. calc (%) for $C_{84}H_{85}BF_{24}IrO_6PS$: C 52.75, H 4.48, S 1.68; found: C 52.81, H 4.54, S 1.63.

[Ir(cod)(**L16e**)]BAr_F. Yield 63 mg (96 %). ^{31}P NMR ($CDCl_3$), δ: 101.8 (s). ^{1}H NMR ($CDCl_3$), δ: 1.23 (s, 3H, CH_3), 1.45 (s, 12H, CH_3 and CH_3, ^{t}Bu), 1.65 (s, 9H, CH_3, ^{t}Bu), 1.76 (b, 6H, CH_3-Ph), 1.78 (b, 4H, CH_2, cod), 1.81 (s, 3H, CH_3-Ph), 2.07 (b, 4H, CH_2, cod), 2.25 (s, 3H, CH_3-Ph), 2.29 (s, 3H, CH_3-Ph), 2.60 (s, 3H, CH_3-Ph), 3.03 (s, 3H, CH_3-Ph), 3.35 (m, 1H, CH=, cod), 3.46 (m, 1H, H-5'), 3.85 (m, 1H, H-5), 4.06 (b, 1H, H-2), 4.25 (m, 2H, H-4 and CH= cod), 4.40 (m, 1H, H-3), 4.55 (m, 1H, CH=, cod), 4.87 (m, 1H, CH=, cod), 5.60 (d, 1H, H-1, $^3J_{1\text{-}2}$ = 3.2 Hz), 7.1-7.8 (m, 17H, CH= aromatics). ^{13}C NMR ($CDCl_3$), δ: 16.5 (CH_3-Ph), 16.8 (CH_3-Ph), 20.5 (CH_3-Ph), 20.6 (CH_3-Ph), 22.5 (CH_3-Ph), 25.8 (CH_3-Ph), 26.4 (CH_3), 27.6 (b, CH_2, cod), 29.4 (b, CH_2, cod), 29.9 (b, CH_2, cod), 31.5 (b, CH_2, cod), 31.8 (CH_3, ^{t}Bu), 32.7 (CH_3, ^{t}Bu), 34.7 (C, tBu), 35.1 (C, tBu), 45.0 (C-5), 68.8 (CH=, cod), 72.5 (C-4), 74.2 (CH=, cod), 78.6 (C-2), 79.9 (C-3), 101.7 (d, CH=, cod, $J_{C\text{-}P}$=15.3 Hz), 104.4 (C-1), 106.1 (d, CH=, cod, $J_{C\text{-}P}$=12.4 Hz), 114.3 (CMe_2), 117.7 (b, CH=, BAr_F), 120-134 (aromatic carbons), 135.0 (b, CH=, BAr_F), 135-144 (aromatic carbons), 161.9 (q, C-B, BAr_F, $^1J_{C\text{-}B}$ = 49 Hz). Anal. calc (%) for $C_{80}H_{77}BF_{24}IrO_6PS$: C 51.76, H 4.18, S 1.73; found: C 51.77, H 4.20, S 1.72.

[Ir(cod)(**L16f**)]BAr_F. Yield 67 mg (98 %). ^{31}P NMR ($CDCl_3$), δ: 112.0 (s). ^{1}H NMR ($CDCl_3$), δ: 1.24 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 1.49 (s, 9H, CH_3, ^{t}Bu), 1.67 (s, 9H, CH_3, ^{t}Bu), 1.78 (b, 6H, CH_3-Ph), 1.83 (b, 4H, CH_2, cod), 1.99 (b, 2H, CH_2, cod), 2.22 (b, 2H, CH_2, cod), 2.26 (s, 3H, CH_3-Ph), 2.29 (s, 3H, CH_3-Ph), 2.65 (s, 3H, CH_3-Ph), 2.67 (s, 3H, CH_3-Ph), 3.43 (m, 1H, CH=, cod), 3.66 (m, 1H, H-5'), 4.26 (m, 1H, H-5), 4.34 (m, 1H, CH= cod), 4.52 (m, 2H, H-4 and CH= cod), 4.62 (m, 2H, H-2 and CH=, cod), 5.00 (m, 1H, H-3), 5.77 (d, 1H, H-1, $^3J_{1\text{-}2}$ = 3.2 Hz), 7.1-7.8 (m, 17H, CH= aromatics). ^{13}C NMR ($CDCl_3$), δ: 16.7 (CH_3-Ph), 16.8 (CH_3-Ph), 20.4 (CH_3-Ph), 20.5 (CH_3-Ph), 22.8 (CH_3-Ph), 23.1 (CH_3-Ph), 26.1 (CH_3), 26.3 (CH_3), 28.1 (b, CH_2, cod), 29.2 (b, CH_2, cod), 31.9 (CH_3, ^{t}Bu), 32.4 (b, CH_2, cod), 33.0 (CH_3, ^{t}Bu), 34.9 (C, tBu), 35.4 (C, tBu), 44.5 (C-5), 68.7 (CH=, cod), 72.7 (C-4), 75.4 (CH=, cod), 76.0 (C-3), 77.4 (C-2), 101.9 (d, CH=, cod, $J_{C\text{-}P}$=14.7 Hz), 103.1 (d, CH=, cod, $J_{C\text{-}P}$=11.5 Hz), 103.8 (C-1), 114.5 (CMe_2), 117.7 (b, CH=, BAr_F), 120-134 (aromatic carbons), 134.9 (b, CH=, BAr_F), 135-144 (aromatic carbons), 161.9 (q, C-B, BAr_F, $^1J_{C\text{-}B}$ = 49 Hz). Anal.

calc (%) for $C_{80}H_{77}BF_{24}IrO_6PS$: C 51.76, H 4.18, S 1.73; found: C 51.79, H 4.21, S 1.71.

[Ir(cod)(**L16i**)]BAr_F. Yield 57 mg (94 %). ^{31}P NMR ($CDCl_3$), δ: 113.3 (s). ^1H NMR ($CDCl_3$), δ: 1.38 (s, 3H, CH_3), 1.57 (s, 3H, CH_3), 1.75 (b, 2H, CH_2, cod), 1.87(b, 2H, CH_2, cod), 2.15 (b, 2H, CH_2, cod), 2.27 (b, 2H, CH_2, cod), 2.45 (s, 3H, CH_3-Ph), 2.58 (s, 3H, CH_3-Ph), 3.25 (d, 1H, H-5', $^3J_{5'-5}$= 14.0 Hz), 3.32 (m, 1H, CH=, cod), 3.38 (m, 1H, CH=, cod), 3.46 (dd, 1H, H-5, $^3J_{5'-5}$= 14.0 Hz, $^3J_{5-4}$= 3.6 Hz), 4.17 (m, 1H, CH= cod), 4.20 (m, 1H, H-4), 4.62 (m, 1H, CH=, cod), 4.85 (m, 1H, H-3), 4.97 (m, 1H, H-2), 5.88 (d, 1H, H-1, $^3J_{1-2}$ = 3.6 Hz), 7.1-8.1 (m, 25H, CH= aromatics). ^{13}C NMR ($CDCl_3$), δ: 22.7 (CH_3-Ph), 23.0 (CH_3-Ph), 26.3 (CH_3), 26.4 (CH_3), 28.5 (b, CH_2, cod), 29.9 (b, CH_2, cod), 32.0 (b, CH_2, cod), 33.5 (b, CH_2, cod), 41.7 (C-5), 69.6 (CH=, cod), 71.3 (C-4), 72.5 (CH=, cod), 77.9 (C-3), 78.2 (d, C-2, J_{C-P}= 10.0 Hz), 97.7 (d, CH=, cod, J_{C-P}= 13.1 Hz), 101.4 (d, CH=, cod, J_{C-P}= 13.1 Hz), 103.7 (C-1), 114.6 (CMe_2), 117.7 (b, CH=, BAr_F), 120-134 (aromatic carbons), 135.0 (b, CH=, BAr_F), 161.9 (q, C-B, BAr_F, $^1J_{C-B}$ = 49 Hz). Anal. calc (%) for $C_{68}H_{55}BF_{24}IrO_4PS$: C 49.25, H 3.34, S 1.93; found: C 49.31, H 3.36, S 1.90.

[Ir(cod)(**L17a**)]BAr_F. Yield 60 mg (90 %). ^{31}P NMR ($CDCl_3$), δ: 120.7 (s). ^1H NMR ($CDCl_3$), δ: 1.11 (s, 3H, CH_3), 1.35 (s, 18H, CH_3, ^{t}Bu), 1.40 (s, 3H, CH_3), 1.45 (s, 9H, CH_3, ^{t}Bu), 1.74 (s, 9H, CH_3, ^{t}Bu), 1.9-2.3 (b, 8H, CH_2, cod), 3.93 (m, 1H, CH=, cod), 4.20 (d, 1H, H-2, $^3J_{2-1}$= 3.2 Hz), 4.34 (m, 1H, H-3), 4.38 (m, 2H, H-5' and H-5), 4.67 (m, 1H, CH=, cod), 4.47 (m, 1H, CH=, cod), 4.82 (m, 1H, H-4), 4.92 (b, 1H, CH=, cod), 5.51 (d, 1H, H-1, $^3J_{1-2}$ = 3.2 Hz), 7.1-7.8 (m, 21H, CH= aromatics). ^{13}C NMR ($CDCl_3$), δ: 26.1 (CH_3), 26.5 (CH_3), 27.5 (b, CH_2, cod), 29.2 (b, CH_2, cod), 31.2 (CH_3, ^{t}Bu), 31.4 (CH_3, ^{t}Bu), 31.5 (CH_3, ^{t}Bu), 32.2 (b, CH_2, cod), 33.7 (b, CH_2, cod), 34.9 (C, tBu), 35.0 (C, tBu), 35.5 (C, tBu), 35.8 (C, tBu), 59.1 (C-3), 63.8 (C-5), 69.5 (b, CH=, cod), 75.8 (b, CH=, cod), 75.9 (C-4), 83.9 (C-2), 104.5 (d, CH=, cod, J_{C-P}= 22.2 Hz), 104.9 (C-1), 105.4 (d, CH=, cod, J_{C-P}= 13 Hz), 113.4 (CMe_2), 117.6 (b, CH=, BAr_F), 130.6-133.8 (aromatic carbons), 134.9 (b, CH=, BAr_F), 138-149 (aromatic carbons), 161.9 (q, C-B, BAr_F, $^1J_{C-B}$ = 49 Hz). Anal. calc (%) for $C_{82}H_{81}BF_{24}IrO_6PS$: C 52.26, H 4.33, S 1.70; found: C 52.31, H 4.39, S 1.67.

[Ir(cod)(**L17i**)]BAr_F. Yield 57 mg (94 %). ^{31}P NMR ($CDCl_3$), δ: 113.6 (s). ^1H NMR ($CDCl_3$), δ: 1.07 (s, 3H, CH_3), 1.37 (s, 3H, CH_3), 1.83 (b, 4H, CH_2, cod), 2.00 (b, 2H, CH_2, cod), 2.26 (b, 2H, CH_2, cod), 3.29 (m, 1H, CH=, cod), 3.48 (m, 2H, H-3 and

CH= cod), 3.98 (d, 1H, H-2, $^{3}J_{2\text{-}1}$ = 3.6 Hz), 4.16 (m, 1H, CH=, cod), 4.61 (m, 1H, H-5'), 4.73 (m, 2H, H-4 and H-5), 4.97 (b, 1H, CH=, cod), 5.70 (d, 1H, H-1, $^{3}J_{1\text{-}2}$ = 3.6 Hz), 7.1-8.1 (m, 27H, CH= aromatics). ^{13}C NMR ($CDCl_3$), δ: 25.5 (CH_3), 26.3 (CH_3), 28.4 (b, CH_2, cod), 28.8 (b, CH_2, cod), 29.6 (b, CH_2, cod), 30.9 (b, CH_2, cod), 53.4 (C-3), 67.2 (C-5), 69.7 (b, CH=, cod), 73.2 (b, CH=, cod), 75.7 (C-2), 83.5 (C-4), 100.4 (b, CH=, cod), 103.1 (b, CH=, cod), 104.2 (C-1), 112.9 (CMe_2), 117.6 (b, CH=, BAr_F), 120-134 (aromatic carbons), 134.8 (b, CH=, BAr_F), 161.9 (q, C-B, BAr_F, $^{1}J_{C\text{-}B}$ = 49 Hz). Anal. calc (%) for $C_{66}H_{51}BF_{24}IrO_4PS$: C 48.63, H 3.15, S 1.97; found: C 48.71, H 3.22, S 1.94.

[Ir(cod)(**L18a**)]BAr_F. Yield 61 mg (91 %). ^{31}P NMR ($CDCl_3$), δ: 118.8 (s). ^{1}H NMR ($CDCl_3$), δ: 1.24 (s, 3H, CH_3), 1.33 (s, 18H, CH_3, ^{t}Bu), 1.42 (s, 9H, CH_3, ^{t}Bu), 1.51 (s, 3H, CH_3), 1.58 (s, 9H, CH_3, ^{t}Bu), 1.60 (b, 4H, CH_2, cod), 1.96 (b, 2H, CH_2, cod), 2.19 (b, 2H, CH_2, cod), 2.77(s, 3H, CH_3-S), 3.58 (m, 1H, H-3), 4.08 (m, 1H, CH=, cod), 4.32 (m, 1H, H-4), 4.46 (m, 1H, H-5'), 4.57 (b, 1H, CH=, cod), 4.74 (m, 1H, H-2), 4.79 (m, 1H, H-5), 5.00 (b, 1H, CH=, cod), 5.12 (b, 1H, CH=, cod), 5.82 (d, 1H, H-1, $^{3}J_{1\text{-}2}$ = 3.6 Hz), 7.1-7.8 (m, 16H, CH= aromatics). ^{13}C NMR ($CDCl_3$), δ: 19.6 (CH_3-S), 26.1 (CH_3), 26.2 (CH_3), 28.2 (b, CH_2, cod), 29.9 (b, CH_2, cod), 31.4 (CH_3, ^{t}Bu), 31.5 (CH_3, ^{t}Bu), 31.5 (CH_3, ^{t}Bu), 31.9 (CH_3, ^{t}Bu), 32.0 (b, CH_2, cod), 33.3 (b, CH_2, cod), 34.9 (C, tBu), 35.6 (C, tBu), 35.7 (C, tBu), 35.8 (C, tBu), 53.7 (C-3), 65.3 (C-5), 72.3 (b, CH=, cod), 75.6 (b, CH=, cod), 75.9 (C-4), 80.5 (C-2), 100.6 (d, CH=, cod, $J_{C\text{-}P}$= 8.6 Hz), 103.1 (b, CH=, cod), 104.0 (C-1), 114.2 (CMe_2), 117.6 (b, CH=, BAr_F), 120-131 (aromatic carbons), 135.0 (b, CH=, BAr_F), 138-149 (aromatic carbons), 161.9 (q, C-B, BAr_F, $^{1}J_{C\text{-}B}$ = 49 Hz). Anal. calc (%) for $C_{77}H_{79}BF_{24}IrO_6PS$: C 50.75, H 4.37, S 1.76; found: C 50.79, H 4.39, S 1.75.

[Ir(cod)(**L19a**)]BAr_F. Yield 68 mg (94 %). ^{31}P NMR ($CDCl_3$), δ: 120.7 (s). ^{1}H NMR ($CDCl_3$), δ: 1.05 (s, 3H, CH_3), 1.13 (s, 3H, CH_3), 1.37 (s, 18H, CH_3, ^{t}Bu), 1.51 (s, 9H, CH_3, ^{t}Bu), 1.73 (s, 9H, CH_3, ^{t}Bu), 1.9-2.4 (b, 8H, CH_2, cod), 3.77 (m, 1H, H-3), 4.02 (m, 1H, CH=, cod), 4.41 (m, 1H, H-4), 4.50 (m, 1H, H-5'), 4.58 (m, 1H, H-2), 4.69 (m, 2H, CH=, cod), 4.91 (m, 1H, H-5), 4.97 (b, 1H, CH=, cod), 5.74 (d, 1H, H-1, $^{3}J_{1\text{-}2}$ = 3.6 Hz), 7.1-7.8 (m, 21H, CH= aromatics). ^{13}C NMR ($CDCl_3$), δ: 25.2 (CH_3), 25.6 (CH_3), 28.0 (b, CH_2, cod), 28.3 (b, CH_2, cod), 31.0 (CH_3, ^{t}Bu), 32.0 (CH_3, ^{t}Bu), 32.5 (b, CH_2, cod), 32.8 (b, CH_2, cod), 34.6 (C, tBu), 34.7 (C, tBu), 35.3 (C, tBu), 35.5 (C, tBu), 57.2 (C-3), 55.8 (C-5), 70.0 (b, CH=, cod), 74.9 (b, CH=, cod), 75.3 (C-4), 81.2 (C-2),

103.8 (C-1), 104.7 (d, CH=, cod, $J_{C\text{-}P}$= 14.5 Hz), 105.0 (d, CH=, cod, $J_{C\text{-}P}$= 16 Hz), 113.8 (CMe_2), 117.4 (b, CH=, BAr_F), 120.5-132.7 (aromatic carbons), 134.7 (b, CH=, BAr_F), 135-149 (aromatic carbons), 161.9 (q, C-B, BAr_F, $^1J_{C\text{-}B}$ = 49 Hz). Anal. calc (%) for $C_{82}H_{81}BF_{24}IrO_6PS$: C 52.26, H 4.33, S 1.70; found: C 52.33, H 4.38, S 1.72.

[Ir(cod)(**L20a**)]BAr_F. Yield 61 mg (91 %). ^{31}P NMR ($CDCl_3$), δ: 118.8 (s). ^{1}H NMR ($CDCl_3$), δ: 1.24 (s, 3H, CH_3), 1.33 (s, 18H, CH_3, ^{t}Bu), 1.42 (s, 9H, CH_3, ^{t}Bu), 1.51 (s, 3H, CH_3), 1.58 (s, 9H, CH_3, ^{t}Bu), 1.60 (b, 4H, CH_2, cod), 1.96 (b, 2H, CH_2, cod), 2.19 (b, 2H, CH_2, cod), 2.77(s, 3H, CH_3-S), 3.58 (m, 1H, H-3), 4.08 (m, 1H, CH=, cod), 4.32 (m, 1H, H-4), 4.46 (m, 1H, H-5'), 4.57 (b, 1H, CH=, cod), 4.74 (m, 1H, H-2), 4.79 (m, 1H, H-5), 5.00 (b, 1H, CH=, cod), 5.12 (b, 1H, CH=, cod), 5.82 (d, 1H, H-1, $^3J_{1\text{-}2}$ = 3.6 Hz), 7.1-7.8 (m, 16H, CH= aromatics). ^{13}C NMR ($CDCl_3$), δ: 19.6 (CH_3-S), 26.1 (CH_3), 26.2 (CH_3), 28.2 (b, CH_2, cod), 29.9 (b, CH_2, cod), 31.4 (CH_3, ^{t}Bu), 31.5 (CH_3, ^{t}Bu), 31.5 (CH_3, ^{t}Bu), 31.9 (CH_3, ^{t}Bu), 32.0 (b, CH_2, cod), 33.3 (b, CH_2, cod), 34.9 (C, tBu), 35.6 (C, tBu), 35.7 (C, tBu), 35.8 (C, tBu), 53.7 (C-3), 65.3 (C-5), 72.3 (b, CH=, cod), 75.6 (b, CH=, cod), 75.9 (C-4), 80.5 (C-2), 100.6 (d, CH=, cod, $J_{C\text{-}P}$= 8.6 Hz), 103.1 (b, CH=, cod), 104.0 (C-1), 114.2 (CMe_2), 117.6 (b, CH=, BAr_F), 120-131 (aromatic carbons), 135.0 (b, CH=, BAr_F), 138-149 (aromatic carbons), 161.9 (q, C-B, BAr_F, $^1J_{C\text{-}B}$ = 49 Hz). Anal. calc (%) for $C_{77}H_{79}BF_{24}IrO_6PS$: C 50.75, H 4.37, S 1.76; found: C 50.79, H 4.39, S 1.75.

[Ir(cod)(**L27a**)]BAr_F. Yield 65 mg (98 %). ^{31}P NMR ($CDCl_3$), δ: 99.8 (s). ^{1}H NMR ($CDCl_3$), δ: 1.32 (s, 9H, CH_3, ^{t}Bu), 1.39 (s, 9H, CH_3, ^{t}Bu), 1.48 (s, 9H, CH_3, ^{t}Bu), 1.52 (s, 9H, CH_3, ^{t}Bu), 1.64 (s, 9H, CH_3, ^{t}Bu), 1.6-2.4 (b, 16H, CH_2 and CH_2 cod), 2.71 (m, 1H, CH-S), 4.19 (m, 1H, CH-O), 4.61 (m, 1H, CH=, cod), 4.87 (m, 2H, CH=, cod), 5.76 (m, 1H, CH=, cod), 6.9-7.8 (m, 16H, CH= aromatics). ^{13}C NMR ($CDCl_3$), δ: 23.8 (CH_2), 25.8 (CH_2), 26.8 (CH_2), 30.2 (CH_2), 31.3 (CH_2), 31.5 (CH_3, ^{t}Bu), 31.8 (CH_3, ^{t}Bu), 32.3 (CH_2), 33.6 (CH_2), 34.2 (CH_2), 35.0 (C, ^{t}Bu), 35.7 (C, ^{t}Bu), 47.6 (CH-S), 58.7 (C-S), 77.4 (CH=, cod), 78.0 (CH-O), 78.2 (CH=, cod), 99.2 (d, CH=, cod, $J_{C\text{-}P}$= 21.1 Hz), 100.7 (d, CH=, cod, $J_{C\text{-}P}$= 13.9 Hz), 117.6 (b, CH=, BAr_F), 120-131 (aromatic carbons), 134.9 (b, CH=, BAr_F), 138-150 (aromatic carbons), 161.8 (q, C-B, BAr_F, $^1J_{C\text{-}B}$ = 49 Hz). Anal. calc (%) for $C_{78}H_{83}BF_{24}IrO_3PS$: C 52.32, H 4.67, S 1.79; found: C 52.29, H 4.62, N 1.76.

[Ir(cod)(**L27b**)]BAr_F. Yield 62 mg (96 %). ^{31}P NMR ($CDCl_3$), δ: 102.9 (s). ^{1}H NMR ($CDCl_3$), δ: 1.44 (s, 9H, CH_3, ^{t}Bu), 1.51 (s, 9H, CH_3, ^{t}Bu), 1.59 (s, 9H, CH_3, ^{t}Bu),

1.6-2.4 (b, 16H, CH_2 and CH_2 cod), 2.73 (m, 1H, CH-S), 3.79 (s, 3H, CH_3-O), 3.84 (s, 3H, CH_3-O), 4.26 (m, 1H, CH-O), 4.76 (m, 2H, CH=, cod), 4.91 (m, 1H, CH=, cod), 5.73 (m, 1H, CH=, cod), 6.5-7.8 (m, 16H, CH= aromatics). ^{13}C NMR ($CDCl_3$), δ: 23.8 (CH_2), 25.8 (CH_2), 27.2 (CH_2), 29.9 (CH_2), 30.6 (CH_2), 31.2 (CH_3, ^{t}Bu), 31.8 (CH_3, ^{t}Bu), 33.9 (CH_2), 34.1 (CH_2), 35.1 (C, ^{t}Bu), 35.9 (C, ^{t}Bu), 47.7 (CH-S), 55.8 (CH_3-O), 55.9 (CH_3-O), 58.4 (C-S), 75.8 (CH=, cod), 78.1 (CH-O), 79.4 (CH=, cod), 99.6 (d, CH=, cod, $J_{C\text{-}P}$= 19.6 Hz), 110.9 (d, CH=, cod, $J_{C\text{-}P}$= 13.6 Hz), 112-116 (aromatic carbons), 117.7 (b, CH=, BAr_F), 120-131 (aromatic carbons), 134.9 (b, CH=, BAr_F), 138-158 (aromatic carbons), 161.8 (q, C-B, BAr_F, $^1J_{C\text{-}B}$ = 49 Hz). Anal. calc (%) for $C_{72}H_{71}BF_{24}IrO_5PS$: C 49.75, H 4.12, S 1.84; found: C 49.69, H 4.08, N 1.82.

[Ir(cod)(**L27c**)]BAr_F. Yield 60 mg (95 %). ^{31}P NMR ($CDCl_3$), δ: 99.0 (s). ^{1}H NMR ($CDCl_3$), δ: 0.44 (s, 18H, CH_3-Si), 1.56 (s, 9H, CH_3, ^{t}Bu), 1.6-2.4 (b, 16H, CH_2 and CH_2 cod), 2.65 (m, 1H, CH-S), 4.16 (m, 1H, CH-O), 4.69 (m, 1H, CH=, cod), 4.93 (m, 2H, CH=, cod), 5.89 (m, 1H, CH=, cod), 7.2-7.8 (m, 18H, CH= aromatics). ^{13}C NMR ($CDCl_3$), δ: 0.7 (CH_3-Si), 0.9 (CH_3-Si), 24.1 (CH_2), 25.9 (CH_2), 26.7 (CH_2), 29.9 (CH_2), 30.3 (CH_2), 31.7 (CH_3, ^{t}Bu), 32.3 (CH_2), 33.4 (CH_2), 34.6 (CH_2), 34.9 (C, ^{t}Bu), 47.6 (CH-S), 58.8 (C-S), 77.4 (CH= cod), 77.9 (CH-O), 78.5 (CH= cod), 100.1 (d, CH=, cod, $J_{C\text{-}P}$= 21.9 Hz), 111.5 (d, CH=, cod, $J_{C\text{-}P}$= 14.0 Hz), 117.7 (b, CH=, BAr_F), 120-133 (aromatic carbons), 134.9 (b, CH=, BAr_F), 136-154 (aromatic carbons), 161.8 (q, C-B, BAr_F, $^1J_{C\text{-}B}$ = 49 Hz). Anal. calc (%) for $C_{68}H_{67}BF_{24}IrO_3PSSi_2$: C 47.75, H 3.95, S 1.87; found: C 47.73, H 3.96, N 1.85.

3.3.4.5. Preparation of cis-dihydridoiridium(III) complexes

Hydrogen was bubbled through a solution of [Ir(cod)(P-S)]BAr_F (91.1 mg, 0.05 mmol) in CD_2Cl_2 (0.5 mL) at 0 °C in an NMR spectrometer tube. After 15 min, the solution was analyzed by NMR (^{1}H NMR and ^{31}P NMR were recorded to the desired temperature).

[IrH_2(cod)(**L7a**)]BAr_F. ^{31}P NMR (CD_2Cl_2), δ: 104.4 (s). ^{1}H NMR (CD_2Cl_2), δ: -14.07 (d, 1H, $^3J_{H\text{-}P}$= 9.8 Hz), -13.41 (d, 1H, $^3J_{H\text{-}P}$= 19.2 Hz), 1.28 (s, 3H, CH_3), 1.34 (s, 9H, CH_3, ^{t}Bu), 1.42 (s, 9H, CH_3, ^{t}Bu), 1.43 (s, 9H, CH_3, ^{t}Bu), 1.50 (s, 3H, CH_3), 1.55 (s, 9H, CH_3, ^{t}Bu), 1.84 (b, 1H, CH_2, cod), 2.14 (b, 3H, CH_2, cod), 2.37 (b, 2H, CH_2, cod), 2.54 (b, 1H, CH_2, cod), 2.71 (b, 1H, CH_2, cod), 2.82 (s, 3H, CH_3-S), 3.14 (m, 1H, H-5'), 3.88 (m, 1H, H-5), 4.35 (m, 2H, CH=, cod), 4.56 (m, 1H, CH=, cod), 4.64 (m, 1H, H-4),

4.75 (d, 1H, H-2, $^{3}J_{2\text{-}1}$= 3.6 Hz), 5.24 (bd, 1H, H-3, $^{3}J_{H\text{-}P}$= 13.6 Hz), 5.38 (m, 1H, CH=, cod), 5.85 (d, 1H, H-1, $^{3}J_{1\text{-}2}$= 3.6 Hz), 7.0-8.0 (m, 16H, CH= aromatics). ^{13}C NMR (CD_2Cl_2), δ: 24.5 (CH_3-S), 25.6 (CH_3), 26.1 (CH_3), 27.1 (b, CH_2, cod), 28.0 (b, CH_2, cod), 28.7 (b, CH_2, cod), 30.2 (CH_3, ^{t}Bu), 30.8 (CH_3, ^{t}Bu), 30.9 (CH_3, ^{t}Bu), 31.8 (CH_3, ^{t}Bu), 33.9 (b, CH_2, cod), 34.5 (C, tBu), 34.6 (C, tBu), 35.1 (C, tBu), 36.5 (C-5), 75.0 (b, CH=, cod), 78.9 (C-3), 82.8 (C-4), 87.2 (d, C-2, $J_{C\text{-}P}$= 6.2 Hz), 89.1 (b, CH=, cod), 95.4 (b, CH=, cod), 104.1 (C-1), 112.9 (CMe_2), 117.5 (b, CH=, BAr_F), 120-131 (aromatic carbons), 134.6 (b, CH=, BAr_F), 139-150 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^{1}J_{C\text{-}B}$ = 49 Hz). T_1 min (-13.41 ppm)= 481 ± 7 ms. T_1 min (-14.07 ppm)= 482 ± 10 ms

[IrH_2(cod)(**L14a**)]BAr_F. ^{31}P NMR (CD_2Cl_2), δ: 103.4 (s). ^{1}H NMR (CD_2Cl_2), δ: -14.10 (s, 1H), -12.76 (d, 1H, $^{3}J_{H\text{-}P}$= 19.6 Hz), 1.26 (s, 3H, CH_3), 1.32 (s, 9H, CH_3, ^{t}Bu), 1.39 (s, 3H, CH_3), 1.41 (s, 9H, CH_3, ^{t}Bu), 1.46 (s, 9H, CH_3, ^{t}Bu), 1.53 (s, 9H, CH_3, ^{t}Bu), 1.81 (b, 1H, CH_2, cod), 2.06 (b, 3H, CH_2, cod), 2.21 (b, 21H, CH_2, cod), 2.51 (b, 1H, CH_2, cod), 2.63 (b, 2H, CH_2, cod), 2.66 (dd, 1H, H-5', $^{2}J_{5'\text{-}5}$= 14.0 Hz, $^{3}J_{5'\text{-}4}$= 6.2 Hz) 2.91 (s, 3H, CH_3-S), 4.19 (m, 2H, H-5 and CH= cod), 4.39 (m, 1H, CH=, cod), 4.54 (m, 1H, H-4), 4.71 (m, 1H, CH= cod), 4.78 (m, 1H, H-2), 4.84 (m, 1H, H-3), 5.46 (m, 1H, CH=, cod), 5.84 (d, 1H, H-1, $^{3}J_{1\text{-}2}$= 3.6 Hz), 7.0-7.9 (m, 16H, CH= aromatics). ^{13}C NMR (CD_2Cl_2), δ: 19.3 (CH_3-S), 25.9 (CH_3), 26.6 (CH_3), 27.3 (b, CH_2, cod), 29.6 (b, CH_2, cod), 29.9 (b, CH_2, cod), 30.4 (CH_3, ^{t}Bu), 30.9 (CH_3, ^{t}Bu), 31.0 (CH_3, ^{t}Bu), 33.0 (CH_3, ^{t}Bu), 34.6 (C, tBu), 34.7 (C, tBu), 35.1 (C, tBu), 40.9 (C-5), 77.2 (b, CH=, cod), 74.3 (b, CH=, cod), 77.5 (C-3), 78.0 (C-4), 86.9 (C-2), 93.4 (b, CH=, cod), 97.2 (d, CH=, cod, $J_{C\text{-}P}$= 9.2 Hz), 104.0 (C-1), 114.1 (CMe_2), 117.4 (b, CH=, BAr_F), 120-130 (aromatic carbons), 134.7 (b, CH=, BAr_F), 138-151 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^{1}J_{C\text{-}B}$ = 49 Hz). T_1 min (-12.76 ppm)= 460 ± 14 ms. T_1 min (-14.10 ppm)= 465 ± 18 ms.

[IrH_2(cod)(**L18a**)]BAr_F. ^{31}P NMR (CD_2Cl_2), δ: 107.4 (s). ^{1}H NMR (CD_2Cl_2), δ: -14.32 (d, 1H, $^{3}J_{H\text{-}P}$= 9.2 Hz), -13.27 (d, 1H, $^{3}J_{H\text{-}P}$= 18.8 Hz), 1.33 (s, 9H, CH_3, ^{t}Bu), 1.36 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 1.41 (s, 9H, CH_3, ^{t}Bu), 1.43 (s, 9H, CH_3, ^{t}Bu), 1.49 (s, 9H, CH_3, ^{t}Bu), 1.96 (b, 1H, CH_2, cod), 2.09 (b, 5H, CH_2, cod), 2.43 (b, 1H, CH_2, cod), 2.64 (b, 1H, CH_2, cod), 2.79 (s, 3H, CH_3-S), 3.62 (m, 1H, H-3), 4.30 (m, 1H, CH=, cod), 4.37 (m, 1H, CH=, cod), 4.54 (m, 1H, CH=, cod), 4.63 (m, 1H, H-4), 4.91 (m, 2H, H-5' and H-5), 5.05 (d, 1H, H-2, $^{3}J_{2\text{-}1}$= 3.2 Hz), 5.41 (m, 1H, CH= cod), 6.02 (d, 1H, H-1, $^{3}J_{1\text{-}2}$= 3.2 Hz), 7.1-7.8 (m, 16H, CH= aromatics). ^{13}C NMR (CD_2Cl_2), δ:

19.9 (CH_3-S), 26.3 (CH_3), 26.5 (CH_3), 28.1 (b, CH_2, cod), 28.6 (b, CH_2, cod), 30.3 (b, CH_2, cod), 31.5 (CH_3, ^{t}Bu), 31.6 (CH_3, ^{t}Bu), 31.7 (CH_3, ^{t}Bu), 32.2 (b, CH_2, cod), 33.5 (CH_3, ^{t}Bu), 35.2 (C, tBu), 35.3 (C, tBu), 35.7 (C, tBu), 60.1 (C-3), 65.2 (C-5), 76.5 (b, CH=, cod), 76.9 (b, CH=, cod), 77.3 (C-4), 87.0 (C-2), 96.6 (d, CH=, cod, $J_{C\text{-}P}$= 6.2 Hz), 97.3 (b, CH=, cod), 104.0 (C-1), 113.5 (CMe_2), 117.6 (b, CH=, BAr_F), 121-131 (aromatic carbons), 134.7 (b, CH=, BAr_F), 139-150 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^1J_{C\text{-}B}$ = 49 Hz). T_1 min (-13.27 ppm)= 361 ± 25 ms. T_1 min (-14.32 ppm)= 395 ± 10 ms.

[IrH_2(cod)(**L20a**)]BAr_F. ^{31}P NMR (CD_2Cl_2), δ: 100.9 (s). ^{1}H NMR (CD_2Cl_2), δ: -14.40 (d, 1H, $^3J_{H\text{-}P}$= 6.4 Hz), -12.95 (d, 1H, $^3J_{H\text{-}P}$= 21.6 Hz), 1.25 (s, 3H, CH_3), 1.32 (s, 9H, CH_3, ^{t}Bu), 1.37 (s, 9H, CH_3, ^{t}Bu), 1.39 (s, 9H, CH_3, ^{t}Bu), 1.43 (s, 3H, CH_3), 1.52 (s, 9H, CH_3, ^{t}Bu), 1.81 (b, 1H, CH_2, cod), 2.09 (b, 4H, CH_2, cod), 2.38 (b, 1H, CH_2, cod), 2.57 (b, 1H, CH_2, cod), 2.75 (b, 1H, CH_2, cod), 2.85 (s, 3H, CH_3-S), 3.19 (m, 1H, H-3), 4.35 (m, 1H, CH=, cod), 4.53 (m, 3H, H-4, 2 x CH= cod), 4.75 (m, 1H, H-5'), 5.02 (m, 1H, H-2), 5.31 (m, 1H, H-5), 5.42 (m, 1H, CH=, cod), 5.84 (d, 1H, H-1, $^3J_{1\text{-}2}$= 3.6 Hz), 7.1-7.8 (m, 16H, CH= aromatics). ^{13}C NMR (CD_2Cl_2), δ: 20.2 (CH_3-S), 26.1 (CH_3), 26.4 (CH_3), 28.1 (b, CH_2, cod), 30.2 (b, CH_2, cod), 30.8 (CH_3, ^{t}Bu), 31.0 (b, CH_2, cod), 31.3 (CH_3, ^{t}Bu), 31.5 (CH_3, ^{t}Bu), 31.7 (b, CH_2, cod), 32.8 (CH_3, ^{t}Bu), 35.2 (C, tBu), 35.4 (C, tBu), 35.7 (C, tBu), 52.4 (C-3), 67.4 (C-5), 72.2 (b, CH=, cod), 78.0 (b, CH=, cod), 78.3 (C-4), 84.5 (C-2), 94.6 (b, CH=, cod), 97.5 (b, CH=, cod), 104.3 (C-1), 114.1 (CMe_2), 117.6 (b, CH=, BAr_F), 121-130 (aromatic carbons), 134.7 (b, CH=, BAr_F), 139-150 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^1J_{C\text{-}B}$ = 49 Hz). T_1 min (-12.95 ppm)= 345 ± 12 ms. T_1 min (-14.40 ppm)= 382 ± 26 ms.

3.3.4.6. Typical procedure for the hydrogenation of olefins

The alkene (1 mmol) and Ir complex (2 mol%) were dissolved in CH_2Cl_2 (2 mL) 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 depressurised 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 ^{1}H NMR or GC and enantiomeric excess was determined by chiral GC or chiral HPLC as previously described.[5h]

3.3.4.7. Synthesis of ligand precursors

1,2-O-Isopropylidene-5-O-trifluoromethanesulfonyl-α-D-ribofuranose

Diol **2** (1 g, 5.2 mmol) was azeotropically dried with toluene (3 x 2 mL) and then dissolved in CH_2Cl_2 (24.5 mL) to which pyridine (0.57 mL, 7.6 mmol) was added. The alcohol solution was cooled to -15 ºC and Tf_2O (0.9 mL, 5.3 mmol) was added slowly over 2 min aprox. The reaction mixture was stirred at -15 ºC for 2 h. Evaporation of the solvent gave a yellow foam, which was purified by flash chromatography (AcOEt/hexane= 1/2) to produce the corresponding triflate as a white solid. Yield: 1.1 g, 65 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.38 (s, 3H, CH_3), 1.57 (s, 3H, CH_3), 3.97 (m, 2H, H-3 and H-4), 4.60 (m, 2H, H-5' and H2), 4.82 (dd, 1H, H-5, $^2J_{5\text{-}5'}$= 11.2 Hz, $^3J_{5\text{-}4}$= 1.8 Hz), 5.84 (d, 1H, H-1, $^3J_{1\text{-}2}$= 3.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 26.7 (CH_3), 71.2 (C-3), 73.8 (C-5), 78.0 (C-4), 78.1 (C-2), 104.2 (C-1), 113.4 (CMe_2).

1,2-O-Isopropylidene-5-phenylsulfanyl-α-D-ribofuranose ***12***

To a suspension of NaH (0.5 g, 20.8 mmol) in THF (7 mL) a solution of PhSH (0.5 mL, 4.8 mmol) in THF (5 mL) was added. After 2 min, the suspension was cooled to -78 °C and a solution of 1,2-*O*-isopropylidene-5-*O*-trifluoromethanesulfonyl-α-D-ribofuranose (0.85 g, 2.6 mmol) in THF (8.5 mmol) was added. After 90 min, water (25 mL) was added and the THF was evaporated. The crude product was extracted in CH_2Cl_2 (3 x 25 mL), dried with $MgSO_4$ and dried in the rotavapor. The crude was purified by flash chromatography (AcOEt/hexane= 1/3) to produce **12** as a white solid. Yield: 0.5 g, 67 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.36 (s, 3H, CH_3), 1.53 (s, 3H, CH_3), 3.15 (dd, 1H, H-5', $^2J_{5'\text{-}5}$= 14.0 Hz, $^3J_{5'\text{-}4}$= 6 Hz), 3.37 (dd, 1H, H-5, $^2J_{5\text{-}5'}$= 14.0 Hz, $^3J_{5\text{-}4}$= 4.0 Hz), 3.88 (m, 1H, H-3), 3.97 (m, 1H, H-4), 4.88 (dd, 1H, H-2, $^3J_{2\text{-}1}$= 4.0 Hz, $^3J_{2\text{-}3}$= 5.2 Hz), 5.82 (d, 1H, H-1, $^3J_{1\text{-}2}$= 4.0 Hz), 7.14 (m, 1H, CH=), 7.23 (m, 2H, CH=), 7.43 (m, 2H, CH=). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 26.6 (CH_3), 26.7 (CH_3), 35.7 (C-5), 74.7 (C-3), 78.7 (C-2), 78.9 (C-4), 104.0 (C-1), 112.9 (CMe_2) 128.7 (CH=), 128.9 (CH=), 135.8 (C).

1,2-O-Isopropylidene-5-methylsulfanyl-α-D-ribofuranose ***13***

Treatment of sodium methanethiolate (374 mg, 4.8 mmol) with 1,2-*O*-isopropylidene-5-*O*-trifluoromethanesulfonyl-α-D-ribofuranose (0.85 g, 2.6 mmol) as described for **12** produces **13** as a white solid. Yield: 410 mg, 66 %. ^{1}H NMR (400

MHz, $CDCl_3$) δ: 1.36 (s, 3H, CH_3), 1.57 (s, 3H, CH_3), 2.16 (b, 1H, OH), 2.19 (s, 3H, CH_3-S), 2.74 (dd, 1H, H-5', $^2J_{5'-5}$= 14.0 Hz, $^3J_{5'-4}$= 6.4 Hz), 2.89 (dd, 1H, H-5, $^2J_{5-5'}$= 14.0 Hz, $^3J_{5-4}$= 4.0 Hz), 3.86 (m, 1H, H-3), 3.96 (m, 1H, H-4), 4.57 (m, 1H, H-2), 5.81 (d, 1H, H-1, $^3J_{1-2}$= 4.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 17.7 (CH_3-S), 26.6 (CH_3), 26.7 (CH_3), 35.6 (C-5), 74.7 (C-3), 78.6 (C-2), 80.1 (C-4), 103.9 (C-1), 112.8 (CMe_2).

*1,2-O-Isopropylidene-5-tert-butylsulfanyl-α-D-ribofuranose **14***

Treatment of 2-methyl-2-propanethiol (0.54 mL, 4.8 mmol) with 1,2-*O*-isopropylidene-5-*O*-trifluoromethanesulfonyl-α-D-ribofuranose (0.85 g, 2.6 mmol) as described for **12** produces **14** as a white solid. Yield: 600 mg, 88 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.34 (s, 3H, CH_3, ^{t}Bu), 1.36 (s, 3H, CH_3), 1.56 (s, 3H, CH_3), 2.51 (b, 1H, OH), 2.80 (dd, 1H, H-5', $^2J_{5'-5}$= 13.2 Hz, $^3J_{5'-4}$= 5.8 Hz), 2.94 (dd, 1H, H-5, $^2J_{5-5'}$= 13.2 Hz, $^3J_{5-4}$= 4.8 Hz), 3.84 (m, 1H, H-3), 3.94 (m, 1H, H-4), 4.57 (dd, 1H, H-2, $^3J_{2-1}$= 4.0 Hz, $^3J_{2-3}$= 5.0 Hz), 5.80 (d, 1H, H-1, $^3J_{1-2}$= 4.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 26.4 (CH_3), 26.5 (CH_3), 31.0 (CH_3, ^{t}Bu), 29.8 (C, ^{t}Bu), 44.9 (C-5), 74.9 (C-3), 78.6 (C-2), 79.2 (C-4), 103.8 (C-1), 112.6 (CMe_2).

*1,2-O-Isopropylidene-5-(2,6-dimethyl-phenyl)sulfanyl-α-D-ribofuranose **15***

Treatment of 2,6-dimethylbenzenethiol (0.64 mL, 4.8 mmol) with 1,2-*O*-isopropylidene-5-*O*-trifluoromethanesulfonyl-α-D-ribofuranose (0.85 g, 2.6 mmol) as described for **12** produces **15** as a white solid. Yield: 565 mg, 70 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.35 (s, 3H, CH_3), 1.49 (s, 3H, CH_3), 2.30 (b, 1H, OH), 2.57 (s, 6H, CH_3-Ar), 2.76 (dd, 1H, H-5', $^2J_{5'-5}$= 13.4 Hz, $^3J_{5'-4}$= 7.0 Hz), 3.11 (dd, 1H, H-5, $^2J_{5-5'}$= 13.4 Hz, $^3J_{5-4}$= 2.8 Hz), 3.80 (m, 2H, H-3 and H-4), 4.56 (m, 1H, H-2), 5.82 (d, 1H, H-1, $^3J_{1-2}$= 3.6 Hz), 7.!2 (m, 3H, CH=). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 22.2 (CH_3-Ar), 26.5 (CH_3), 26.8 (CH_3), 36.6 (C-5), 74.8 (C-3), 78.7 (C-2), 78.9 (C-4), 103.9 (C-1), 112.8 (CMe_2), 128.3 (CH=), 128.6 (CH=), 130.0 (C), 143.5 (C).

1,2-O-Isopropylidene-5-O-benzoyl-3-O-trifluoromethanesulfonyl-α-D-ribofuranose

Treatment of alcohol **3** (1.53 g, 5.2 mmol) with Tf_2O (0.9 mL, 5.3 mmol) as previously described for **2** afforded the desired crude product. After 2 hours, water (10 mL) was added and the reaction mixture was extracted with dichloromethane (3 x 50 mL), dried with $MgSO_4$ and all the volatiles were removed in the rotavapor. To the crude product petroleum ether (25 mL) was added and the insoluble impurities were removed by filtration. Evaporation of the solvent provided 1,2-*O*-isopropylidene-5-*O*-

benzoyl-3-*O*-trifluoromethanesulfonyl-α-D-ribofuranose as a white solid. Yield: 1.75 g, 79 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.39 (s, 3H, CH_3), 1.62 (s, 3H, CH_3), 4.44 (dd, 1H, H-5', $^{2}J_{5'-5}$= 12.4 Hz, $^{3}J_{5'-4}$= 4.0 Hz), 4.53 (m, 1H), 4.77 (dd, 1H, H-5, $^{2}J_{5-5'}$= 12.4 Hz, $^{3}J_{5-4}$= 2.8 Hz), 4.82 (m, 1H), 4.94 (m, 1H), 5.88 (d, 1H, H-1, $^{3}J_{1-2}$= 3.2 Hz), 7.48 (m, 2H, CH=), 7.60 (m, 1H, CH=), 8.02 (m, 2H, CH=).

1,2-O-Isopropylidene-5-O-benzoyl-3-phenylsulfanyl-α-D-xylofuranose ***16***

Treatment of benzenethiol (0.50 mL, 4.8 mmol) with 1,2-*O*-isopropylidene-5-*O*-benzoyl-3-*O*-trifluoromethanesulfonyl-α-D-ribofuranose (1.1 g, 2.6 mmol) as described for **12** produces **16** as a white solid together with small amount of **17** (8% yield). Yield: 472 mg, 47 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.31 (s, 3H, CH_3), 1.53 (s, 3H, CH_3), 3.85 (d, 1H, H-3, $^{3}J_{3-4}$= 4.0 Hz), 4.59 (dd, 1H, H-5', $^{2}J_{5'-5}$= 11.6 Hz, $^{3}J_{5'-4}$= 3.2 Hz), 4.73 (m, 2H, H-5, H-2), 4.81 (m, 1H, H-4), 5.79 (d, 1H, H-1, $^{3}J_{1-2}$= 3.2 Hz), 7.2-8.1 (m, 10 H, CH=).

1,2-O-Isopropylidene-3-phenylsulfanyl-α-D-xylofuranose ***17***

To a solution of **16** (386.5 mg, 1 mmol) in methanol (4 mL) ammonia 30% (4 mL) was added. The reaction was stirred overnight at room temperature. Then, the volatiles were removed and the crude was purified by flash chromatography (AcOEt/hexane= 1/3) to produce **17** as a white solid. Yield: 133 mg, 47%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.29 (s, 3H, CH_3), 1.53 (s, 3H, CH_3), 2.01 (b, 1H, OH), 3.82 (d, 1H, H-3, $^{3}J_{3-4}$= 4.0 Hz), 3.88 (dd, 1H, H-5', $^{2}J_{5'-5}$= 12.0 Hz, $^{3}J_{5'-4}$= 4.8 Hz), 3.98 (dd, 1H, H-5, $^{2}J_{5-5'}$= 12.0 Hz, $^{3}J_{5-4}$= 6.8 Hz), 4.64 (m, 2H, H-4 and H-2), 5.96 (d, 1H, H-1, $^{3}J_{1-2}$= 3.6 Hz), 7.28 (m, 1H, CH=), 7.35 (m, 2H, CH=), 7.43 (m, 2 H, CH=). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 26.6 (CH_3), 26.8 (CH_3), 53.2 (C-3), 62.4 (C-5), 79.5 (C-2), 85.8 (C-4), 105.1 (C-1), 112.2 (CMe_2), 127.3 (CH=), 129.6 (CH=), 130.5 (CH=), 133.8 (C).

1,2-O-Isopropylidene-5-O-benzoyl-3-methylsulfanyl-α-D-xylofuranose ***18***

Treatment of sodium methanethiolate (374 mg, 4.8 mmol) with 1,2-*O*-isopropylidene-5-*O*-benzoyl-3-*O*-trifluoromethanesulfonyl-α-D-ribofuranose (1.1 g, 2.6 mmol) as described for **12** produces **18** as a white solid. Yield: 557 mg, 66 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.34 (s, 3H, CH_3), 1.53 (s, 3H, CH_3), 2.19 (s, 3H, CH_3-S), 3.26 (d, 1H, H-3, $^{3}J_{3-4}$= 3.6 Hz), 4.48 (dd, 1H, H-5', $^{2}J_{5'-5}$= 11.6 Hz, $^{3}J_{5'-4}$= 7.6 Hz), 4.69 (m, 2H, H-5 and H-4), 4.74 (d, 1H, H-2, $^{3}J_{1-2}$= 3.6 Hz), 5.95 (d, 1H, H-1, $^{3}J_{1-2}$= 3.6 Hz), 7.45 (m, 2H, CH=), 7.56 (m, 1H, CH=), 8.05 (m, 2 H, CH=). ^{13}C NMR (100 MHz,

$CDCl_3$) δ: 15.3 (CH_3-S), 26.4 (CH_3), 26.8 (CH_3), 53.3 (C-3), 64.2 (C-5), 77.3 (C-2), 85.6 (C-4), 105.3 (C-1), 112.0 (CMe_2), 128.5 (CH=), 129.6 (CH=), 129.9 (CH=), 133.3 (C), 166.3 (CO).

*1,2-O-Isopropylidene-3-methylsulfanyl-α-D-xylofuranose **19***

Treatment of **18** (162 mg, 0.5 mmol), as previously described for **17,** afforded the desired product as a white solid. Yield: 101 mg, 92 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.33 (s, 3H, CH_3), 1.52 (s, 3H, CH_3), 2.14 (b, 1H, OH), 2.17 (s, 3H, CH_3-S), 3.21 (d, 1H, H-3, $^3J_{3\text{-}4}$= 3.6 Hz), 3.79 (dd, 1H, H-5', $^2J_{5'\text{-}5}$= 12.0 Hz, $^3J_{5'\text{-}4}$= 5.2 Hz), 3.88 (dd, 1H, H-5, $^2J_{5\text{-}5'}$= 12.0 Hz, $^3J_{5\text{-}4}$= 2.4 Hz), 4.52 (m, 1H, H-4), 4.69 (d, 1H, H-2, $^3J_{1\text{-}2}$= 3.6 Hz), 5.93 (d, 1H, H-1, $^3J_{1\text{-}2}$= 3.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 15.1 (CH_3-S), 26.5 (CH_3), 26.8 (CH_3), 53.0 (C-3), 62.5 (C-5), 79.7 (C-2), 85.7 (C-4), 105.1 (C-1), 112.0 (CMe_2).

1,2-O-Isopropylidene-5-O-benzoyl-3-O-trifluoromethanesulfonyl-α-D-xylofuranose

Treatment of alcohol **4** (1.53 g, 5.2 mmol) with Tf_2O (0.9 mL, 5.3 mmol) as previously described for 1,2-*O*-isopropylidene-5-*O*-benzoyl-3-*O*-trifluoromethanesulfonyl-α-D-ribofuranose afforded the desired product as a white solid. Yield: 1.53 g, 69 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.36 (s, 3H, CH_3), 1.54 (s, 3H, CH_3), 4.48 (m, 1H), 4.68 (m, 2H), 4.80 (d, 1H, H-2, $^3J_{2\text{-}1}$= 3.6 Hz), 5.34 (d, 1H, ^3J= 2 Hz), 6.07 (d, 1H, H-1, $^3J_{1\text{-}2}$= 3.6 Hz), 7.4 – 8.2 (m, 5H, CH=).

*1,2-O-Isopropylidene-5-O-benzoyl-3-phenylsulfanyl-α-D-ribofuranose **20***

Treatment of benzenethiol (0.50 mL, 4.8 mmol) with 1,2-*O*-isopropylidene-5-*O*-benzoyl-3-*O*-trifluoromethanesulfonyl-α-D-xylofuranose (1.1 g, 2.6 mmol) as described for **12** were stirred overnight at room temperature. After the same work up as **12**, compound **20** was obtained as a white solid together with small amount of **21** (6% yield). Yield: 100 mg, 10 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.38 (s, 3H, CH_3), 1.59(s, 3H, CH_3), 3.41 (dd, 1H, H-3, $^3J_{3\text{-}4}$= 6.4 Hz, $^3J_{3\text{-}2}$= 3.2 Hz), 4.26 (dd, 1H, H-5', $^2J_{5'\text{-}5}$= 12.0 Hz, $^3J_{5'\text{-}4}$= 3.6 Hz), 4.35 (m, 1H, H-4), 4.81 (dd, 1H, H-5, $^2J_{5\text{-}5'}$= 12.0 Hz, $^3J_{5\text{-}4}$= 2.0 Hz), 4.87 (m, 1H, H-2), 5.85 (d, 1H, H-1, $^3J_{1\text{-}2}$= 4.0 Hz), 7.2-8.1 (m, 10 H, CH=).

*1,2-O-Isopropylidene-3-phenylsulfanyl-α-D-ribofuranose **21***

Treatment of **20** (193 mg, 0.5 mmol), as previously described for **17,** afforded the desired product as a white solid. Yield: 89 mg, 63 %. ^{1}H NMR (400 MHz, $CDCl_3$)

δ: 1.36 (s, 3H, CH_3), 1.55 (s, 3H, CH_3), 1.88 (b, 1H, OH), 3.52 (dd, 1H, H-3, $^3J_{3\text{-}4}$= 10.2 Hz, $^3J_{3\text{-}4}$= 4.6 Hz), 3.62 (dd, 1H, H-5', $^2J_{5'\text{-}5}$= 12.6 Hz, $^3J_{5'\text{-}4}$= 2.6 Hz), 3.93 (dd, 1H, H-5, $^2J_{5\text{-}5'}$= 12.6 Hz, $^3J_{5\text{-}4}$= 2.4 Hz), 4.09 (m, 1H, H-4), 4.79 (m, 1H, H-2), 5.80 (d, 1H, H-1, $^3J_{1\text{-}2}$= 3.6 Hz), 7.28 (m, 3H, CH=), 7.48 (m, 2H, CH=). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 26.5 (CH_3), 26.8 (CH_3), 49.6 (C-3), 60.0 (C-5), 81.8 (C-2), 82.1 (C-4), 104.4 (C-1), 112.6 (CMe_2), 127.3 (CH=), 129.3 (CH=), 131.1 (CH=), 134.8 (C).

*1,2-O-Isopropylidene-5-O-benzoyl-3-methylsulfanyl-α-D-ribofuranose **22***

Treatment of sodium methanethiolate (374 mg, 4.8 mmol) with 1,2-*O*-isopropylidene-5-*O*-benzoyl-3-*O*-trifluoromethanesulfonyl-α-D-xylofuranose (1.1 g, 2.6 mmol) as described for **12** were stirred overnight at room temperature. After the same work up as **12**, compound **22** was obtained as a white solid together with small amount of **23** (7% yield). Yield: 34 mg, 4 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.34 (s, 3H, CH_3), 1.54 (s, 3H, CH_3), 2.19 (s, 3H, CH_3-S), 2.85 (dd, 1H, H-3, $^3J_{3\text{-}4}$= 10.4 Hz, $^3J_{3\text{-}2}$= 3.6 Hz), 4.26 (m, 1H, H-4), 4.44 (dd, 1H, H-5', $^2J_{5'\text{-}5}$= 12.4 Hz, $^3J_{5'\text{-}4}$= 4.8 Hz), 4.75 (dd, 1H, H-5, $^2J_{5\text{-}5'}$= 12.4 Hz, $^3J_{5\text{-}4}$= 2.4 Hz), 4.77 (m, 1H, H-2), 5.82 (d, 1H, H-1, $^3J_{1\text{-}2}$= 3.6 Hz), 7.41 (m, 2H, CH=), 7.54 (m, 1 H, CH=), 8.03 (m, 2H, CH=). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 15.8 (CH_3-S), 26.4 (CH_3), 26.7 (CH_3), 49.9 (C-3), 63.3 (C-5), 79.1 (C-4), 81.4 (C-2), 104.4 (C-1), 112.5 (CMe_2), 128.5 (CH=), 129.8 (CH=), 133.3 (C), 166.3 (CO).

*1,2-O-Isopropylidene-3-phenylsulfanyl-α-D-ribofuranose **23***

Treatment of **22** (65 mg, 0.2 mmol), as previously described for **17,** afforded the desired product as a white solid. Yield: 36 mg, 81 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.34 (s, 3H, CH_3), 1.52 (s, 3H, CH_3), 2.02 (b, 1H, OH), 2.21 (s, 3H, CH_3-S), 2.97 (dd, 1H, H-3, $^3J_{3\text{-}4}$= 10.0 Hz, $^3J_{3\text{-}4}$= 4.4 Hz), 3.73 (dd, 1H, H-5', $^2J_{5'\text{-}5}$= 13.6 Hz, $^3J_{5'\text{-}4}$= 3.6 Hz), 4.00 (m, 2H, H-5 and H-4), 4.74 (m, 1H, H-2), 5.79 (d, 1H, H-1, $^3J_{1\text{-}2}$= 3.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 15.7 (CH_3-S), 26.4 (CH_3), 26.7 (CH_3), 48.2 (C-3), 60.5 (C-5), 81.5 (C-4), 81.8 (C-2), 104.4 (C-1), 112.5 (CMe_2).

3.3.5. Acknowledgements

We would like to thank the Spanish Government for providing grants Consolider Ingenio Intecat-CSD2006-0003, 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.

3.3.6. References

[1] a) *Asymmetric Catalysis in Industrial Scale: Challenges, Approaches and Solutions*; eds. Blaser, H. U.; Schmidt, E.; Wiley:Weinheim, Germany, **2003**; b) Ojima, I. *Catalytic Asymmetric Synthesis*; Wiley-VCH: New York, **2000**; c) Brown, J. M. in *Comprehensive Asymmetric Catalysis*; eds. Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H.; Springer-Verlag: Berlin, **1999**; Vol. I, pp 121-182; d) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, **1994**.

[2] For recent reviews, see: a) Källström, K.; Munslow, I.; Andersson, P. G. *Chem. Eur. J.* **2006**, *12*, 3194; b) Roseblade, S. J.; Pfaltz, A. *Acc. Chem. Res.* **2007**, *40*, 1402; c) Church, T. L.; Andersson, P. G. *Coord. Chem. Rev.* **2008**, *252*, 513; d) Cui, X.; Burgess, K. *Chem. Rev.* **2005**, *105*, 3272; e) Pàmies, O.; Andersson, P. G.; Diéguez, M. *Chem. Eur. J.* **2010**, *16*, 14232; f) Woodmansee, D. H.; Pfaltz, A. *Chem. Commun.* **2011**, *47*, 7912.

[3] a) Lighfoot, A.; Schnider, P.; Pfaltz, A. *Angew. Chem. Int. Ed.* **1998**, *37*, 3897; b) Hou, D.-R.; Reibenspies, J. H.; Colacot, T. J.; Burgess, K. *Chem. Eur. J.* **2001**, *7*, 5391; c) Tang, W.; Wang, W.; Zhang, X. *Angew. Chem. Int. Ed.* **2003**, *42*, 943; d) Cozzi, P. G.; Menges, F.; Kaiser, S. *Synlett* **2003**, 833; e) Liu, D.; Tang, W.; Zhang, X. *Org. Lett.* **2004**, *6*, 513.

[4] Crabtree, R. H. *Acc. Chem. Res.* **1979**, *12*, 331.

[5] See for instance: (a) Drury III, W. J.; Zimmermann, N.; Keenan, M.; Hayashi, M.; Kaiser, S.; Goddard, R.; Pfaltz, A. *Angew. Chem. Int. Ed.* **2004**, *43*, 70; b) Perry, M. C.; Cui, X.; Powell, M. T.; Hou, D.-R.; Reibenspies, J. H.; Burgess, K. *J. Am. Chem. Soc.* **2003**, *125*, 5391; c) Blankestein, J.; Pfaltz, A. *Angew. Chem. Int. Ed.* **2001**, *40*, 4445; d) Kaiser, S.; Smidt, S. P.; Pfaltz, A. *Angew. Chem. Int. Ed.* **2006**, *45*, 5194; e) Källström, K.; Hedberg, C.; Brandt, P.; Bayer, P.; Andersson, P. G. *J. Am. Chem. Soc.* **2004**, *126*, 14308; f) Diéguez, M.; Mazuela, J.; Pàmies, O.; Verendel, J. J.; Andersson, P. G. *J. Am. Chem. Soc.* **2008**, *130*, 7208; g) Diéguez, M.; Mazuela, J.; Pàmies, O.; Verendel, J. J.; Andersson, P. G. *Chem. Commun.* **2008**, 3888; h) Mazuela, J.; Verendel, J. J.; Coll, M.; Schäffner, B.; Börner, A.; Andersson, P. G.; Pàmies, O.; Diéguez, M. *J. Am. Chem. Soc.* **2009**, *131*, 12344; i) Mazuela, J.; Paptchikhine, A.; Pàmies, O.; Andersson, P. G.;

Diéguez, M. *Chem. Eur. J.* **2010**, *16*, 4567; j) Zhao, J.; Burgess, K. *J. Am. Chem. Soc.* **2009**, *131*, 13236; k) Wang, A.; Fraga, R. P. A.; Hormann, E.; Pfaltz, A. *Chem. Asian J.* **2011**, *6*, 599; l) Lu, S.-M.; Bolm, C. *Angew. Chem. Int. Ed.* **2008**, *47*, 8920; m) Lu, W.-J.; Chen, Y.-W.; Hou, X.-L. *Adv. Synth. Catal.* **2010**, *352*, 103.

[6] For representative examples on the use of P,S-ligands in asymmetric hydrogenation of enamides and ketones, see: a) Evans, D. A.; Michael, F. E.; Tedrow, J. S.; Campos, K. R. *J. Am. Chem. Soc.* **2003**, *125*, 3534; b) Guimet, E.; Diéguez, M.; Ruiz, A.; Claver, C. *Dalton Trans.* **2005**, 2557; c) Hauptman, E.; Fagan, P. J.; Marshall, W. *Organometallics* **1999**, *18*, 2061; d) Le Roux, E.; Malacea, R.; Manoury, E.; Poli, R.; Gonsalvi, L.; Peruzzini, M. *Adv. Synth. Catal.* **2007**, *349*, 309.

[7] For a recent review on the use of P,S-ligands in asymmetric catalysis, see: Malacea, R.; Manoury, E. in *Phosphorus Ligands in Asymmetric Catalysis*; ed. Börner, A. Wiley-VCH, Weinheim, **2008**; Vol. 2, pp 749-784.

[8] See for example: a) Diéguez, M.; Pàmies, O.; Claver, C. *Chem. Rev.* **2004**, *104*, 3189; b) Woodward, S.; Diéguez, M.; Pàmies, O. *Coord. Chem. Rev.* **2010**, *254*, 2007; c) Diéguez, M.; Pàmies, O.; Ruiz, A.; Díaz, Y.; Castillón, S.; Claver, C. *Coord. Chem. Rev.* **2004**, *248*, 2165 ; d) Diéguez, M.; Ruiz, A.; Claver, C. *Dalton Trans.* **2003**, 2957; e) Castillón, S.; Díaz, Y.; Claver, C. *Chem. Soc. Rev.* **2005**, *34*, 702 ; f) Diéguez, M.; Claver, C.; Pàmies, O. *Eur. J. Org. Chem.* **2007**, 4621; g) Woodward, S.; Diéguez, M.; Pàmies, O. *Coord. Chem. Rev.* **2010**, *254*, 2007; h) Boysen, M. M. K. *Chem. Eur. J.* **2007**, *13*, 8648; i) Benessere, V.; Del Litto, R.; De Roma, A.; Ruffo, F. *Coord. Chem. Rev.* **2010**, *254*, 390; j) van Leeuwen, P.W.N.M.; Kamer, P.C.J.; Claver, C.; Pàmies, O.; Diéguez, M. *Chem. Rev.* **2011**, *111*, 2077; k) Claver, C.; Pàmies, O.; Diéguez, M. in *Phosphorus Ligands in Asymmetric Catalysis*; ed. Börner, A. Wiley-VCH, Weinheim, **2008**; Vol. 2, pp 506-528.

[9] See for instante: a) Masdeu-Bultó, A. M.; Diéguez, M.; Martin, E.; Gómez, M. *Coord. Chem. Rev.* **2003**, *242*, 159; b) Mellah, M.; Voituriez, A.; Schulz, E. *Chem. Rev.* **2007**, *107*, 5133.

[10] Ligands **L6-L8a** has been previously synthesized, see: Pàmies, O.; Diéguez, M.; Net, G.; Ruiz, A.; Claver, C. *Organometallics* **2000**, *19*, 1488.

[11] a) Kartha, K. P. R. *Tetrahedron Lett.* **1986**, *27*, 3415; b) Vogel, A. I.; *Vogel's Textbook of Practical Organic Chemistry*, 5th ed., Longman, New York, **1994**; c)

Lucas, S. D.; Rauter, A. P.; Schneider, J.; Wessel, H. P. *J. Carbohydr. Chem.* **2009**, *28*, 431.

[12] Thioether-alcohol compounds **5-11** were prepared as previously described. See: a) Diéguez, M.; Pàmies, O.; Claver, C. *J. Organomet. Chem.* **2006**, *691*, 2257; b) ref. 10.

[13] Hydrides *trans* to the phosphorus donor generally have coupling constants of 80-100 Hz. See: a) Hälg, W. J.; Öhrström, L. R.; Rüegger, H.; Venanzi, L. M. *Magn. Reson.* **1993**, *31*, 677; b) Kimmich, B. F. M.; Somsook, E.; Landis, C. R. *J. Am. Chem. Soc.* **1998**, *120*, 10115.

[14] Crabtree, R. H. *The Organometallic Chemistry of the Transition Metals*; John Wiley & Sons: New York, **1998**.

[15] Evans, D. A.; Michael, F. E.; Tedrow, J. S.; Campos, K. R. *J. Am. Chem. Soc.* **2003**, *125*, 3534.

[16] See for instance: a) Rovner, E. S.; Wein, A. *J. Eur. Urol.* **2002**, *41*, 6; b) Wefer, J.; Truss, M. C.; Jonas, U. *World J. Urol.* **2001**, *19*, 312; c) Hills, C. J.; Winter, S. A.; Balfour, J. A. *Drugs* **1998**, *55*, 813; d) McRae, A. L.; Brady, K. T. *Expert Opin. Pharmacother.* **2001**, *2*, 883; e) Gordaliza, M.; García, P. A.; Miguel del Corral, J. M.; Castro, M. A.; Gómez-Zurita, M. A. *Toxicon* **2004**, *44*, 441.

[17] a) Tolstoy, P.; Engman, M.; Paptchikhine, A.; Bergquist, J.; Church, T. L.; Leung, A. W.–M.; Andersson, P. G. *J. Am. Chem. Soc.* **2009**, *131*, 8855; b) Mazuela, J.; Norby, P. O.; Andersson, P. G.; Pàmies, O.; Diéguez, M. *J. Am. Chem. Soc.* **2011**, *133*, 13634.

[18] See, for example: a) Kabalka, G. W. *J. Organomet. Chem.* **1984**, *274*, 1; b) Kabalka G. W.; Marks, R. C. *J. Organomet. Chem*. **1993**, *457*, 25; c) Morgan J. B.; Morken, J. P. *J. Am. Chem. Soc.* **2004**, *126*, 15338; d) Moran W. J.; Morken, J. P. *Org. Lett*. **2006**, *8*, 2413.

[19] For successful application of Ir-catalysts, see: a) McIntyre, S.; Hörmann, E.; Menges, F.; Smidt, S. P.; Pfaltz, A. *Adv. Synth. Catal.* **2005**, *347*, 282; b) ref. 5h.

[20] For successful applications of Sm-, Ru- and Rh-complexes, see: a) Conticello, V. P.; Brard, L.; Giardello, M. A.; Tsuji, Y.; Sabat, M.; Stern, C. L.; Marks, T. J. *J. Am. Chem. Soc.* **1992**, *114*, 2761; b) Giardello, M. A.; Conticello, V. P.; Brard, L.; Gagné, M. R.; Marks, T. J. *J. Am. Chem. Soc.* **1994**, *116*, 10241; c) Co, T. T.; Kim, T. J. *Chem. Commun.* **2006**, 3537; d) Forman, G. S.; Ohkuma, T.; Hems, W. P.; Noyori, R. *Tetrahedron Lett.* **2000**, *41*, 9471.

[21] a) Fessard, T. C.; Andrews, S. P.; Motoyohsi, H.; Carreira, E. *Angew. Chem. Int. Ed.* **2007**, *46*, 9331; b) Prat, L.; Dupas, G.; Duflos, J.; Quéguiner, G.; Bourguignon, J.; Levacher, V. *Tetrahedron Lett.* **2001**, *42*, 4515; c) Wilkinson, J. A.; Rossington, S. B.; Ducki, S.; Leonard, J.; Hussain, N. *Tetrahedron* **2006**, *62*, 1833.

[22] a) Okamoto, K.; Nishibayashi, Y.; Uemura, S.; Toshimitsu, A. *Angew. Chem. Int. Ed.* **2005**, *44*, 3588; b) Hatanaka, Y.; Hiyama, T. *J. Am. Chem. Soc.* **1990**, *112*, 7793.

[23] See for instance: a) Abate, A.; Brenna, E. Fuganti, C.; Gatti, G. G.; Givenzana, T.; Malpezzi, L.; Serra, S. *J. Org. Chem.* **2005**, *70*, 1281; b) Drescher, K.; Haupt, A.; Unger, L.; Rutner, S. C.; Braje, W:; Grandel, R.; Henry, C.; Backfisch, G:; Beyerbach, A.; Bisch, W. *WO Patent* 2006/040182 A1.

[24] Buisman, G. J. H.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Tetrahedron: Asymmetry* **1993**, *4*, 1625.

[25] Guimet, E.; Diéguez, M.; Ruiz, A. ; Claver, C. *Tetrahedron: Asymmetry* **2005**, *16*, 959.

[26] Iida, T.; Yamamoto, N.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1997**, *119*, 4783.

3.3.7. Supporting Information

1. Table 3.3.5. Asymmetric Ir-catalyzed hydrogenation of **S2** and **S3** using the furanoside P,S-ligand library **L6-L20a-i**.

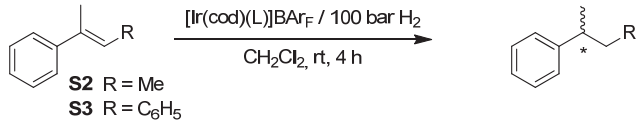
2. Table 3.3.6. Asymmetric Ir-catalyzed hydrogenation of **S4** using the furanoside P,S-ligand library **L6-L20a-i**.

3. Table 3.3.7. Asymmetric Ir-catalyzed hydrogenation of **S6** and **S7** using the furanoside P,S-ligand library **L6-L20a-i**.

4. Table 3.3.8. Asymmetric Ir-catalyzed hydrogenation of **S10** and **S13-S16** using the furanoside P,S-ligand library **L6-L20a-i**.

5. Table 3.3.9. Asymmetric Ir-catalyzed hydrogenation of **S19** using the furanoside P,S-ligand library **L6-L20a-i**.

Table 3.3.5. Asymmetric Ir-catalyzed hydrogenation of **S2** and **S3** using the furanoside P,S-ligand library **L6-L20a-i**.[a]

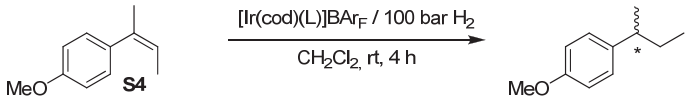


S2 R = Me
S3 R = C_6H_5

		S2		**S3**	
Entry	Ligand	% Conv[b]	% ee[b]	% Conv[c,d]	% ee[d]
1	**L6a**	100	11 (*R*)	100	15 (*R*)
2	**L7a**	100	15 (*R*)	100	16 (*R*)
3	**L8a**	100	23 (*R*)	100	25 (*R*)
4	**L9a**	100	26 (*R*)	100	28 (*R*)
5	**L10a**	100	12 (*R*)	100	13 (*R*)
6	**L11a**	100	11 (*R*)	100	16 (*R*)
7	**L12a**	100	30 (*R*)	100	29 (*R*)
8	**L13a**	100	63 (*R*)	100	61 (*R*)
9	**L16a**	100	98 (*R*)	100	99 (*R*)
10	**L16b**	100	98 (*R*)	100	99 (*R*)
11	**L16d**	100	26 (*R*)	100	18 (*R*)
12	**L16e**	100	99 (*R*)	100	99 (*R*)
13	**L16f**	100	48 (*S*)	100	37 (*S*)
14	**L17a**	100	67 (*R*)	100	63 (*R*)
15	**L19a**	100	68 (*S*)	100	65 (*S*)
16	**L6i**	100	15 (*R*)	100	18 (*R*)
17	**L13i**	100	68 (*R*)	100	69 (*R*)
18	**L16i**	100	78 (*R*)	100	77 (*R*)

[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 time 8 h. [d] Conversion measured by ^{1}H-NMR. Enantiomeric excess measured by HPLC.

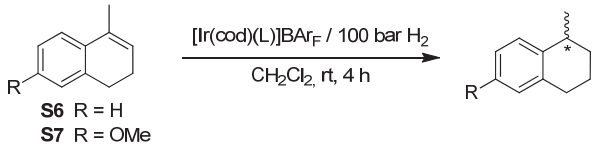
Table 3.3.6. Asymmetric Ir-catalyzed hydrogenation of **S4** using the furanoside P,S-ligand library **L6-L20a-i**.[a]



Entry	Ligand	% Conv[b]	% ee[b]	Entry	Ligand	% Conv[b]	% ee[b]
1	**L6a**	100	10 (*S*)	17	**L13h**	100	16 (*R*)
2	**L6f**	100	42 (*S*)	18	**L14a**	100	29 (*S*)
3	**L6g**	100	43 (*S*)	19	**L15a**	100	44 (*S*)
4	**L7a**	100	12 (*S*)	20	**L16a**	100	85 (*S*)
5	**L8a**	100	21 (*S*)	21	**L16e**	100	93 (*S*)
6	**L9a**	100	20 (S)	22	**L16f**	100	4 (*R*)
7	**L10a**	100	8 (*S*)	23	**L17a**	100	63 (*S*)
8	**L11a**	100	9 (*S*)	24	**L19a**	100	37 (*R*)
9	**L12a**	100	32 (*S*)	25	**L6i**	100	31 (*S*)
10	**L13a**	100	62 (*S*)	26	**L7i**	100	12 (*S*)
11	**L13b**	100	64 (*S*)	27	**L9i**	100	14 (*S*)
12	**L13c**	100	63 (*S*)	28	**L10i**	100	30 (*S*)
13	**L13d**	100	4 (*S*)	29	**L12i**	100	41 (*S*)
14	**L13e**	100	12 (*S*)	30	**L13i**	100	63 (*S*)
15	**L13f**	100	1 (*S*)	31	**L16i**	100	83 (*S*)
16	**L13g**	100	10 (*S*)	32	**L17i**	100	54 (*S*)

[a] Reactions carried out using 1 mmol of **S4** and 2 mol% of Ir-catalyst precursor.[b] Conversion and enantiomeric excesses determined by chiral GC. [c] Reaction carried out at 0.5 mol% of Ir-catalyst precursor.

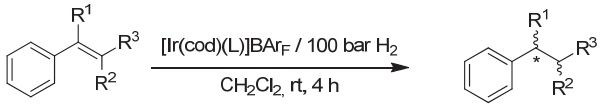
Table 3.3.7. Asymmetric Ir-catalyzed hydrogenation of **S6** and **S7** using the furanoside P,S-ligand library **L6-L20a-i**.[a]



		S6		S7	
Entry	Ligand	% Conv[b]	% ee[b]	% Conv[b]	% ee[b]
1	**L6a**	100	8 (*S*)	100	7 (*S*)
2	**L7a**	100	9 (*S*)	100	11 (*S*)
3	**L10a**	100	9 (*S*)	100	6 (*S*)
4	**L11a**	100	6 (*S*)	100	7 (*S*)
5	**L12a**	100	18 (*S*)	100	21 (*S*)
6	**L13a**	100	58 (*S*)	100	60 (*S*)
7	**L16a**	100	75 (*S*)	100	85 (*S*)
8	**L16e**	100	75 (S)	100	86 (S)
9	**L16f**	100	27 (*R*)	100	24 (*R*)
10	**L17a**	100	51 (*S*)	100	58 (*S*)
11	**L19a**	100	28 (*R*)	100	34 (*R*)
12	**L6i**	100	30 (*S*)	100	29 (*S*)
13	**L13i**	100	49 (*S*)	100	60 (*S*)
14	**L16i**	100	63 (*S*)	100	71 (*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.

Table 3.3.8. Asymmetric Ir-catalyzed hydrogenation of **S10** and **S13-S16** using the furanoside P,S-ligand library **L6-L20a-i**.[a]

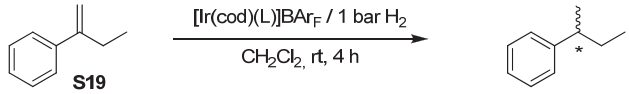


S10 R^1 = Me; R^2 = H; R^3 = COOEt
S13 R^1 = H; R^2 = Me; R^3 = CH_2OH
S14 R^1 = H; R^2 = Me; R^3 = CH_2OAc
S15 R^1 = Me; R^2 = H; R^3 = $SiMe_3$
S16 R^1 = Bpin; R^2 = H; R^3 = Bpin

Entry	Ligand	Substrate	% Conv[b]	% ee[c]	Entry	Ligand	Substrate	% Conv[b]	% ee[c]
1	**L6a**	**S10**	100	14 (*R*)	14	**L13a**	**S14**	98	38 (*R*)
2	**L13a**	**S10**	100	65 (*R*)	15	**L16a**	**S14**	100	90 (*R*)
3	**L16a**	**S10**	100	98 (*R*)	16	**L16e**	**S14**	100	92 (*R*)
4	**L16e**	**S10**	100	99 (*R*)	17	**L16f**	**S14**	100	40 (*S*)
5	**L17a**	**S10**	100	59 (*R*)	18	**L17a**	**S14**	100	66 (*R*)
6	**L6a**	**S13**	100	9 (*S*)	19	**L16a**	**S15**	100	60 (*R*)
7	**L13a**	**S13**	98	40 (*R*)	20	**L16e**	**S15**	100	64 (*R*)
8	**L16a**	**S13**	100	89 (*R*)	21	**L16f**	**S15**	100	42 (*S*)
9	**L16e**	**S13**	100	90 (*R*)	22	**L6a**	**S16**	100	26 (*R*)
10	**L16f**	**S13**	100	36 (*S*)	23	**L13a**	**S16**	100	59 (*R*)
11	**L17a**	**S13**	100	68 (*R*)	24	**L16a**	**S16**	100	89 (*R*)
12	**L19a**	**S13**	100	35 (*S*)	25	**L16e**	**S16**	100	91 (*R*)
13	**L6a**	**S14**	100	9 (*S*)	26	**L16f**	**S16**	100	30 (*S*)

[a] Reactions carried out using 0.5 mmol of substrate and 2 mol% of Ir-catalyst precursor.[b] Conversion measured by ^{1}H-NMR. [c] Enantiomeric excesses determined by chiral GC or HPLC.

Table 3.3.9. Asymmetric Ir-catalyzed hydrogenation of **S19** using the furanoside P,S-ligand library **L6-L20a-i**.[a]



Entry	Ligand	% Conv[b]	% ee[b]	Entry	Ligand	% Conv[b]	% ee[b]
1	**L6a**	100	29 (*R*)	17	**L15a**	100	30 (*S*)
2	**L7a**	100	4 (*R*)	18	**L16a**	100	77 (*S*)
3	**L8a**	100	16 (*R*)	19	**L16e**	100	79 (*S*)
4	**L9a**	100	17 (*R*)	20	**L16f**	100	77 (*R*)
5	**L10a**	100	27 (*R*)	21	**L17a**	100	48 (*S*)
6	**L11a**	100	25 (*R*)	22	**L18a**	100	11 (*S*)
7	**L12a**	100	42 (*R*)	23	**L19a**	100	63 (*R*)
8	**L13a**	100	67 (*S*)	24	**L20a**	100	14 (*R*)
9	**L13b**	100	66 (*S*)	25	**L6i**	100	2 (*S*)
10	**L13c**	100	67 (*S*)	26	**L7i**	100	3 (*S*)
11	**L13d**	100	3 (*S*)	27	**L8i**	100	1 (*S*)
12	**L13e**	100	67 (*S*)	28	**L9i**	100	0 (*S*)
13	**L13f**	100	66 (*R*)	29	**L12i**	100	30 (*S*)
14	**L13g**	100	32 (*S*)	30	**L13i**	100	11 (*S*)
15	**L13h**	100	5 (*R*)	31	**L16i**	100	20 (*S*)
16	**L14a**	100	8 (*S*)				

[a] Reactions carried out using 0.5 mmol of **S19** and 2 mol% of Ir-catalyst precursor.[b] Conversion and enantiomeric excesses determined by chiral GC.

3.4. Asymmetric hydrogenation of alkenes lacking coordinating groups with a furanoside thioether-phosphoroamidite ligand library

Mercedes Coll, Oscar Pàmies and Montserrat Diéguez in preparation.

Abstract. A series of furanoside thioether-phosphoroamidite ligands has been applied to the Ir-catalyzed asymmetric hydrogenation of minimally functionalized olefins. Our results show that the enantiomeric excesses are strongly dependent on the configuration of C-3 of the sugar backbone, the steric properties of the substituent in the thioether moiety, the subtituents/configuration at the biaryl phosphoroamidite moiety and the substrate structure. Enantiomeric excesses of up to 53% and 87% were obtained in the asymmetric reduction of tri- and di-substituted olefins, respectively.

3.4.1. Introduction

Asymmetric hydrogenation is a fundamental technology of the modern organic chemists' repertoire of reliable catalytic methods for the construction of optically active compounds. High enantioselectivity, low catalyst loadings, essentially quantitative yields, perfect atom economy, and mild conditions are attractive features of this transformation as evident in the ever growing list of publications using these methods.[1] 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, the asymmetric hydrogenation of minimally functionalized olefins is less developed because these substrates have not adjacent polar group to direct the reaction.[2] A breakthrough in the hydrogenation of this type of substrates came when Pfaltz and coworkers[3] used Ir-complexes [Ir(**PHOX**)(cod)]BAr_F modified with phosphine-oxazoline **PHOX** ligands as chiral analogues of Crabtree's catalyst[4] ([Ir(py)(PCy_3)(cod)]PF_6). Since then, the composition of the ligands has been extended by replacing the phosphine moiety with a phosphinite, phosphite or a carbene group, and the oxazoline moiety with other N-donor groups (such as pyridine, thiazole and oxazole). The structure of the chiral ligand's backbone has also been modified. These

modifications have led to the discovery of new ligands that have considerably broadened the scope of Ir-catalyzed hydrogenation.[5] 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 minimally functionalized tri- and tetra-substituted olefins.[2] However, the possibility of changing the nature of the N-donor atom in these heterodonor ligands has only been contemplated very recently. In this context in 2011 we have communicated the first application of non-N-donor heterodonor ligands –thioether-phosphite– for the asymmetric hydrogenation of minimally functionalized olefins.[6] These ligands have provided excellent enantioselectivities (up to 99% ee) in the asymmetric reduction of several alkenes (see Section 3.3). Despite this success little attention has been paid to this new class of efficient thioether-containing ligands for this process and their potential as new ligands still needs to be systematically studied. To fully investigate this potential, we therefore decided to go one step further and to study whether the thioether maintains its effectiveness in combination with other electron-poor phosphorus groups other than phosphites. For this purpose, we here report the synthesis and application of a furanoside thioether-phosphoroamidite ligand library (Figure 3.4.1) in the Ir-catalyzed hydrogenation of minimally functionalized olefins. Ligands **L21-L26a-f** are based on the previous successfully furanoside thioether-phosphite ligands **L6-L20a-f**, in which a biaryl phosphoroamidite moiety was used instead of a biaryl phosphite motif. These ligands, derived from D-(+)-xylose, have the advantages of phosphoroamidite and sugar cores: they are cheap, easily constructed with modules and highly resistant to oxidation.[7] All these features enable series of chiral ligands to be synthetized and screened in the search for high activity and selectivity. With this library we therefore fully investigated the effect of systematically varying the configurations of the ligand backbones at C-3, the substituents in the thioether group and the substituents/configurations in the biaryl phosphoroamidite moiety (**a-f**).

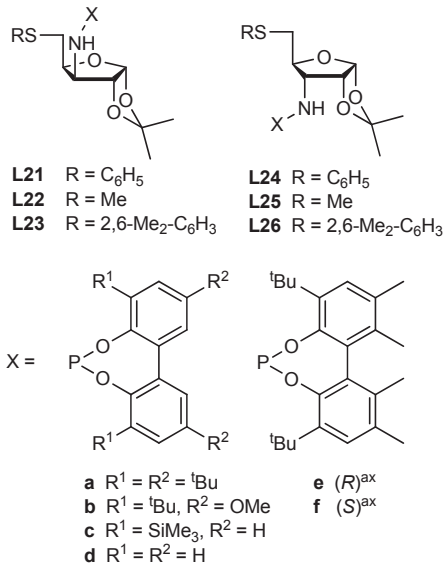


Figure 3.4.1. Thioether-phosphoroamidite ligands **L21-L26a-f**.

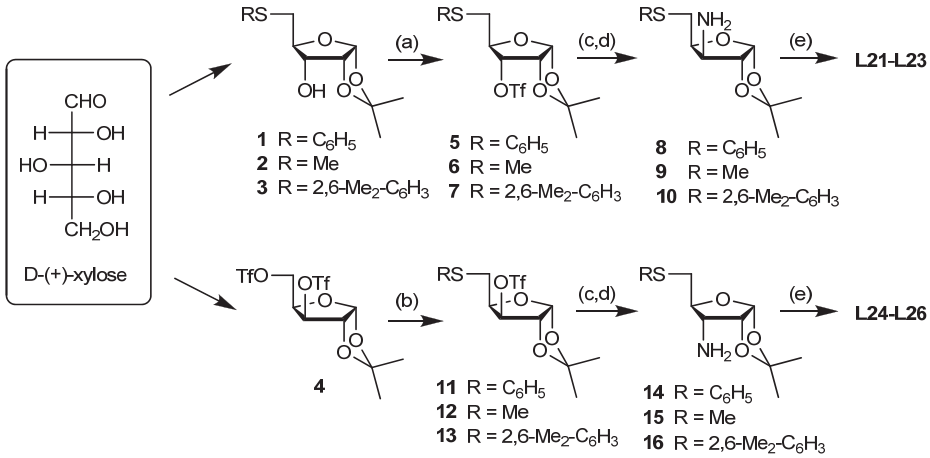
3.4.2. Results and discussions

3.4.2.1. Synthesis of ligands

The synthesis of the thioether-phosphoroamidite ligands **L21-L26a-f** is straightforward (Scheme 3.4.1). They were efficiently synthesized from the corresponding easily accessible thioether-triflates **5-7** and **11-13**. These latter compounds are easily made in few steps from inexpensive D-(+)-xylose (Scheme 3.4.1). Ribofuranoside thioether-triflates **5-7** were easily obtained by tryflation of the previously described thioether-acohols **1-3** (Section 3.3). However, xylofuranoside thioether-triflates **11-13**[8], which differ from **5-7** in the configuration of C-3, were obtained from ditriflate **4**[9] by selective nucleophilic substitution at C-5 position (Scheme 3.4.1, step (b)). Compounds **5-7** and **11-13** were then treated with sodium azide to produce the desired azido compounds (Scheme 3.4.1, step (c)). Note that the azide formation follows an S_N2-like pathway, so the absolute configuration of the stereogenic C-3 is inverted. Subsequent reduction of the corresponding azide provided the desired thioether-amine compounds **8-10** and **14-16** (Scheme 3.4.1, step (d)). The last step of the ligand synthesis is the reaction of the corresponding sugar thioether-

amine (**8-10** and **14-16**) with 1 equiv of the corresponding biaryl phosphorochloridite ($ClP(OR)_2$; $(OR)_2$ = **a-f**) in the presence of pyridine (Scheme 3.4.1, step (e)).

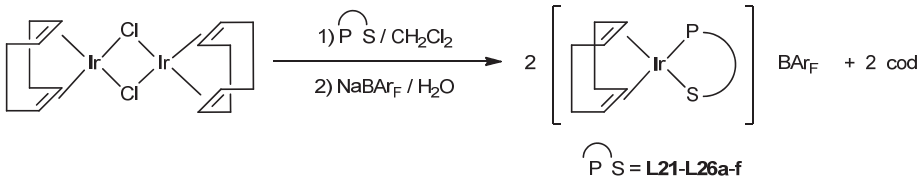
All the ligands were stable during purification on neutral alumina under an atmosphere of argon and isolated in good yields as white solids. They were stable at room temperature and very stable to hydrolysis. The elemental analyses were in agreement with the assigned structure. The ^{1}H, ^{13}C and ^{31}P NMR spectra were as expected for these C_1 ligands.



Scheme 3.4.1. Synthesis of thioether-phosphoroamidite **L21-L26a-f**. (a) Tf_2O, Py, CH_2Cl_2, -15 °C. (b) NaSR, THF, rt. (c) NaN_3/DMF/Bu_4NCl. (d) $LiAlH_4/Et_2O$. (e) $ClP(OR)_2$, Py, toluene, 80 °C.

3.4.2.2. Synthesis of the Ir-catalyst precursors

The catalyst precursors were made by refluxing a dichloromethane solution of the appropriate ligand (**L21-L26a-f**) 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). 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 C_1 iridium complexes. VT-NMR (+40 °C to -70 °C) experiments indicate the presence of a single isomer in all cases.



Scheme 3.4.2. Synthesis of catalyst precursors [Ir(cod)(P-S)]BAr_F (P-S = **L21-L26a-f**).

3.4.2.3. Asymmetric hydrogenation of minimally functionalized trisubstituted olefins

In a first set of experiments we used the Ir-catalyzed hydrogenation of substrates *E*-2-(4-methoxyphenyl)-2-butene **S1** and *Z*-2-(4-methoxyphenyl)-2-butene **S2** to study the potential of ligands **L21-L26a-f**. Substrate **S1** was chosen as a model for the hydrogenation of *E*-isomers 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] In order to assess the potential of the ligand library **L21-L26a-f** for the more demanding *Z*-isomers, which are usually hydrogenated less enantioselectively than the corresponding *E*-isomers,[5] we chose substrate **S2** as a model. The results, which are summarized in Table 3.4.1, indicate that enantioselectivity are highly affected by the thioether substituents, the configuration of C-3 and the substituents/configuration in the biaryl phosphoroamidite moiety (**a**–**f**).

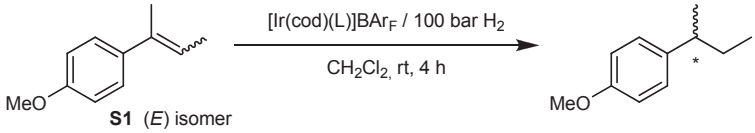
Results showed that enantioselectivity is dependent on the steric properties of the substituents in the thioether moiety. Enantioselectivities were therefore best with ligands containing a bulky thioether group (i.e. 2,6-Me_2-C_6H_3>Ph>Me; Table 3.4.1, entries 8 and 11 *vs* 1, 7, 9 and 10). This behavior is in line with the thioether substituent effect observed for related thioether-phosphite ligands **L6-L20a** (Chapter 3, Section 3.3.2.4), for which enantioselectivities also increased by increasing the steric bulk of the thioether substituent.

The effect of the phosphoroamidite moieties were studied using ligands **L21a-f** (Table 3.4.1, entries 1-6). The results indicated that: (a) the presence of bulky substituents at the biaryl phosphoroamidite moiety has a positive effect on enantioselectivity (Table 3.4.1, entries 1-3 *vs* 4); and (b) there is a cooperative effect between the configuration of the bulky biphenyl moiety and the configuration of the

ligand backbone on enantioselectivity. This led to a matched combination for ligand **L21e**, which contains an (*R*)-biaryl moiety (Table 3.4.1, entry 5).

Results also indicated that enantioselectivity is dependent on the configuration of stereogenic carbon atom C-3 of the furanoside backbone. In general, the best enantioselectivities were achieved with 5-deoxy-ribofuranoside derived ligands **L24-L26**, which have an (*R*)-configuration of carbon atom C-3 (entries 9-11 *vs* 1 and 7-8).

Table 3.4.1. Ir-catalyzed hydrogenation of **S1** and **S2** using the furanoside thioether-phosphoroamidite ligand library **L21-L26a-f**.[a]



S1 (*E*) isomer
S2 (*Z*) isomer

		S1		**S2**	
Entry	Ligand	% Conv[b]	% ee[b]	% Conv[b]	% ee[b]
1	**L21a**	100	36 (*R*)	100	3 (*S*)
2	**L21b**	100	34 (*R*)	100	4 (*S*)
3	**L21c**	100	35 (*R*)	100	2 (*S*)
4	**L21d**	100	6 (*R*)	100	0
5	**L21e**	100	48 (*R*)	100	6 (*S*)
6	**L21f**	100	10 (*S*)	100	12 (*R*)
7	**L22a**	100	25 (*R*)	100	1 (*S*)
8	**L23a**	100	42 (*R*)	100	19 (*S*)
9	**L24a**	100	33 (*R*)	100	13 (*S*)
10	**L25a**	100	31 (*R*)	100	12 (*S*)
11	**L26a**	100	53 (*R*)	100	40 (*S*)

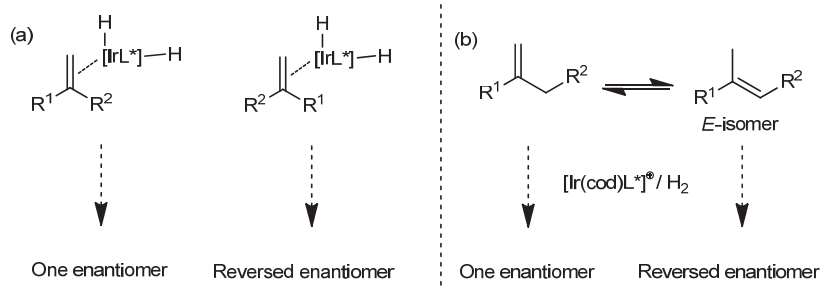
[a] Reactions carried out using 0.5 mmol of substrate and 2 mol% of Ir-catalyst precursor.[b] Conversion and enantiomeric excesses determined by chiral GC.

Finally, if we compared these results with those obtained with related thioether-phosphite ligands (Chapter 3, Section 3.3.2.4), we can conclude that replacing the

phosphite moiety by a phosphoroamidite group had a negative effect on enantioselectivity.

3.4.2.4. Asymmetric hydrogenation of minimally functionalized 1,1-disubstituted terminal olefins

We next screened ligands **L21-L26a-f** in the asymmetric hydrogenation of more demanding terminal olefins. Enantioselectivity is more difficult to control in these substrates than in trisubstituted olefins. To achieve high enantioselectivities the catalyst has to: (a) create an appropriate chiral environment that favors the coordination of the alkene through one of its faces (Scheme 3.4.3 (a)); and (b) minimize the thermodynamically favored isomerization of the terminal double bond to form the more stable internal alkene (Scheme 3.4.3 (b)).[2] Few known catalytic systems therefore provide high enantioselectivities for these substrates, and those that do are usually limited in substrate scope.[2e,10,11] 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.[10a]



Scheme 3.4.3.

In a first set of experiments we used the Ir-catalyzed asymmetric hydrogenation of 3,3-dimethyl-2-phenyl-1-butene **S3** to assess the potential of the thioether-phosphoroamidite ligand library in the reduction of this class of more demanding substrates. The results are shown in Table 3.4.2. Enantioselectivities were again affected by the thioether substituents, the configuration of C-3 and the substituents/configuration in the biaryl phosphoroamidite moiety (**a**–**f**). However, the effect of these parameters were different from the effect observed in the reduction of **S1** and **S2**. Thus, while the

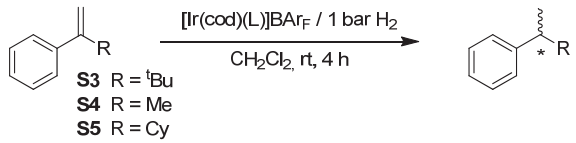
effect of the configuration of C-3 and the substituents at the biaryl phosphoroamidite moiety follows the same trend as for the reduction of trisubstituted olefins, the effects of the substituents at the thioether group and the configuration of the biaryl phosphoroamidite moiety are different.

The effect of the substituent at the thioether group depends on the configuration of C-3. Thus, while for ligands **L21-L23**, with an (*S*)-configuration at C-3, enantioselectivities were best using ligand **L22** that contains a methyl substituent (Table 3.4.2, entry 7 *vs* 1 and 8), for ligands **L24-L26**, with an (*R*)-configuration at C-3, enantioselectivities were best with ligand **L26** with a bulky 2,6-Me_2-C_6H_3 substituent (Table 3.4.2, entry 11 *vs* 9 and 10).

Regarding the effect of the configuration of the biaryl phosphoroamidite moiety, we were pleased to observe that the use of enantiopure biaryl phosphoroamidite moiety has a extremely positive effect on enantioselectivity (ee's increase from 14% for ligands **L21a-c** containing tropoisomeric biphenyl moieties until 87% ee for ligands containing chiral biphenyl moieties; Table 3.4.2, entries 1-3 *vs* 5 and 6). Moreover, both enantiomers of the hydrogenation product can be therefore obtained in high enantioselectivities (ee's up to 87%) using pseudo-enantiomeric ligands **L21e** and **L21f** (Table 3.4.2, entries 5 and 6). This behavior contrast with the previous cooperative effect observed for trisubstituted olefins that lead to higher ee's with ligands containing enantiopure bulky (*R*)-biaryl moieties (**e**).

Our results with several 1,1-disubstituted aryl-alkyl substrates (**S3-S5**) indicated that enantioselectivity is highly affected by the nature of the alkyl chain (ee's ranging from 28% to 87%, Table 3.4.2, entries 1, 5, 6 and 12-16). This behavior has also been observed for related thioether-phosphite ligands **L6-L20a-f**. Again, a plausible explanation can be found in the competition between direct hydrogenation *vs* isomerization for the different substrates. This is supported by the fact that the hydrogenation of substrate **S3** bearing a *tert*-butyl group, for which isomerization cannot occur, provides the highest levels of enantioselectivity (ee's up to 87%; Table 3.4.2, entries 5 and 6).

Table 3.4.2. Ir-catalyzed hydrogenation of 1,1-disubstituted substrates **S3-S5** using the furanoside thioether-phosphoroamidite ligand library **L21-L26a-f**.[a]



Entry	Ligand	Substrate	% Conv[b]	% ee[b]
1	**L21a**	**S3**	100	13 (*S*)
2	**L21b**	**S3**	100	14 (*S*)
3	**L21c**	**S3**	100	14 (*S*)
4	**L21d**	**S3**	100	2 (*R*)
5	**L21e**	**S3**	100	87 (*S*)
6	**L21f**	**S3**	100	84 (*R*)
7	**L22a**	**S3**	100	27 (*S*)
8	**L23a**	**S3**	100	17 (*S*)
9	**L24a**	**S3**	100	21 (*S*)
10	**L25a**	**S3**	100	23 (*S*)
11	**L26a**	**S3**	100	61 (*S*)
12	**L21a**	**S4**	100	28 (*S*)
13	**L21e**	**S4**	100	35 (S)
14	**L21f**	**S4**	100	32 (*R*)
15	**L21e**	**S5**	45	39 (*S*)
16	**L21f**	**S5**	100	31 (*R*)

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

3.4.3. Conclusions

A series of furanoside thioether-phosphoroamidite ligands, prepared from readily available D-(+)-xylose, was screened in the Ir-catalyzed asymmetric

hydrogenation of minimally functionalized olefins. Our results show that the enantiomeric excesses are strongly dependent on the configuration of C-3 of the sugar backbone, the steric properties of the substituent in the thioether moiety, the subtituents/configuration at the biaryl phosphoroamidite moiety and the substrate structure. In addition by comparing with the results obtained in the previous Section 3.3., we can conclude that the introduction of a phosphoroamidite moiety in the ligand design has a negative effect on enantioselectivity. However, this effect is less pronounced in the reduction of 1,1-disubstitued terminal alkenes (ee's up to 87%) than in the hydrogenation of trisubstituted olefins (ee's up to 53%).

3.4.4. Experimental section

3.4.4.1. General considerations

All reactions were carried out using standard Schlenk techniques under an atmosphere of argon. Solvents were purified and dried by standard procedures. Phosphorochloridites are easily prepared in one step from the corresponding biaryls.[12] Thioether-alcohols **1**-**3**,[13] ditriflate **4**[9] and thioether-triflates **11** and **12**[8] were prepared as previously described. ^{1}H, $^{13}C\{^{1}H\}$, $^{31}P\{1H\}$ NMR spectra and NOESY experiments were recorded using a 400 MHz spectrometer. Chemical shifts are relative to that of $SiMe_4$ (^{1}H and ^{13}C) as internal standard or H_3PO_4 (^{31}P) as external standard. ^{1}H and ^{13}C assignments were done based on ^{1}H-^{1}H gCOSY and ^{1}H-^{13}C gHSQC experiments.

3.4.4.2. Typical procedure for the preparation of thioether-phosphoroamidite ligands L21-L26a-f

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-amine 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.

L21a: Yield: 302 mg, 42 %. ^{31}P NMR (400 MHz, C_6D_6) δ: 149.2 (s). ^{1}H NMR (400 MHz, C_6D_6) δ: 1.05 (s, 3H, CH_3), 1.27 (s, 9H, CH_3, ^{t}Bu), 1.28 (s, 3H, CH_3), 1.29 (s, 9H, CH_3, ^{t}Bu), 1.55 (s, 9H, CH_3, ^{t}Bu), 1.59 (s, 9H, CH_3, ^{t}Bu), 2.75 (m, 1H, NH), 3.15 (m, 2H, H-5' and H-5), 3.84 (m, 1H, H-3), 4.32 (m, 1H, H-4), 4.39 (d, 1H, H-2, $^2J_{2\text{-}1}$= 3.6 Hz), 5.50 (d, 1H, H-1, $^3J_{1\text{-}2}$= 3.6 Hz), 6.8-7.6 (m, 9H, CH=). ^{13}C NMR (400 MHz, C_6D_6) δ: 26.8 (CH_3), 27.1 (CH_3), 32.1 (CH_3, ^{t}Bu), 32.2 (CH_3, ^{t}Bu), 32.3 (CH_3, ^{t}Bu), 34.1 (C-5), 35.2 (C, ^{t}Bu), 36.3 (C, ^{t}Bu), 59.2 (d, C-3, $J_{C\text{-}P}$= 13.9 Hz), 79.4 (d, C-4, $J_{C\text{-}P}$= 3.8 Hz), 86.4 (d, C-2, $J_{C\text{-}P}$= 6.2 Hz), 104.8 (C-1), 111.9 (CMe_2), 124.9 (CH=), 126.3 (CH=), 127.2 (C), 127.7 (C), 129.1 (CH=), 129.7 (CH=), 129.9 (CH=), 131.3 (CH=), 134.5 (C), 134.6 (C), 134.7 (C), 137.1 (C), 140.9 (C), 141.5 (C), 147.2 (C), 147.8 (C), 147.9 (C). Anal. calcd (%) for $C_{42}H_{58}NO_5PS$: C 70.07, H 8.12, N 1.95, S 4.45; found: C 70.02, H 8.10, S 1.93, N 4.42.

L21b: Yield: 274 mg, 41 %. ^{31}P NMR (400 MHz, C_6D_6) δ: 142.3 (s). ^{1}H NMR (400 MHz, C_6D_6) δ: 1.07 (s, 3H, CH_3), 1.29 (s, 3H, CH_3), 1.43 (s, 9H, CH_3, ^{t}Bu), 1.52 (s, 9H, CH_3, ^{t}Bu), 2.79 (m, 1H, NH), 3.14 (m, 2H, H-5' and H-5), 3.82 (s, 3H, CH_3-O), 3.84 (s, 3H, CH_3-O), 3.86 (m, 1H, H-3), 4.14 (m, 1H, H-4), 4.34 (d, 1H, H-2, $^2J_{2\text{-}1}$= 3.6 Hz), 5.53 (d, 1H, H-1, $^3J_{1\text{-}2}$= 3.6 Hz), 6.8-7.6 (m, 9H, CH=). ^{13}C NMR (400 MHz, C_6D_6) δ: 26.4 (CH_3), 26.9 (CH_3), 32.1 (CH_3, ^{t}Bu), 32.2 (CH_3, ^{t}Bu), 33.4 (C-5), 35.2 (C, ^{t}Bu), 36.3 (C, ^{t}Bu), 55.3 (CH_3-O), 56.8 (d, C-3, $J_{C\text{-}P}$= 7.2 Hz), 78.6 (C-4), 85.9 (d, C-2, $J_{C\text{-}P}$= 4.6 Hz), 104.6 (C-1), 112.6 (CMe_2), 124.8 (CH=), 126.3 (CH=), 127.0 (C), 127.7 (C), 129.0 (CH=), 129.9 (CH=), 130.4 (CH=), 131.3 (CH=), 134.5 (C), 134.6 (C), 134.8 (C), 137.3 (C), 140.9 (C), 145.8 (C), 146.9 (C). Anal. calcd (%) for $C_{36}H_{46}NO_7PS$: C 64.75, H 6.94, N 2.10, S 4.80; found: C 64.71, H 6.89, N 2.08, S 4.77.

L21c: Yield: 294 mg, 46 %. ^{31}P NMR (400 MHz, C_6D_6) δ: 147.6 (s). ^{1}H NMR (400 MHz, C_6D_6) δ: 0.34 (s, 9H, CH_3-Si), 0.44 (s, 9H, CH_3-Si), 1.08 (s, 3H, CH_3), 1.29 (s, 3H, CH_3), 2.72 (m, 1H, NH), 3.15 (m, 2H, H-5' and H-5), 3.93 (m, 1H, H-3), 4.36 (m, 1H, H-4), 4.53 (d, 1H, H-2, $^2J_{2\text{-}1}$= 4.0 Hz), 5.56 (d, 1H, H-1, $^3J_{1\text{-}2}$= 4.0 Hz), 6.8-7.6 (m, 11H, CH=). ^{13}C NMR (400 MHz, C_6D_6) δ: 0.8 (CH_3-Si), 0.9 (CH_3-Si), 26.6 (CH_3), 27.1 (CH_3), 33.8 (C-5), 56.2 (C-3), 78.1 (d, C-4, $J_{C\text{-}P}$= 2.4 Hz), 85.9 (d, C-2, $J_{C\text{-}P}$= 9.2 Hz), 103.6 (C-1), 112.3 (CMe_2), 124.9 (CH=), 126.8 (CH=), 127.2 (C), 127.5 (CH=), 127.7 (C), 129.1 (CH=), 129.3 (CH=), 129.4 (CH=), 130.3 (CH=), 131.1 (CH=), 134.2

(C), 134.3 (C), 137.1 (C), 140.9 (C), 141.5 (C), 142.1 (C), 142.3 (C). Anal. calcd (%) for $C_{32}H_{42}NO_5PSSi_2$: C 60.06, H 6.62, N 2.19, S 5.01; found: C 60.01, H 6.59, N 2.17, S 4.98.

L21d: Yield: 198 mg, 40 %. ^{31}P NMR (400 MHz, C_6D_6) δ: 147.1 (s). ^{1}H NMR (400 MHz, C_6D_6) δ: 1.09 (s, 3H, CH_3), 1.21 (s, 3H, CH_3), 2.71 (m, 1H, NH), 3.11 (m, 2H, H-5' and H-5), 3.86 (m, 1H, H-3), 4.36 (m, 1H, H-4), 4.42 (d, 1H, H-2, $^{2}J_{2\text{-}1}$= 3.2 Hz), 5.49 (d, 1H, H-1, $^{3}J_{1\text{-}2}$= 3.2 Hz), 6.8-7.6 (m, 13H, CH=). ^{13}C NMR (400 MHz, C_6D_6) δ: 26.4 (CH_3), 26.6 (CH_3), 35.3 (C-5), 58.7 (d, C-3, $J_{C\text{-}P}$= 7.2 Hz), 80.1 (C-4), 83.6 (d, C-2, $J_{C\text{-}P}$= 3.2 Hz), 103.6 (C-1), 111.8 (CMe_2), 125.8 (CH=), 126.3 (CH=), 127.7 (C), 128.9 (CH=), 129.1 (CH=), 129.7 (CH=), 129.9 (CH=), 130.6 (CH=), 131.3 (CH=), 134.5 (C), 134.6 (C), 137.1 (C). Anal. calcd (%) for $C_{26}H_{26}NO_5PS$: C 63.02, H 5.29, N 2.83, S 6.47; found: C 63.01, H 5.26, N 2.80, S 6.45.

L21e: Yield: 299 mg, 45 %. ^{31}P NMR (400 MHz, C_6D_6) δ: 144.6 (s). ^{1}H NMR (400 MHz, C_6D_6) δ: 1.04 (s, 3H, CH_3), 1.26 (s, 3H, CH_3), 1.54 (s, 9H, CH_3, ^{t}Bu), 1.61 (s, 9H, CH_3, ^{t}Bu), 1.69 (s, 3H, CH_3-Ar), 1.84 (s, 3H, CH_3-Ar), 2.07 (s, 3H, CH_3-Ar), 2.10 (s, 3H, CH_3-Ar), 2.84 (m, 1H, NH), 3.17 (m, 2H, H-5' and H-5), 3.85 (m, 1H, H-3), 4.35 (m, 1H, H-4), 4.38 (d, 1H, H-2, $^{2}J_{2\text{-}1}$= 4.0 Hz), 5.27 (d, 1H, H-1, $^{3}J_{1\text{-}2}$= 4.0 Hz), 6.8-7.5 (m, 7H, CH=). ^{13}C NMR (400 MHz, C_6D_6) δ: 16.8 (CH_3-Ar), 17.1 (CH_3-Ar), 20.6 (CH_3-Ar), 20.8 (CH_3-Ar), 26.5 (CH_3), 27.0 (CH_3), 31.8 (CH_3, ^{t}Bu), 32.4 (CH_3, ^{t}Bu), 33.9 (C-5), 35.2 (C, ^{t}Bu), 35.4 (C, ^{t}Bu), 59.5 (d, C-3, $J_{C\text{-}P}$= 27.9 Hz), 79.0 (C-4), 86.6 (d, C-2, $J_{C\text{-}P}$= 4.7 Hz), 104.5 (C-1), 111.8 (CMe_2), 126.0 (CH=), 126.8 (CH=), 128.9 (C), 129.5 (CH=), 129.7 (CH=), 132.0 (CH=), 132.6 (C), 135.2 (C), 135.5 (C), 136.8 (C), 138.4 (C), 138.6 (C), 145.3 (C), 148.1 (C). Anal. calcd (%) for $C_{38}H_{50}NO_5PS$: C 68.75, H 7.59, N 2.11, S 4.83; found: C 68.72, H 7.58, N 2.07, S 4.80.

L21f: Yield: 265 mg, 40 %. ^{31}P NMR (400 MHz, C_6D_6) δ: 139.2 (s). ^{1}H NMR (400 MHz, C_6D_6) δ: 1.04 (s, 3H, CH_3), 1.27 (s, 3H, CH_3), 1.51 (s, 9H, CH_3, ^{t}Bu), 1.62 (s, 9H, CH_3, ^{t}Bu), 1.68 (s, 3H, CH_3-Ar), 1.84 (s, 3H, CH_3-Ar), 2.04 (s, 3H, CH_3-Ar), 2.10 (s, 3H, CH_3-Ar), 2.51 (m, 1H, NH), 3.14 (m, 2H, H-5' and H-5), 3.83 (m, 1H, H-3), 4.33 (d, 1H, H-2, $^{2}J_{2\text{-}1}$= 3.6 Hz), 4.36 (m, 1H, H-4), 5.62 (d, 1H, H-1, $^{3}J_{1\text{-}2}$= 3.6 Hz), 6.8-7.6 (m, 7H, CH=). ^{13}C NMR (400 MHz, C_6D_6) δ: 16.8 (CH_3-Ar), 17.2 (CH_3-Ar), 20.7 (CH_3-Ar), 20.8 (CH_3-Ar), 26.4 (CH_3), 26.9 (CH_3), 31.9 (CH_3, ^{t}Bu), 32.4 (CH_3, ^{t}Bu), 33.4 (C-5), 35.2 (C, ^{t}Bu), 35.3 (C, ^{t}Bu), 58.4 (d, C-3, $J_{C\text{-}P}$= 6.2 Hz), 79.2 (C-4), 85.9 (d, C-2, $J_{C\text{-}P}$= 7.7 Hz), 104.8 (C-1), 111.5 (CMe_2), 126.0 (CH=), 126.8 (CH=),

128.9 (C), 129.4 (CH=), 129.6 (CH=), 130.7 (CH=), 132.3 (C), 132.8 (C), 135.3 (C), 135.5 (C), 136.8 (C), 137.8 (C), 138.7 (C), 145.4 (C), 148.0 (C). Anal. calcd (%) for $C_{38}H_{50}NO_5PS$: C 68.75, H 7.59, N 2.11, S 4.83; found: C 68.71, H 7.55, N 2.11, S 4.81

L22a: Yield: 261 mg, 49 %. ^{31}P NMR (400 MHz, C_6D_6) δ: 149.0 (s). ^{1}H NMR (400 MHz, C_6D_6) δ: 1.10 (s, 3H, CH_3), 1.25 (s, 9H, CH_3, ^{t}Bu), 1.26 (s, 9H, CH_3, ^{t}Bu), 1.27 (s, 3H, CH_3), 1.58 (s, 9H, CH_3, ^{t}Bu), 1.61 (s, 9H, CH_3, ^{t}Bu), 2.00 (s, 3H, CH_3-S), 2.54 (dd, 1H, H-5', $^3J_{5'-5}$= 14.4 Hz, $^3J_{5'-4}$= 7.2 Hz), 2.93 (dd, 1H, H-5, $^3J_{5'-5}$= 14.4 Hz, $^3J_{5-4}$= 2.4 Hz), 3.19 (m, 1H, NH), 3.48 (m, 1H, H-3), 3.62 (m, 1H, H-2), 3.83 (m, 1H, H-4), 5.47 (d, 1H, H-1, $^3J_{1-2}$= 4.0 Hz), 7.3-7.6 (m, 4H, CH=). ^{13}C NMR (400 MHz, C_6D_6) δ: 17.0 (CH_3-S), 26.3 (CH_3), 26.7 (CH_3), 31.4 (CH_3, ^{t}Bu), 31.6 (CH_3, ^{t}Bu), 31.7 (CH_3, ^{t}Bu), 31.8 (CH_3, ^{t}Bu), 34.6 (C, ^{t}Bu), 34.7 (C, ^{t}Bu), 35.5 (C, ^{t}Bu), 35.7 (C-5), 57.1 (d, C-3, J_{C-P}= 9.4 Hz), 79.8 (C-2), 82.4 (d, C-4, J_{C-P}= 3.1 Hz), 104.0 (C-1), 111.8 (CMe_2), 124.0 (CH=), 124.5 (CH=), 126.5 (CH=), 127.3 (CH=), 133.8 (C), 133.9 (C), 134.2 (C), 134.3 (C), 140.8 (C), 141.0 (C), 146.4 (C), 146.7 (C), 147.3 (C). Anal. calcd (%) for $C_{37}H_{56}NO_5PS$: C 67.55, H 8.58, N 2.13, S 4.87; found: C 67.52, H 8.53, N 2.10, S 4.85.

L23a: Yield: 284 mg, 38 %. ^{31}P NMR (400 MHz, C_6D_6) δ: 148.8 (s). ^{1}H NMR (400 MHz, C_6D_6) δ: 1.01 (s, 3H, CH_3), 1.19 (s, 3H, CH_3), 1.23 (s, 9H, CH_3, ^{t}Bu), 1.27 (s, 9H, CH_3, ^{t}Bu), 1.47 (s, 9H, CH_3, ^{t}Bu), 1.54 (s, 9H, CH_3, ^{t}Bu), 2.53 (s, 6H, CH_3-Ph), 2.55 (m, 1H, NH), 2.79 (dd, 1H, H-5', $^3J_{5'-5}$= 14.0 Hz, $^3J_{5'-4}$= 8.4 Hz), 2.96 (dd, 1H, H-5, $^3J_{5'-5}$= 14.0 Hz, $^3J_{5'-4}$= 5.2 Hz), 3.53 (m, 1H, H-3), 4.09 (m, 1H, H-4), 4.33 (d, 1H, H-2, $^3J_{2-1}$= 4.0 Hz), 5.49 (d, 1H, H-1, $^3J_{1-2}$= 4.0 Hz), 6.8-7.6 (m, 7H, CH=). ^{13}C NMR (400 MHz, C_6D_6) δ: 21.9 (CH_3-Ph), 25.8 (CH_3), 26.1 (CH_3), 31.1 (CH_3, ^{t}Bu), 31.2 (CH_3, ^{t}Bu), 31.3 (CH_3, ^{t}Bu), 31.4 (CH_3, ^{t}Bu), 34.0 (C, ^{t}Bu), 34.2 (C, ^{t}Bu), 34.3 (C, ^{t}Bu), 35.3 (C-5), 58.5 (d, C-3, J_{C-P}= 14.0 Hz), 78.4 (d, C-4, J_{C-P}= 3.1 Hz), 85.4 (d, C-2, J_{C-P}= 7.8 Hz), 103.7 (C-1), 110.8 (CMe_2), 123.8 (CH=), 123.9 (CH=), 126.5 (CH=), 126.7 (CH=), 128.0 (CH=), 128.1 (CH=), 128.4 (C), 128.9 (CH=), 132.9 (C), 133.6 (C), 133.7 (C), 139.9 (C), 140.5 (C), 143.5 (C), 146.1 (C), 146.3 (C), 146.5 (C). Anal. calcd (%) for $C_{44}H_{62}NO_5PS$: C 70.65, H 8.35, N 1.87, S 4.29; found: C 70.59, H 8.32, N, 1.84, S 4.28.

L24a: Yield: 223 mg, 31 %. ^{31}P NMR (400 MHz, C_6D_6) δ: 143.1 (s). ^{1}H NMR (400 MHz, C_6D_6) δ: 1.09 (s, 3H, CH_3), 1.25 (s, 12H, CH_3 and CH_3, ^{t}Bu), 1.27 (s, 9H, CH_3, ^{t}Bu), 1.55 (s, 9H, CH_3, ^{t}Bu), 1.58 (s, 9H, CH_3, ^{t}Bu), 2.99 (dd, 1H, H-5', $^2J_{5'-5}$= 13.2 Hz, $^3J_{5'-4}$= 8.4 Hz), 3.20 (m, 1H, NH), 3.40 (dd, 1H, H-5, $^2J_{5-5'}$= 13.2 Hz, $^3J_{5-4}$= 2.4 Hz), 3.50 (m, 1H, H-3), 3.58 (m, 1H, H-2), 3.87 (m, 1H, H-4), 5.45 (d, 1H, H-1, $^3J_{1-2}$=

3.6 Hz), 6.8-7.6 (m, 9H, CH=). ^{13}C NMR (400 MHz, C_6D_6) δ: 26.3 (CH_3), 26.7 (CH_3), 31.4 (CH_3, ^{t}Bu), 31.5 (CH_3, ^{t}Bu), 31.6 (CH_3, ^{t}Bu), 31.7 (CH_3, ^{t}Bu), 34.6 (C, ^{t}Bu), 34.7 (C, ^{t}Bu), 35.6 (C, ^{t}Bu), 36.1 (C-5), 57.3 (d, C-3, $J_{C\text{-}P}$= 8.5 Hz), 80.0 (d, C-4, $J_{C\text{-}P}$= 2.3 Hz), 80.1 (C-2), 104.0 (C-1), 111.9 (CMe_2), 124.1 (CH=), 124.5 (CH=), 126.1 (CH=), 126.5 (CH=), 127.3 (CH=), 128.5 (CH=), 128.9 (CH=), 129.3 (CH=), 130.1 (CH=), 133.8 (C), 133.9 (C), 134.2 (C), 134.3 (C), 137.8 (C), 140.9 (C), 141.0 (C), 146.4 (C), 146.5 (C), 146.8 (C). Anal. calcd (%) for $C_{42}H_{58}NO_5PS$: C 70.07, H 8.12, N 1.95, S 4.45; found: C 70.04, H 8.11, S 1.93, N 4.44.

L25a: Yield: 198 mg, 31 %. ^{31}P NMR (400 MHz, C_6D_6) δ: 149.0 (s). ^{1}H NMR (400 MHz, C_6D_6) δ: 1.15 (s, 3H, CH_3), 1.31 (s, 9H, CH_3, ^{t}Bu), 1.32 (s, 9H, CH_3, ^{t}Bu), 1.33 (s, 3H, CH_3), 1.64 (s, 9H, CH_3, ^{t}Bu), 1.66 (s, 9H, CH_3, ^{t}Bu), 2.03 (s, 3H, CH_3-S), 2.58 (dd, 1H, H-5', $^3J_{5'\text{-}5}$= 14.0 Hz, $^3J_{5'\text{-}4}$= 7.2 Hz), 2.98 (dd, 1H, H-5, $^3J_{5'\text{-}5}$= 14.0 Hz, $^3J_{5\text{-}4}$= 2.4 Hz), 3.25 (m, 1H, NH), 3.53 (m, 1H, H-3), 3.65 (m, 1H, H-2), 3.87 (m, 1H, H-4), 5.52 (d, 1H, H-1, $^3J_{1\text{-}2}$= 3.6 Hz), 7.3-7.7 (m, 4H, CH=). ^{13}C NMR (400 MHz, C_6D_6) δ: 16.6 (CH_3-S), 25.9 (CH_3), 26.3 (CH_3), 31.0 (CH_3, ^{t}Bu), 31.1 (CH_3, ^{t}Bu), 31.2 (CH_3, ^{t}Bu), 31.4 (CH_3, ^{t}Bu), 34.2 (C, ^{t}Bu), 34.3 (C, ^{t}Bu), 35.1 (C, ^{t}Bu), 35.3 (C-5), 56.7 (d, C-3, $J_{C\text{-}P}$= 10.1 Hz), 79.4 (C-2), 82.0 (d, C-4, $J_{C\text{-}P}$= 3.1 Hz), 103.6 (C-1), 111.3 (CMe_2), 123.7 (CH=), 124.0 (CH=), 126.1 (CH=), 126.9 (CH=), 133.4 (C), 133.5 (C), 133.8 (C), 133.9 (C), 140.4 (C), 140.5 (C), 140.6 (C), 146.0 (C), 146.3 (C), 146.9 (C). Anal. calcd (%) for $C_{37}H_{56}NO_5PS$: C 67.55, H 8.58, N 2.13, S 4.87; found: C 67.53, H 8.55, N 2.12, S 4.83.

L26a: Yield: 299 mg, 40 %. ^{31}P NMR (400 MHz, C_6D_6) δ: 149.1 (s). ^{1}H NMR (400 MHz, C_6D_6) δ: 1.09 (s, 3H, CH_3), 1.22 (s, 9H, CH_3, ^{t}Bu), 1.25 (s, 9H, CH_3, ^{t}Bu), 1.28 (s, 3H, CH_3), 1.50 (s, 9H, CH_3, ^{t}Bu), 1.56 (s, 9H, CH_3, ^{t}Bu), 2.63 (s, 6H, CH_3-Ph), 2.65 (m, 1H, NH), 2.96 (dd, 1H, H-5', $^3J_{5'\text{-}5}$= 14.0 Hz, $^3J_{5'\text{-}4}$= 7.8 Hz), 3.19 (dd, 1H, H-5, $^3J_{5'\text{-}5}$= 14.0 Hz, $^3J_{5\text{-}4}$= 2.0 Hz), 3.36 (m, 1H, H-3), 3.43 (m, 1H, H-2), 3.69 (m, 1H, H-4), 5.43 (d, 1H, H-1, $^3J_{1\text{-}2}$= 3.6 Hz), 6.9-7.6 (m, 7H, CH=). ^{13}C NMR (400 MHz, C_6D_6) δ: 22.4 (CH_3-Ph), 26.3 (CH_3), 26.6 (CH_3), 31.4 (CH_3, ^{t}Bu), 31.6 (CH_3, ^{t}Bu), 31.7 (CH_3, ^{t}Bu), 34.6 (C, ^{t}Bu), 35.6 (C, ^{t}Bu), 37.4 (C-5), 58.5 (d, C-3, $J_{C\text{-}P}$= 6.2 Hz), 79.8 (d, C-4, $J_{C\text{-}P}$= 3.1 Hz), 80.0 (C-2), 103.8 (C-1), 111.7 (CMe_2), 124.0 (CH=), 124.3 (CH=), 126.3 (CH=), 127.4 (CH=), 128.4 (CH=), 128.5 (CH=), 129.3 (CH=), 133.7 (C), 133.8 (C), 134.2 (C), 134.3 (C), 137.8 (C), 140.9 (C), 141.0 (C), 143.7 (C), 146.4 (C), 146.8 (C).

Anal. calcd (%) for $C_{44}H_{62}NO_5PS$: C 70.65, H 8.35, N 1.87, S 4.29; found: C 70.63, H 8.33, N, 1.86, S 4.26.

3.4.4.3. Typical procedure for the preparation of [Ir(cod)(L)]BAr_F (L= L21-L26a-f)

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 product as red-orange solids.

[Ir(cod)(**L21a**)]BAr_F. Yield 67 mg (96 %). ^{31}P NMR ($CDCl_3$), δ: 113.5 (s). ^{1}H NMR ($CDCl_3$), δ: 1.26 (s, 3H, CH_3), 1.36 (s, 18H, CH_3, ^{t}Bu), 1.40 (s, 3H, CH_3), 1.49 (s, 9H, CH_3, ^{t}Bu), 1.69 (s, 9H, CH_3, ^{t}Bu), 1.72 (b, 2H, CH_2, cod), 2.02 (b, 4H, CH_2, cod), 2.26 (b, 2H, CH_2, cod), 3.51 (m, 1H, H-5'), 3.57 (m, 1H, NH), 3.84 (m, 1H, H-5), 3.99 (m, 1H, CH=, cod), 4.27 (m, 2H, H-2 and CH= cod), 4.44 (m, 1H, H-3), 4.76 (m, 2H, H-4 and CH=, cod), 4.94 (m, 1H, CH=, cod), 5.73 (d, 1H, H-1, $^3J_{1\text{-}2}$= 3.2 Hz), 7.0-7.8 (m, 21H, CH= aromatics). ^{13}C NMR ($CDCl_3$), δ: 26.1 (CH_3), 26.4 (CH_3), 27.9 (CH_2, cod), 28.9 (CH_2, cod), 29.8 (CH_2, cod), 31.1 (CH_3, ^{t}Bu), 31.3 (CH_3, ^{t}Bu), 31.5 (CH_3, ^{t}Bu), 33.5 (CH_2, cod), 34.9 (C, tBu), 35.0 (C, tBu), 35.8 (C, tBu), 39.4 (C-5), 57.8 (d, C-3, $J_{C\text{-}P}$= 16.3 Hz), 70.2 (CH=, cod), 75.8 (CH=, cod), 76.0 (C-4), 85.1 (d, C-2, $J_{C\text{-}P}$= 10.8 Hz), 103.6 (d, CH=, cod, $J_{C\text{-}P}$= 14 Hz), 104.4 (d, CH=, cod, $J_{C\text{-}P}$= 13.4 Hz), 104.6 (C-1), 112.9 (CMe_2), 117.5 (b, CH=, BAr_F), 120-134 (aromatic carbons), 134.9 (b, CH=, BAr_F), 139-150 (aromatic carbons), 161.8 (q, C-B, BAr_F, $^1J_{C\text{-}B}$ = 49 Hz). Anal. calc (%) for $C_{82}H_{82}BF_{24}IrNO_5PS$: C 52.29, H 4.39, N 0.74, S 1.70; found: C 52.27, H 4.38, N 0.72, S 1.69.

[Ir(cod)(**L21b**)]BAr_F. Yield 65 mg (98 %). ^{31}P NMR ($CDCl_3$), δ: 113.2 (s). ^{1}H NMR ($CDCl_3$), δ: 1.21 (s, 3H, CH_3), 1.35 (s, 3H, CH_3, ^{t}Bu), 1.38 (s, 3H, CH_3), 1.45 (s, 3H, CH_3, ^{t}Bu), 1.71 (b, 2H, CH_2, cod), 2.03 (b, 4H, CH_2, cod), 2.21 (b, 2H, CH_2, cod), 3.48 (m, 1H, H-5'), 3.52 (m, 1H, NH), 3.66 (m, 1H, H-5), 3.84 (s, 6H, CH_3-O), 4.01 (m, 1H, CH=, cod), 4.24 (m, 1H, H-2), 4.29 (m, 1H, CH= cod), 4.42 (m, 1H, H-3), 4.78 (m, 2H, H-4 and CH=, cod), 4.99 (m, 1H, CH=, cod), 5.69 (d, 1H, H-1, $^3J_{1\text{-}2}$= 3.6 Hz), 7.0-

7.8 (m, 21H, CH= aromatics). ^{13}C NMR ($CDCl_3$), δ: 26.5 (CH_3), 26.7 (CH_3), 28.1 (CH_2, cod), 28.3 (CH_2, cod), 29.4 (CH_2, cod), 31.4 (CH_3, ^{t}Bu), 31.6 (CH_3, ^{t}Bu), 32.6 (CH_2, cod), 35.4 (C, ^{t}Bu), 38.6 (C-5), 55.3 (CH_3-O), 56.4 (d, C-3, $J_{C\text{-}P}$= 7.8 Hz), 69.8 (CH=, cod), 75.4 (CH=, cod), 75.8 (C-4), 84.9 (d, C-2, $J_{C\text{-}P}$= 4.8 Hz), 102.9 (d, CH=, cod, $J_{C\text{-}P}$= 12 Hz), 104.5 (d, CH=, cod, $J_{C\text{-}P}$= 14 Hz), 104.8 (C-1), 112.6 (CMe_2), 117.5 (b, CH=, BAr_F), 120-134 (aromatic carbons), 134.9 (b, CH=, BAr_F), 139-150 (aromatic carbons), 161.8 (q, C-B, BAr_F, $^1J_{C\text{-}B}$ = 49 Hz). Anal. calc (%) for $C_{76}H_{70}BF_{24}IrNO_5PS$: C 49.84, H 3.85, N 0.76, S 1.75; found: C 49.81, H 3.83, N 0.73, S 1.73.

[Ir(cod)(**L21c**)]BAr_F. Yield 63 mg (95 %). ^{31}P NMR ($CDCl_3$), δ: 112.8 (s). ^{1}H NMR ($CDCl_3$), δ: 0.45 (s, 3H, CH_3-Si), 0.51 (s, 3H, CH_3-Si), 1.23 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 1.73 (b, 2H, CH_2, cod), 1.98 (b, 4H, CH_2, cod), 2.23 (b, 2H, CH_2, cod), 3.51 (m, 1H, H-5'), 3.59 (m, 1H, NH), 3.79 (m, 1H, H-5), 3.99 (m, 1H, CH=, cod), 4.19 (m, 1H, CH= cod), 4.23 (m, 1H, H-2), 4.41 (m, 1H, H-3), 4.69 (m, 1H, CH=, cod), 4.73 (m, 1H, H-4), 4.91 (m, 1H, CH=, cod), 5.68 (d, 1H, H-1, $^3J_{1\text{-}2}$= 3.2 Hz), 7.0-7.8 (m, 23H, CH= aromatics). ^{13}C NMR ($CDCl_3$), δ: 0.5 (CH_3-Si), 1.1 (CH_3-Si), 26.2 (CH_3), 26.6 (CH_3), 27.8 (CH_2, cod), 28.7 (CH_2, cod), 29.9 (CH_2, cod), 32.4 (CH_2, cod), 38.3 (C-5), 57.8 (d, C-3, $J_{C\text{-}P}$= 9.2 Hz), 70.1 (CH=, cod), 75.2 (CH=, cod), 76.8 (C-4), 84.9 (d, C-2, $J_{C\text{-}P}$= 4.4 Hz), 103.5 (d, CH=, cod, $J_{C\text{-}P}$= 19 Hz), 103.8 (C-1), 104.2 (d, CH=, cod, $J_{C\text{-}P}$= 16 Hz), 113.5 (CMe_2), 117.5 (b, CH=, BAr_F), 120-134 (aromatic carbons), 134.9 (b, CH=, BAr_F), 139-150 (aromatic carbons), 161.8 (q, C-B, BAr_F, $^1J_{C\text{-}B}$ = 49 Hz). Anal. calc (%) for $C_{72}H_{66}BF_{24}IrNO_5PSSi_2$: C 47.95, H 3.69, N 0.78, S 1.78; found: C 47.93, H 3.65, N 0.75, S 1.77.

[Ir(cod)(**L21d**)]BAr_F. Yield 58 mg (93 %). ^{31}P NMR ($CDCl_3$), δ: 112.8 (s). ^{1}H NMR ($CDCl_3$), δ: 1.26 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 1.72 (b, 2H, CH_2, cod), 2.01 (b, 4H, CH_2, cod), 2.25 (b, 2H, CH_2, cod), 3.42 (m, 1H, NH), 3.54 (m, 1H, H-5'), 3.79 (m, 1H, H-5), 3.98 (m, 1H, CH=, cod), 4.26 (m, 2H, H-2 and CH= cod), 4.41 (m, 1H, H-3), 4.76 (m, 2H, H-4 and CH=, cod), 4.86 (m, 1H, CH=, cod), 5.71 (d, 1H, H-1, $^3J_{1\text{-}2}$= 3.2 Hz), 7.0-7.8 (m, 25H, CH= aromatics). ^{13}C NMR ($CDCl_3$), δ: 26.1 (CH_3), 26.4 (CH_3), 27.4 (CH_2, cod), 29.1 (CH_2, cod), 30.1 (CH_2, cod), 32.4 (CH_2, cod), 38.7 (C-5), 57.6 (d, C-3, $J_{C\text{-}P}$= 14.0 Hz), 70.1 (CH=, cod), 75.3 (CH=, cod), 76.4 (C-4), 85.0 (C-2), 102.4 (d, CH=, cod, $J_{C\text{-}P}$= 14 Hz), 103.4 (C-1), 104.1 (d, CH=, cod, $J_{C\text{-}P}$= 13.2 Hz), 113.2 (CMe_2), 117.5 (b, CH=, BAr_F), 120-134 (aromatic carbons), 134.9 (b, CH=, BAr_F), 139-150 (aromatic carbons), 161.8 (q, C-B, BAr_F, $^1J_{C\text{-}B}$ = 49 Hz). Ana. calc (%) for

$C_{66}H_{50}BF_{24}IrNO_5PS$: C 47.78, H 3.04, N, 0.84, S 1.93; found: C 47.76, H 3.01, N 0.82, S 1.90.

[Ir(cod)(**L21e**)]BAr_F. Yield 66 mg (97 %). ^{31}P NMR ($CDCl_3$), δ: 108.4 (s). ^1H NMR ($CDCl_3$), δ: 1.25 (s, 3H, CH_3), 1.39 (s, 3H, CH_3), 1.44 (s, 9H, CH_3, ^{t}Bu), 1.66 (s, 9H, CH_3, ^{t}Bu), 1.71 (s, 3H, CH_3-Ar), 1.72 (b, 2H, CH_2, cod), 1.83 (s, 3H, CH_3-Ar), 1.95 (b, 4H, CH_2, cod), 2.11 (b, 2H, CH_2, cod), 2.27 (s, 6H, CH_3-Ar), 3.16 (m, 1H, H-5'), 3.52 (m, 1H, NH), 3.71 (m, 1H, CH=, cod), 3.80 (m, 1H, H-5), 4.24 (m, 2H, H-2 and CH= cod), 4.37 (m, 1H, H-3), 4.70 (m, 2H, H-4 and CH=, cod), 4.85 (m, 1H, CH=, cod), 5.73 (d, 1H, H-1, $^3J_{1\text{-}2}$= 4.0 Hz), 7.0-7.8 (m,19, CH= aromatics). ^{13}C NMR ($CDCl_3$), δ: 16.6 (CH_3-Ar), 16.7 (CH_3-Ar), 20.5 (CH_3-Ar), 26.1 (CH_3), 26.4 (CH_3), 28.1 (CH_2, cod), 28.6 (CH_2, cod), 29.9 (CH_2, cod), 31.3 (CH_3, ^{t}Bu), 32.4 (CH_2, cod), 32.8 (CH_3, ^{t}Bu), 35.0 (C, tBu), 39.2 (C-5), 57.5 (d, C-3, $J_{C\text{-}P}$= 13.8 Hz), 70.1 (CH=, cod), 75.8 (CH=, cod), 76.1 (C-4), 85.2 (d, C-2, $J_{C\text{-}P}$= 10.2 Hz), 103.4 (d, CH=, cod, $J_{C\text{-}P}$= 13.5 Hz), 104.0 (d, CH=, cod, $J_{C\text{-}P}$= 16.1 Hz), 104.5 (C-1), 112.8 (CMe_2), 117.5 (b, CH=, BAr_F), 120-134 (aromatic carbons), 134.9 (b, CH=, BAr_F), 139-150 (aromatic carbons), 161.8 (q, C-B, BAr_F, $^1J_{C\text{-}B}$ = 49 Hz). Anal. calc (%) for $C_{78}H_{74}BF_{24}IrNO_5PS$: C 51.26, H 4.08, N 0.77, S 1.75; found: C 51.24, H 4.06, N 0.78, S 1.73.

[Ir(cod)(**L21f**)]BAr_F. Yield 62 mg (96 %). ^{31}P NMR ($CDCl_3$), δ: 101.9 (s). ^1H NMR ($CDCl_3$), δ: 1.23 (s, 3H, CH_3), 1.39 (s, 3H, CH_3), 1.42 (s, 9H, CH_3, ^{t}Bu), 1.67 (b, 2H, CH_2, cod), 1.72 (s, 9H, CH_3, ^{t}Bu), 1.76 (s, 3H, CH_3-Ar), 1.79 (s, 3H, CH_3-Ar), 1.95 (b, 4H, CH_2, cod), 2.11 (b, 2H, CH_2, cod), 2.25 (s, 3H, CH_3-Ar), 2.29 (s, 3H, CH_3-Ar), 2.95 (m, 1H, NH), 3.47 (m, 1H, H-5'), 3.87 (, 1H, CH=, cod), 3.96 (m, 1H, H-5), 4.02 (m, 1H, H-2), 4.18 (m, 1H, CH= cod), 4.19 (m, 1H, H-3), 4.57 (m, 2H, H-4 and CH=, cod), 4.79 (m, 1H, CH=, cod), 5.88 (d, 1H, H-1, $^3J_{1\text{-}2}$= 3.2 Hz), 7.0-7.8 (m,19, CH= aromatics). ^{13}C NMR ($CDCl_3$), δ: 16.6 (CH_3-Ar), 16.7 (CH_3-Ar), 20.5 (CH_3-Ar), 20.7 (CH_3-Ar), 26.1 (CH_3), 26.4 (CH_3), 29.9 (CH_2, cod), 30.5 (CH_2, cod), 30.9 (CH_2, cod), 32.0 (CH_3, ^{t}Bu), 32.4 (CH_3, ^{t}Bu), 32.6 (CH_2, cod), 34.8 (C-5), 35.1 (C, tBu), 64.9 (C-3), 68.9 (CH=, cod), 74.5 (CH=, cod), 80.2 (C-4), 84.3 (C-2), 102.4 (d, CH=, cod, $J_{C\text{-}P}$= 14.0 Hz), 104.1 (d, CH=, cod, $J_{C\text{-}P}$= 13.5 Hz), 104.4 (C-1), 113.1 (CMe_2), 117.5 (b, CH=, BAr_F), 120-134 (aromatic carbons), 134.9 (b, CH=, BAr_F), 139-150 (aromatic carbons), 161.8 (q, C-B, BAr_F, $^1J_{C\text{-}B}$ = 49 Hz). Anal. calc (%) for $C_{78}H_{74}BF_{24}IrNO_5PS$: C 51.26, H 4.08, N 0.77, S 1.75; found: C 51.25, H 4.09, N 0.76, S 1.74.

[Ir(cod)(**L22a**)]BAr_F. Yield 62 mg (91 %). ^{31}P NMR ($CDCl_3$), δ: 111.9 (s). ^1H NMR ($CDCl_3$), δ: 1.24 (s, 3H, CH_3), 1.37 (s, 18H, CH_3, ^{t}Bu), 1.46 (s, 3H, CH_3), 1.51 (s, 9H, CH_3, ^{t}Bu), 1.63 (b, 2H, CH_2, cod), 1.69 (s, 9H, CH_3, ^{t}Bu), 1.89 (b, 2H, CH_2, cod), 2.04 (b, 2H, CH_2, cod), 2.42 (b, 2H, CH_2, cod), 2.84 (s, 3H, CH_3-S), 3.33 (m, 1H, NH), 3.53 (m, 1H, H-5'), 3.70 (m, 1H, H-5), 3.95 (m, 2H, H-2 and CH=, cod), 4.37 (m, 3H, H-3 and 2 x CH= cod), 4.81 (m, 2H, H-4 and CH=, cod), 5.67 (d, 1H, H-1, $^3J_{1\text{-}2}$= 3.2 Hz), 7.0-7.8 (m, 16H, CH= aromatics). ^{13}C NMR ($CDCl_3$), δ: 23.8 (CH_3-S), 25.8 (CH_3), 26.4 (CH_3), 27.3 (CH_2, cod), 29.8 (CH_2, cod), 31.2 (CH_3, ^{t}Bu), 31.5 (CH_3, ^{t}Bu), 31.6 (CH_3, ^{t}Bu), 32.2 (CH_3, ^{t}Bu), 34.9 (C, tBu), 35.0 (C, tBu), 35.7 (CH_2, cod), 35.8 (CH_2, cod), 41.5 (C-5), 59.7 (b, C-3), 67.6 (CH=, cod), 74.7 (C-4), 76.9 (CH=, cod), 85.1 (C-2), 101.8 (d, CH=, cod, $J_{C\text{-}P}$= 13.8 Hz), 104.6 (C-1), 105.9 (d, CH=, cod, $J_{C\text{-}P}$= 14 Hz), 112.8 (CMe_2), 117.6 (b, CH=, BAr_F), 120-134 (aromatic carbons), 134.9 (b, CH=, BAr_F), 139-150 (aromatic carbons), 161.8 (q, C-B, BAr_F, $^1J_{C\text{-}B}$ = 49 Hz). Anal. calc (%) for $C_{77}H_{80}BF_{24}IrNO_5PS$: C 50.77, H 4.43, N 0.77, S 1.76; found: C 50.81, H 4.46, N 0.75, S 1.74.

[Ir(cod)(**L23a**)]BAr_F. Yield 67 mg (95 %). ^{31}P NMR ($CDCl_3$, 218 K), δ: 111.5 (s). ^1H NMR ($CDCl_3$, 218 K), δ: 1.19 (s, 3H, CH_3), 1.30 (s, 9H, CH_3, ^{t}Bu), 1.33 (s, 9H, CH_3, ^{t}Bu), 1.37 (s, 9H, CH_3, ^{t}Bu), 1.56 (s, 3H, CH_3), 1.71 (b, 2H, CH_2, cod), 1.89 (b, 2H, CH_2, cod), 2.11 (b, 2H, CH_2, cod), 2.15 (s, 6H, CH_3-Ph), 2.35 (b, 2H, CH_2, cod), 3.46 (m, 1H, H-5'), 3.55 (m, 1H, NH), 3.96 (m, 1H, H-5), 4.08 (m, 1H, CH=, cod), 4.14 (m, 1H, H-3), 4.34 (m, 1H, CH=, cod), 4.60 (m, 1H, H-4), 4.84 (m, 1H, CH=, cod), 5.16 (m, 1H, CH=, cod), 5.85 (d, 1H, H-1, $^3J_{1\text{-}2}$= 3.2 Hz), 7.1-7.8 (m, 19H, CH= aromatics). ^{13}C NMR ($CDCl_3$, 218 K), δ: 25.7 (CH_3-Ph), 25.8 (CH_3-Ph), 26.1 (CH_3), 26.5 (CH_3), 29.4 (CH_2, cod), 29.9 (CH_2, cod), 31.3 (CH_3, ^{t}Bu), 31.5 (CH_3, ^{t}Bu), 31.6 (CH_3, ^{t}Bu), 34.7 (C, tBu), 35.1 (CH_2, cod), 35.4 (C, tBu), 42.8 (C-5), 56.7 (b, C-3), 64.7 (CH=, cod), 74.4 (C-4), 75.6 (CH=, cod), 89.6 (C-2), 99.2 (b, CH=, cod), 103.9 (C-1), 105.3 (b, CH=, cod), 113.2 (CMe_2), 117.6 (b, CH=, BAr_F), 120-134 (aromatic carbons), 134.9 (b, CH=, BAr_F), 139-150 (aromatic carbons), 161.8 (q, C-B, BAr_F, $^1J_{C\text{-}B}$ = 49 Hz). Anal. calc (%) for $C_{84}H_{86}BF_{24}IrNO_5PS$: C 52.78, H 4.53, N 0.73, S 1.68; found: C 52.75, H 4.51, N 0.70, S 1.69.

[Ir(cod)(**L24a**)]BAr_F. Yield 67 mg (97 %). ^{31}P NMR ($CDCl_3$), δ: 111.3 (s). ^1H NMR ($CDCl_3$), δ: 1.23 (s, 3H, CH_3), 1.35 (s, 18H, CH_3, ^{t}Bu), 1.42 (s, 9H, CH_3, ^{t}Bu), 1.47 (s, 3H, CH_3), 1.65 (b, 2H, CH_2, cod), 1.74 (s, 9H, CH_3, ^{t}Bu), 1.78 (b, 2H, CH_2,

cod), 1.92 (b, 2H, CH_2, cod), 2.15 (b, 2H, CH_2, cod), 3.48 (m, 1H, NH), 3.81 (m, 1H, H-5'), 3.94 (m, 1H, H-3), 3.97 (m, 1H, H-5), 4.09 (m, 3H, H-4 and 2 x CH=, cod), 4.54 (m, 1H, H-2), 4.61 (m, 1H, CH=, cod), 5.06 (b, 1H, CH=, cod), 5.82 (d, 1H, H-1, $^3J_{1\text{-}2}$ = 3.6 Hz), 7.1-7.8 (m, 21H, CH= aromatics). ^{13}C NMR ($CDCl_3$), δ: 26.2 (CH_3), 26.4 (CH_3), 29.9 (CH_2, cod), 30.5 (CH_2, cod), 31.1 (CH_3, ^{t}Bu), 31.5 (CH_3, ^{t}Bu), 31.6 (CH_3, ^{t}Bu), 32.4 (CH_3, ^{t}Bu), 33.5 (CH_2, cod), 33.9 (CH_2, cod), 34.9 (C, tBu), 35.5 (C, tBu), 36.0 (C, tBu), 43.5 (C-5), 57.7 (C-3), 66.6 (CH=, cod), 72.7 (CH=, cod), 75.9 (C-4), 79.3 (C-2), 101.3 (b, CH=, cod), 102.6 (b, CH=, cod), 104.4 (C-1), 113.6 (CMe_2), 117.6 (b, CH=, BAr_F), 120-133 (aromatic carbons), 135.0 (b, CH=, BAr_F), 139-150 (aromatic carbons), 161.9 (q, C-B, BAr_F, $^1J_{C\text{-}B}$ = 49 Hz). Anal. calc (%) for $C_{82}H_{82}BF_{24}IrNO_6PS$: C 52.29, H 4.39, N 0.74, S 1.70; found: C 52.27, H 4.34, N 0.71, S 1.68.

[Ir(cod)(**L25a**)]BAr_F. Yield 65 mg (97 %). ^{31}P NMR ($CDCl_3$), δ: 111.5 (s). ^{1}H NMR ($CDCl_3$), δ: 1.26 (s, 3H, CH_3), 1.34 (s, 9H, CH_3, ^{t}Bu), 1.36 (s, 9H, CH_3, ^{t}Bu), 1.42 (s, 12H, CH_3 and CH_3, ^{t}Bu), 1.60 (s, 9H, CH_3, ^{t}Bu), 1.72 (b, 4H, CH_2, cod), 1.95 (b, 2H, CH_2, cod), 2.11 (b, 2H, CH_2, cod), 2.48 (s, 3H, CH_3-S), 3.45 (m, 1H, H-5'), 3.53 (m, 1H, H-5), 3.91 (m, 1H, H-3), 4.10 (m, 3H, NH, H-4 and CH=, cod), 4.51 (m, 1H, CH= cod), 4.58 (m, 1H, H-2), 4.89 (m, 1H, CH=, cod), 5.17 (m, 1H, CH=, cod), 5.81 (d, 1H, H-1, $^3J_{1\text{-}2}$= 3.6 Hz), 7.0-7.8 (m, 16H, CH= aromatics). ^{13}C NMR ($CDCl_3$), δ: 19.4 (CH_3-S), 26.2 (CH_3), 26.3 (CH_3), 29.9 (CH_2, cod), 30.2 (CH_2, cod), 31.1 (CH_2, cod), 31.4 (CH_3, ^{t}Bu), 31.5 (CH_3, ^{t}Bu), 31.7 (CH_3, ^{t}Bu), 32.0 (CH_3, ^{t}Bu), 34.3 (CH_2, cod), 34.9 (C, tBu), 35.7 (C, tBu), 42.6 (C-5), 57.7 (b, C-3), 73.7 (CH=, cod), 75.5 (CH=, cod), 76.5 (C-4), 78.7 (C-2), 99.3 (d, CH=, cod, $J_{C\text{-}P}$= 15.4 Hz), 99.9 (d, CH=, cod, $J_{C\text{-}P}$= 13.4 Hz), 104.4 (C-1), 113.5 (CMe_2), 117.7 (b, CH=, BAr_F), 120-134 (aromatic carbons), 134.9 (b, CH=, BAr_F), 139-150 (aromatic carbons), 161.8 (q, C-B, BAr_F, $^1J_{C\text{-}B}$ = 49 Hz). Anal. calc (%) for $C_{77}H_{80}BF_{24}IrNO_5PS$: C 50.77, H 4.43, N 0.77, S 1.76; found: C 50.74, H 4.38, N 0.76, S 1.75.

[Ir(cod)(**L26a**)]BAr_F. Yield 65 mg (93 %). ^{31}P NMR ($CDCl_3$), δ: 114.9 (s). ^{1}H NMR ($CDCl_3$), δ: 1.23(s, 3H, CH_3), 1.38 (s, 18H, CH_3, ^{t}Bu), 1.44 (s, 12H, CH_3 and CH_3, ^{t}Bu), 1.65 (s, 9H, CH_3, ^{t}Bu), 1.78 (b, 4H, CH_2, cod), 1.89 (b, 2H, CH_2, cod), 2.06 (b, 2H, CH_2, cod), 2.63 (s, 3H, CH_3-Ph), 2.79 (s, 3H, CH_3-Ph), 3.21 (m, 1H, NH), 3.87 (m, 2H, H-5' and H-5), 4.03 (m, 1H, H-3), 4.08 (m, 1H, CH=, cod), 4.13 (m, 1H, H-4), 4.43 (m, 1H, CH= cod), 4.47 (m, 1H, H-2), 4.81 (m, 1H, CH=, cod), 5.11 (m, 1H, CH=, cod), 5.83 (d, 1H, H-1, $^3J_{1\text{-}2}$= 3.2 Hz), 7.0-7.8 (m, 19H, CH= aromatics). ^{13}C NMR

($CDCl_3$), δ: 22.4 (CH_3-Ph), 23.1 (CH_3-Ph), 26.5 (CH_3), 26.6 (CH_3), 29.8 (CH_2, cod), 30.1 (CH_2, cod), 31.5 (CH_2, cod), 31.8 (CH_3, ^{t}Bu), 32.0 (CH_3, ^{t}Bu), 32.2 (CH_3, ^{t}Bu), 33.1 (CH_2, cod), 34.9 (C, tBu), 35.5 (C, tBu), 43.6 (C-5), 58.6 (b, C-3), 71.6 (CH=, cod), 73.6 (CH=, cod), 75.9 (C-4), 80.2 (C-2), 100.5 (b, CH= cod), 103.2 (b, CH=, cod), 104.1 (C-1), 113.6(CMe_2), 117.7 (b, CH=, BAr_F), 120-134 (aromatic carbons), 134.9 (b, CH=, BAr_F), 139-150 (aromatic carbons), 161.8 (q, C-B, BAr_F, $^1J_{C\text{-}B}$ = 49 Hz). Anal. calc (%) for $C_{84}H_{86}BF_{24}IrNO_5PS$: C 52.78, H 4.53, N 0.73, S 1.68; found: C 52.71, H 4.48, N 0.71, S 1.65.

3.4.4.4. Typical procedure for the hydrogenation of olefins

The alkene (0.5 mmol) and Ir complex (2 mol%) were dissolved in CH_2Cl_2 (2 mL) 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 depressurised 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 ^{1}H NMR or GC and enantiomeric excess was determined by chiral GC or chiral HPLC as previously described.[5n]

3.4.4.5. Synthesis of ligand precursors

3.4.4.5.1. General procedure for the preparation of thioether-triflates 5-7

The corresponding thioether-alcohol (2.5 mmol) was dissolved in CH_2Cl_2 (18 mL) to which pyridine (0.42 mL, 5.6 mmol) was added. The alcohol solution was cooled to -10ºC and Tf_2O (0.6 mL, 3.5 mmol) was added slowly over 2 min aprox. The reaction mixture was stirred at -10 ºC for 1.5 h. Water (20 mL) was added and the product extracted with dichloromethane (3 x 20 mL). The organic phase was then dried over $MgSO_4$ and evaporated to dryness. Petroleum ether (20 mL) was added and the insoluble impurities were removed by filtration. Evaporation of the solution yielded the corresponding triflate.

*1,2-O-Isopropylidene-5-(phenyl)sulfanyl-3-O-trifluoromethanesulfonyl-α-D-ribofuranose (**5**).* Yield: 0.90 g, 90 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.37 (s, 3H, CH_3), 1.54 (s, 3H, CH_3), 3.15 (dd, 1H, H-5', $^2J_{5'\text{-}5}$= 14 Hz, $^3J_{5'\text{-}4}$= 4.8 Hz), 3.38 (dd, 1H, H-5,

$^{2}J_{5'-5}$= 14 Hz, $^{3}J_{5-4}$= 4.4 Hz), 4.43 (m, 1H, H-4), 4.77 (m, 1H, H-2), 4.91(m, 1H, H-3), 5.83 (d, 1H, H-1, $^{3}J_{1-2}$= 4.0 Hz), 7.2-7.5 (m, 5H, CH=).

*1,2-O-Isopropylidene-5-(methyl)sulfanyl-3-O-trifluoromethanesulfonyl-α-D-ribofuranose (**6**).* Yield: 0.52 g, 59 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.38 (s, 3H, CH_3), 1.59 (s, 3H, CH_3), 2.19 (s, 3H, CH_3-S), 2.70 (dd, 1H, H-5', $^{2}J_{5'-5}$= 14.8 Hz, $^{3}J_{5'-4}$= 4.8 Hz), 2.99 (dd, 1H, H-5, $^{2}J_{5'-5}$= 14.8 Hz, $^{3}J_{5-4}$= 4.0 Hz), 4.45 (m, 1H, H-4), 4.77 (m, 1H, H-2), 4.92(m, 1H, H-3), 5.85 (d, 1H, H-1, $^{3}J_{1-2}$= 3.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 17.4 (CH_3-S), 26.6 (CH_3), 26.8 (CH_3), 34.4 (C-5), 76.8 (C-4), 77.4 (C-3), 83.4 (C-2), 104.0 (C-1), 114.4 (CMe_2).

1,2-O-Isopropylidene-5-(2,6-dimethyl-phenyl)sulfanyl-3-O-trifluoromethanesulfonyl-α-D-ribofuranose (7). Yield: 0.87 g, 81 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.32 (s, 3H, CH_3), 1.51 (s, 3H, CH_3), 2.79 (s, 6H, CH_3-Ar), 2.81 (dd, 1H, H-5', $^{2}J_{5'-5}$= 15.2 Hz, $^{3}J_{5'-4}$= 6.8 Hz), 3.08 (dd, 1H, H-5, $^{2}J_{5'-5}$= 15.2 Hz, $^{3}J_{5-4}$= 3.6 Hz), 4.23 (m, 1H, H-4), 4.75 (m, 2H, H-2 and H-3), 5.83 (d, 1H, H-1, $^{3}J_{1-2}$= 3.2 Hz), 7.1-7.3 (m, 3H, CH=). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 22.1 (CH_3-Ar), 26.5 (CH_3), 26.9 (CH_3), 35.5 (C-5), 75.7 (C-4), 77.4 (C-3), 84.0 (C-2), 103.9 (C-1), 114.4 (CMe_2), 128.5 (CH=), 128.9 (CH=), 132.3 (C), 143.3 (C).

3.4.4.5.2. Preparation of 1,2-O-Isopropylidene-5-(2,6-dimethyl-phenyl)sulfanyl-3-O-trifluoromethanesulfonyl-α-D-xylofuranose 13

To a suspension of NaH (2.8 g, 116 mmol) in THF (40 mL) a solution of thiol (2.93 mL, 22 mmol) in THF (30 mL) was added. After 10 min, the suspension was cooled to 0 °C and a solution of 1,2-*O*-isopropylidene-3,5-*O*-bistrifluoromethane-sulfonyl-α-D-xylofuranose (5 g, 11 mmol) in THF (50 mmol) was added. After 1 h, water (250 mL) was added and the THF was evaporated. The crude product was extracted in CH_2Cl_2 (3 x 50 mL), dried with $MgSO_4$ and dried in the rotavapor. The crude was purified by flash chromatography (AcOEt/hexane= 1/10) to produce **12** as a white solid. Yield: 2.8 g, 57 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.32 (s, 3H, CH_3), 1.39 (s, 3H, CH_3), 2.54 (s, 6H, CH_3-Ar), 2.92 (m, 2H, H-5' and H-5), 4.18 (m, 1H, H-4), 4.75 (d, 1H, H-2, $^{3}J_{2-1}$= 3.6 Hz), 5.19 (d, 1H, H-3, $^{3}J_{3-4}$= 3.6 Hz), 5.98 (d, 1H, H-1, $^{3}J_{1-2}$= 3.6 Hz), 7.1-7.3 (m, 3H, CH=). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 22.1 (CH_3-Ar), 26.4 (CH_3),

26.5 (CH_3), 32.2 (C-5), 76.7 (C-4), 83.2 (C-2), 88.7 (C-3), 104.4 (C-1), 113.1 (CMe_2), 128.6 (CH=), 129.1 (CH=), 132.2 (C), 143.6 (C).

3.4.4.5.3. General procedure for the preparation of thioether-azide compounds with xylofuranoside backbone

The corresponding ribofuranoside thioether-triflate (2.17 mmol) was dissolved in DMF (18 mL) to which NaN_3 (0.86 g, 13,2 mmol) was added. The reaction mixture was stirred at room temperature for 24 h. DMF was then evaporated. Water (20 mL) was added and the product extracted with dichloromethane (3 x 20 mL). The organic phase was then dried over $MgSO_4$ and evaporated to dryness. The crude was purified by flash chromatography (AcOEt/hexane= 1/3) to produce the desired xylofuranoside thioether-azide compounds as yellowish oils.

1,2-O-Isopropylidene-5-(phenyl)sulfanyl-3-azido-α-D-xylofuranose. Yield: 0.6 g, 89 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.29 (s, 3H, CH_3), 1.41 (s, 3H, CH_3), 3.10 (dd, 1H, H-5', $^2J_{5'-5}$= 14 Hz, $^3J_{5'-4}$= 9.6 Hz), 3.24 (dd, 1H, H-5, $^2J_{5'-5}$= 14 Hz, $^3J_{5-4}$= 5.6 Hz), 4.00 (d, 1H, H-3, $^3J_{3-4}$= 3.2 Hz), 4.30 (m, 1H, H-4), 4.65 (d, 1H, H-2, $^3J_{2-1}$= 3.6 Hz), 5.86 (d, 1H, H-1, $^3J_{1-2}$= 3.6 Hz), 7.2-7.5 (m, 5H, CH=).

1,2-O-Isopropylidene-5-(methyl)sulfanyl-3-azido-α-D-xylofuranose. Yield: 0.38 g, 72 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.31 (s, 3H, CH_3), 1.51 (s, 3H, CH_3), 2.18 (s, 3H, CH_3-S), 2.72 (dd, 1H, H-5', $^2J_{5'-5}$= 13.6 Hz, $^3J_{5'-4}$= 8.8 Hz), 2.81 (dd, 1H, H-5, $^2J_{5'-5}$= 13.6 Hz, $^3J_{5-4}$= 3.2 Hz), 4.03 (d, 1H, H-3, $^3J_{3-4}$= 3.2 Hz), 4.35 (m, 1H, H-4), 4.66 (d, 1H, H-2, $^3J_{2-1}$= 4.0 Hz), 5.87 (d, 1H, H-1, $^3J_{1-2}$= 4.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 16.5 (CH_3-S), 26.3 (CH_3), 26.7 (CH_3), 32.9 (C-5), 66.6 (C-3), 78.9 (C-4), 83.4 (C-2), 104.7 (C-1), 112.2 (CMe_2).

1,2-O-Isopropylidene-5-(2,6-dimethyl-phenyl)sulfanyl-3-azido-α-D-xylofuranose.
Yield: 0.53 g, 74 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.29 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 2.84 (s, 3H, CH_3-Ar), 2.86 (dd, 1H, H-5', $^2J_{5'-5}$= 13.2 Hz, $^3J_{5'-4}$= 5.6 Hz), 2.96 (dd, 1H, H-5, $^2J_{5'-5}$= 13.2 Hz, $^3J_{5-4}$= 8.8 Hz), 3.86 (d, 1H, H-3, $^3J_{3-4}$= 3.2 Hz), 4.17 (m, 1H, H-4), 4.63 (d, 1H, H-2, $^3J_{2-1}$= 4.0 Hz), 5.84 (d, 1H, H-1, $^3J_{1-2}$= 4.0 Hz), 7.1-7.3 (m, 3H, CH=). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 22.1 (CH_3-Ar), 26.4 (CH_3), 26.6 (CH_3), 33.0

(C-5), 66.8 (C-3), 78.8 (C-4), 83.6 (C-2), 104.5 (C-1), 112.2 (CMe_2), 128.5 (CH=), 128.8 (CH=), 132.4 (C), 143.3 (C).

3.4.4.5.4. General procedure for the preparation of thioether-azide compounds with ribofuranoside backbone

To a heated solution (50 °C) solution of NaN_3 (1.62 g, 25 mmol) and Bu_4NCl (60 mg, 0,22 mmol) in DMF a solution of the corresponding xylofuranoside thioether-triflate (7 mmol) in DMF (16 mL) was slowly added. The reaction mixture was stirred at 50 °C for 24 h. DMF was then evaporated. Water (20 mL) was added and the product extracted with dichloromethane (3 x 20 mL). The organic phase was then dried over $MgSO_4$ and evaporated to dryness. The crude was purified by flash chromatography (AcOEt/hexane= 1/3) to produce the desired ribofuranoside thioether-azide compounds as yellowish oils.

1,2-O-Isopropylidene-5-(phenyl)sulfanyl-3-azido-α-D-ribofuranose. Yield: 0.83 g, 38 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.35 (s, 3H, CH_3), 1.54 (s, 3H, CH_3), 3.18 (dd, 1H, H-5', $^2J_{5'-5}$= 14 Hz, $^3J_{5'-4}$= 3.2 Hz), 3.36 (d, 1H, H-3, $^3J_{3-4}$= 4.4 Hz), 3.42 (dd, 1H, H-5, $^2J_{5'-5}$= 14 Hz, $^3J_{5-4}$= 3.2 Hz), 4.29 (m, 1H, H-4), 4.73 (m, 1H, H-2), 5.81 (d, 1H, H-1, $^3J_{1-2}$= 4.0 Hz), 7.2-7.5 (m, 5H, CH=). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 26.5 (CH_3), 26.6 (CH_3), 35.9 (C-5), 63.6 (C-3), 76.4 (C-4), 80.4 (C-2), 104.2 (C-1), 113.4 (CMe_2), 126.8 (CH=), 129.2 (CH=), 130.0 (CH=), 133.1 (C).

1,2-O-Isopropylidene-5-(methyl)sulfanyl-3-azido-α-D-ribofuranose. Yield: 0.74 g, 43 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.34 (s, 3H, CH_3), 1.55 (s, 3H, CH_3), 2.17 (s, 3H, CH_3-S), 2.70 (dd, 1H, H-5', $^2J_{5'-5}$= 14.4 Hz, $^3J_{5'-4}$= 5.2 Hz), 2.93 (dd, 1H, H-5, $^2J_{5'-5}$= 14.4 Hz, $^3J_{5-4}$= 3.6 Hz), 3.43 (m, 1H, H-3), 4.26 (m, 1H, H-4), 4.73 (m, 1H, H-2), 5.79 (d, 1H, H-1, $^3J_{1-2}$= 3.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 17.4 (CH_3-S), 26.4 (CH_3), 26.5 (CH_3), 35.4 (C-5), 62.9 (C-3), 77.5 (C-4), 80.1 (C-2), 104.0 (C-1), 113.2 (CMe_2).

1,2-O-Isopropylidene-5-(2,6-dimethyl-phenyl)sulfanyl-3-azido-α-D-ribofuranose. Yield: 1.0 g, 43 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.35 (s, 3H, CH_3), 1.51 (s, 3H, CH_3), 2.717 (s, 6H, CH_3-Ar), 2.79 (dd, 1H, H-5', $^2J_{5'-5}$= 13.6 Hz, $^3J_{5'-4}$= 6.4 Hz), 3.12 (dd, 1H, H-5, $^2J_{5'-5}$= 13.6 Hz, $^3J_{5-4}$= 2.0 Hz), 3.38 (m, 1H, H-3), 4.12 (m, 1H, H-4), 4.73 (m, 1H, H-2), 5.81 (d, 1H, H-1, $^3J_{1-2}$= 4.0 Hz), 7.1-7.3 (m, 3H, CH=). ^{13}C NMR (100 MHz,

$CDCl_3$) δ: 22.1 (CH_3-Ar), 26.4 (CH_3), 26.7 (CH_3), 36.5 (C-5), 63.4 (C-3), 76.3 (C-4), 80.3 (C-2), 104.2 (C-1), 113.3 (CMe_2), 128.4 (CH=), 128.8 (CH=), 132.8 (C), 143.3 (C).

3.4.4.5.5. General procedure for the preparation of thioether-amines 8-10 and 14-16

To a suspension of $LiAlH_4$ (0.45 g, 11,8 mmol) in Et_2O (16.5 mL) a solution of the corresponding thioether-azide (3 mmol) in Et_2O (16.5 mL) was slowly added. The reaction mixture was stirred at 35 °C for 2 h. The mixture was then cooled to 0 °C and water (0.45 mL), AcOEt (0.45 mL) and water (1.35 mL) were sequentially and slowly added. The reaction mixture was stirred for 20 minutes. The formed insoluble salts were then removed by filtration. The resulting solution was dried over $MgSO_4$ and evaporated to dryness. The crude was purified by flash chromatography (CH_2Cl_2/MeOH= 10/1) to produce the desired thioether-amines.

1,2-O-Isopropylidene-5-(phenyl)sulfanyl-3-amino-α-D-xylofuranose (***8***). Yield: 0.55 g, 65 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.29 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 3.11 (dd, 1H, H-5', $^2J_{5'-5}$= 13.2 Hz, $^3J_{5'-4}$= 8.8 Hz), 3.31 (dd, 1H, H-5, $^2J_{5'-5}$= 13.2 Hz, $^3J_{5-4}$= 5.6 Hz), 3.53 (d, 1H, H-3, $^3J_{3-4}$= 3.2 Hz), 4.31 (m, 1H, H-4), 4.49 (d, 1H, H-2, $^3J_{2-1}$= 3.6 Hz), 5.92 (d, 1H, H-1, $^3J_{1-2}$= 3.6 Hz), 7.2-7.5 (m, 5H, CH=). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 26.3 (CH_3), 26.7 (CH_3), 32.0 (C-5), 57.4 (C-3), 78.4 (C-4), 86.0 (C-2), 104.5 (C-1), 111.9 (CMe_2), 127.0 (CH=), 129.3 (CH=), 130.5 (CH=), 135.0 (C).

1,2-O-Isopropylidene-5-(methyl)sulfanyl-3- amino-α-D-xylofuranose (***9***). Yield: 0.36 g, 55 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.26 (s, 3H, CH_3), 1.47 (s, 3H, CH_3), 2.15 (s, 3H, CH_3-S), 2.66 (dd, 1H, H-5', $^2J_{5'-5}$= 12.8 Hz, $^3J_{5'-4}$= 8.8 Hz), 2.78 (dd, 1H, H-5, $^2J_{5'-5}$= 12.8 Hz, $^3J_{5-4}$= 6.4 Hz), 3.41 (d, 1H, H-3, $^3J_{3-4}$= 3.2 Hz), 4.27 (m, 1H, H-4), 4.38 (d, 1H, H-2, $^3J_{2-1}$= 4.0 Hz), 5.83 (d, 1H, H-1, $^3J_{1-2}$= 4.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 16.2 (CH_3-S), 26.1 (CH_3), 26.7 (CH_3), 31.9 (C-5), 57.5 (C-3), 78.9 (C-4), 86.6 (C-2), 104.4 (C-1), 111.4 (CMe_2).

1,2-O-Isopropylidene-5-(2,6-dimethyl-phenyl)sulfanyl-3-amine-α-D-xylofuranose (***10***). Yield: 0.63 g, 68 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.28 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 2.57 (s, 3H, CH_3-Ar), 2.89 (m, 2H, H-5' and H-5), 3.37 (d, 1H, H-3, $^3J_{3-4}$= 2.4

Hz), 4.15 (m, 1H, H-4), 4.33 (d, 1H, H-2, $^{3}J_{2\text{-}1}$= 4.0 Hz), 5.83 (d, 1H, H-1, $^{3}J_{1\text{-}2}$= 4.0 Hz), 7.1-7.3 (m, 3H, CH=). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 22.2 (CH_3-Ar), 26.3 (CH_3), 26.6 (CH_3), 32.9 (C-5), 57.7 (C-3), 79.2 (C-4), 86.8 (C-2), 104.3 (C-1), 111.6 (CMe_2), 128.4 (CH=), 128.7 (CH=), 132.7 (C), 143.3 (C).

*1,2-O-Isopropylidene-5-(phenyl)sulfanyl-3-amino-α-D-ribofuranose (**14**).* Yield: 0.26 g, 32 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.33 (s, 3H, CH_3), 1.51 (s, 3H, CH_3), 3.12 (m, 1H, H-3), 3.23 (dd, 1H, H-5', $^{2}J_{5'\text{-}5}$= 13.6 Hz, $^{3}J_{5'\text{-}4}$= 5.6 Hz), 3.33 (dd, 1H, H-5, $^{2}J_{5'\text{-}5}$= 13.6 Hz, $^{3}J_{5\text{-}4}$= 4.4 Hz), 3.89 (m, 1H, H-4), 4.49 (m, 1H, H-2), 5.79 (d, 1H, H-1, $^{3}J_{1\text{-}2}$= 3.6 Hz), 7.2-7.5 (m, 5H, CH=). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 26.5 (CH_3), 26.7 (CH_3), 35.8 (C-5), 58.3 (C-3), 76.6 (C-4), 80.8 (C-2), 104.2 (C-1), 112.1 (CMe_2), 126.2 (CH=), 129.0 (CH=), 129.4 (CH=), 136.5 (C).

*1,2-O-Isopropylidene-5-(methyl)sulfanyl-3-amino-α-D-ribofuranose (**15**).* Yield: 0.34 g, 52 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.32 (s, 3H, CH_3), 1.52 (s, 3H, CH_3), 2.17 (s, 3H, CH_3-S), 2.72 (dd, 1H, H-5', $^{2}J_{5'\text{-}5}$= 14.0 Hz, $^{3}J_{5'\text{-}4}$= 5.6 Hz), 2.86 (dd, 1H, H-5, $^{2}J_{5'\text{-}5}$= 14.0 Hz, $^{3}J_{5\text{-}4}$= 4.0 Hz), 3.06 (m, 1H, H-3), 3.83 (m, 1H, H-4), 4.46 (m, 1H, H-2), 5.77 (d, 1H, H-1, $^{3}J_{1\text{-}2}$= 4.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 17.1 (CH_3-S), 26.5 (CH_3), 26.7 (CH_3), 35.8 (C-5), 58.4 (C-3), 80.7 (C-4), 81.0 (C-2), 104.1 (C-1), 111.9 (CMe_2).

*1,2-O-Isopropylidene-5-(2,6-dimethyl-phenyl)sulfanyl-3-amine-α-D-ribofuranose (**16**).* Yield: 0.58 g, 66 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.33 (s, 3H, CH_3), 1.48 (s, 3H, CH_3), 2.54 (s, 6H, CH_3-Ar), 2.82 (dd, 1H, H-5', $^{2}J_{5'\text{-}5}$= 13.2 Hz, $^{3}J_{5'\text{-}4}$= 6.4 Hz), 3.04 (m, 2H, H-5 and H-3), 3.74 (m, 1H, H-4), 4.52 (m, 1H, H-2), 5.80 (d, 1H, H-1, $^{3}J_{1\text{-}2}$= 4.0 Hz), 7.1-7.3 (m, 3H, CH=). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 22.3 (CH_3-S), 26.7 (CH_3), 37.0 (C-5), 58.3 (C-3), 77.5 (C-4), 80.6 (C-2), 104.2 (C-1), 112.3 (CMe_2), 128.3 (CH=), 128.6 (CH=), 133.4 (C), 143.4 (C).

3.4.5. Acknowledgements

We would like to thank the Spanish Government for providing 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.

3.4.6. References

[1] a) *Asymmetric Catalysis in Industrial Scale: Challenges, Approaches and Solutions*; eds. Blaser, H. U.; Schmidt, E.; Wiley:Weinheim, Germany, **2003**; b) Ojima, I. in *Catalytic Asymmetric Synthesis*; Wiley-VCH: New York, **2000**; c) Brown, J. M. in *Comprehensive Asymmetric Catalysis*; eds. Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H.; Springer-Verlag: Berlin, **1999**; Vol. I, pp 121-182; d) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, **1994**.

[2] For recent reviews, see: a) Källström, K.; Munslow, I.; Andersson, P. G. *Chem. Eur. J.* **2006**, *12*, 3194; b) Roseblade, S. J.; Pfaltz, A. *Acc. Chem. Res.* **2007**, *40*, 1402; c) Church, T. L.; Andersson, P. G. *Coord. Chem. Rev.* **2008**, *252*, 513; d) Cui, X.; Burgess, K. *Chem. Rev.* **2005**, *105*, 3272; e) Pàmies, O.; Andersson, P. G.; Diéguez, M. *Chem. Eur. J.* **2010**, *16*, 14232; f) Woodmansee, D. H.; Pfaltz, A. *Chem. Commun.* **2011**, *47*, 7912.

[3] Lighfoot, A.; Schnider, P.; Pfaltz, A. *Angew. Chem. Int. Ed.* **1998**, *37*, 3897.

[4] Crabtree, R. H. *Acc. Chem. Res.* **1979**, *12*, 331.

[5] See for instance: (a) Drury III, W. J.; Zimmermann, N.; Keenan, M.; Hayashi, M.; Kaiser, S.; Goddard, R.; Pfaltz, A. *Angew. Chem. Int. Ed.* **2004**, *43*, 70; b) Perry, M. C.; Cui, X.; Powell, M. T.; Hou, D.-R.; Reibenspies, J. H.; Burgess, K. *J. Am. Chem. Soc.* **2003**, *125*, 5391; c) Blankestein, J.; Pfaltz, A. *Angew. Chem. Int. Ed.* **2001**, *40*, 4445; d) Kaiser, S.; Smidt, S. P.; Pfaltz, A. *Angew. Chem. Int. Ed.* **2006**, *45*, 5194; e) Källström, K.; Hedberg, C.; Brandt, P.; Bayer, P.; Andersson, P. G. *J. Am. Chem. Soc.* **2004**, *126*, 14308; f) Diéguez, M.; Mazuela, J.; Pàmies, O.; Verendel, J. J.; Andersson, P. G. *J. Am. Chem. Soc.* **2008**, *130*, 7208; g) Diéguez, M.; Mazuela, J.; Pàmies, O.; Verendel, J. J.; Andersson, P. G. *Chem. Commun.* **2008**, 3888; h) Mazuela, J.; Verendel, J. J.; Coll, M.; Schäffner, B.; Börner, A.; Andersson, P. G.; Pàmies, O.; Diéguez, M. *J. Am. Chem. Soc.* **2009**, *131*, 12344; i) Mazuela, J.; Paptchikhine, A.; Pàmies, O.; Andersson, P. G.; Diéguez, M. *Chem. Eur. J.* **2010**, 16, 4567; j) Zhao, J.; Burgess, K. *J. Am. Chem. Soc.* **2009**, *131*, 13236; k) Wang, A.; Fraga, R. P. A.; Hormann, E.; Pfaltz, A. *Chem. Asian J.* **2011**, *6*, 599; l) Lu, S.-M.; Bolm, C. *Angew. Chem. Int. Ed.* **2008**, *47*, 8920; m) Lu, W.-J.; Chen, Y.-W.; Hou, X.-L. *Adv. Synth. Catal.* **2010**, *352*, 103; n) Mazuela, J.; Norby, P. O.; Andersson, P. G.; Pàmies, O.; Diéguez, M. *J. Am. Chem. Soc.* **2011**, *133*, 13634.

[6] Coll, M. ; Pàmies, O. ; Diéguez M. *Chem. Commun.* **2011**, *47*, 9215.

[7] See for example: a) Diéguez, M.; Pàmies, O.; Claver, C. *Chem. Rev.* **2004**, *104*, 3189; b) Woodward, S.; Diéguez, M.; Pàmies, O. *Coord. Chem. Rev.* **2010**, *254*, 2007; c) Diéguez, M.; Pàmies, O.; Ruiz, A.; Díaz, Y.; Castillón, S.; Claver, C. *Coord. Chem. Rev.* **2004**, *248*, 2165; d) Diéguez, M.; Ruiz, A.; Claver, C. *Dalton Trans.* **2003**, 2957; e) Castillón, S.; Díaz, Y.; Claver, C. *Chem. Soc. Rev.* **2005**, *34*, 702; f) Diéguez, M.; Claver, C.; Pàmies, O. *Eur. J. Org. Chem.* **2007**, 4621; g) Woodward, S.; Diéguez, M.; Pàmies, O. *Coord. Chem. Rev.* **2010**, *254*, 2007; h) Boysen, M. M. K. *Chem. Eur. J.* **2007**, *13*, 8648; i) Benessere, V.; Del Litto, R.; De Roma, A.; Ruffo, F. *Coord. Chem. Rev.* **2010**, *254*, 390; j) van Leeuwen, P.W.N.M.; Kamer, P.C.J.; Claver, C.; Pàmies, O.; Diéguez, M. *Chem. Rev.* **2011**, *111*, 2077; k) Claver, C.; Pàmies, O.; Diéguez, M. in *Phosphorus Ligands in Asymmetric Catalysis*; ed. Börner, A.; Wiley-VCH, Weinheim, **2008**; Vol. 2, pp 506-528.

[8] Compounds **11** and **12** have been previously reported in the literature, see: Pàmies, O.; Diéguez, M.; Net, G.; Ruiz, A.; Claver, C. *J. Chem. Soc., Dalton Trans.* **1999**, 3439.

[9] Pàmies, O.; Net, G.; Ruiz, A.; Bo, C.; Poblet, J. M.; Claver, C. *J. Organomet. Chem.* **1999**, *586*, 125.

[10] For successful application of Ir-catalysts, see: a) McIntyre, S.; Hörmann, E.; Menges, F.; Smidt, S. P.; Pfaltz, A. *Adv. Synth. Catal.* **2005**, *347*, 282; b) ref. 5h.

[11] For successful applications of Sm-, Ru- and Rh-complexes, see: a) Conticello, V. P.; Brard, L.; Giardello, M. A.; Tsuji, Y.; Sabat, M.; Stern, C. L.; Marks, T. J. *J. Am. Chem. Soc.* **1992**, *114*, 2761; b) Giardello, M. A.; Conticello, V. P.; Brard, L.; Gagné, M. R.; Marks, T. J. *J. Am. Chem. Soc.* **1994**, *116*, 10241; c) Co, T. T.; Kim, T. J. *Chem. Commun.* **2006**, 3537; d) Forman, G. S.; Ohkuma, T.; Hems, W. P.; Noyori, R. *Tetrahedron Lett.* **2000**, *41*, 9471.

[12] Buisman, G. J. H.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Tetrahedron: Asymmetry* **1993**, *4*, 1625.

[13] See Section 3.3.

UNIVERSITAT ROVIRA I VIRGILI
SUGAR-BASED LIGAND LIBRARIES FOR ASYMMETRIC REDUCTIONS AND C-C BOND FORMING REACTIONS
M. Mercè Coll Serrahima
DL:T. 150-2012

CHAPTER 4

Asymmetric transfer hydrogenation of ketones

UNIVERSITAT ROVIRA I VIRGILI
SUGAR-BASED LIGAND LIBRARIES FOR ASYMMETRIC REDUCTIONS AND C-C BOND FORMING REACTIONS
M. Mercè Coll Serrahima
DL:T. 150-2012

4. Asymmetric transfer hydrogenation of ketones

4.1. Background

The enantioselective reduction of prochiral ketones has emerged as an efficient and direct synthetic tool for preparing enantiopure secondary alcohols, which are important precursors for synthesizing natural, pharmaceutical and agricultural products. In this context, asymmetric metal-catalyzed transfer hydrogenation (ATH) is an alternative method that is operationally simpler and significantly safer than direct hydrogenation with molecular hydrogen.[1] The most commonly used catalysts in transfer hydrogenations are based on transition metal catalysts (i.e ruthenium, rhodium, or iridium complexes) modified with monosulfonated diamines, β-amino alcohols, or 2-(aminomethyl)pyridines as chiral ligands.[1] Recently, iron-based catalysts have also shown useful activity and selectivity.[2] Nowadays, many types of chiral ligands have been developed, some of which have been successfully applied in selective transfer hydrogenation. In this context, Adolfsson's group reported that amino acid-derived pseudo-dipeptides **1** and thioamides **2** (Figure 4.1.1) in combination with Ru or Rh half-sandwich complexes are excellent catalysts for the ATH of aryl-alkyl ketones.[3] These ligands are based on the combination of different *N*-Boc-protected α-amino acids and β-amino alcohols (for type **1**) or on thioamides (for type **2**), respectively. Both showed the advantage of possessing a modular ligand building block: the amino acid part.

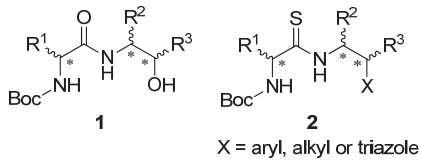


Figure 4.1.1. General structure of pseudo-dipeptide ligands **1** and thioamide ligands **2**.

Despite all these important contributions, there is still a lack of a catalyst able to provide the desired secondary alcohols in enantiopure form (>99% ee) for a broad range of substrates as the enzymes do. The most successful catalysts developed to date afford the desired alcohols in a range of 95-99% ee. Therefore, the development of extremely enantioselective ATH catalysts containing ligands based on simple starting materials

and that have high modularity still need to be further explored. For this purpose, carbohydrates are particularly useful because they are cheap, they have several stereogenic centers and their modular constructions are easy. Despite this advantages, carbohydrate-based ligands have hardly been used for this transformation and in all the examples low-to-moderate enantioselectivities (<78% ee) have been reported.

In this chapter, we therefore report the synthesis and application of several carbohydrate-based, pseudo-dipeptide and thioamide ligand libraries in the Rh and Ru-catalyzed asymmetric transfer hydrogenation of prochiral ketones. More specifically, in section 4.2 we describe the successfully evaluation of a new pseudo-dipeptide ligand library (**L28**-**L30a-i**) in the Ru-catalyzed ATH of several ketones. The ligand library is based on the combination of various *N*-Boc-protected α-amino acids and a sugar amino alcohol unit. Interestingly, we have demonstrated that the introduction of a furanoside amino sugar moiety into the ligand design is highly advantageous and it efficiently transfers the chiral information to the products (ee's ranging from 98% to >99% in the reduction of a range of ketones). In contrast to previous successful pseudo-dipeptides, the enantioselectivity is exclusively controlled by the sugar moiety which enables the use of inexpensive achiral or racemic α-amino acid derivatives. Moreover, catalysts formed with the carbohydrate-based pseudo-dipeptides showed a higher degree of substrate versatility than the corresponding pseudo-dipeptides analogues **1**. Finally in section 4.3, we describe the preparation and evaluation of two new carbohydrate-based libraries of 36 potential pseudo-dipeptides and 36 potential thioamide ligands. The first set (ligands **L31**-**L34a-i**) is based on the previous sugar-based pseudo-dipeptide ligands (**L28**-**L30a-i**), in which a 1,3-amino alcohol sugar core was used instead of a classical 1,2-amino alcohol motif. In the second set (carbohydrate-thioamide **L35**-**L38a-i** ligands), the peptide bond in the previous ligands **L31**-**L34a-i** was converted to a thioamide group. As well as being prepared from commercially available D-(+)-glucose or D-(+)-xylose, both ligand libraries also have the advantage of a flexible ligand scaffold. With these libraries, then, we investigated the effect of systematically varying the position of the amino acids/thioamide groups at either C-5 (ligands **L31**-**L32** and **L35**-**L36**) or C-3 (ligands **L33**-**L34** and **L37**-**L38**) of the furanoside backbone, the configuration at C-3 of the furanoside backbone and substituents/configurations (**a-i**) in the amino acid/thioamide moieties. By carefully selecting the ligand components, we have developed the first carbohydrate-based thioamide ligand library that provides high

enantioselectivity in a broad range of aryl-alkyl ketones (ee's up to 99%). It should be noted that both enantiomers of alcohol products can be obtained with high enantioselectivities by simply changing the absolute configuration of the thioamide substituent.

4.1.1. References

[1] See, for instance: a) Noyori, R.; Hashiguchi, S. *Acc. Chem. Res.* **1997**, *30*, 97; b) Naota, T.; Takaya, H.; Murahashi, S. I. *Chem. Rev.* **1998**, *98*, 2599; c) Gladiali, S.; Alberico, E. *Chem. Soc. Rev.* **2006**, *35*, 226; d) Wang, C.; Wu, X.; Xiao, J. *Chem. Asian J.* **2008**, *3*, 1750.

[2] Junge, K.; Schröder, K.; Beller, M. *Chem. Commun.* **2011**, *47*, 4849.

[3] See, for example: a) Zaitsev, A. B.; Adolfsson, H. *Org. Lett.* **2006**, *8*, 5129. b) Pastor, I. M.; Västilä, P.; Adolfsson, H. *Chem. Commun.* **2002**, 2046.

UNIVERSITAT ROVIRA I VIRGILI
SUGAR-BASED LIGAND LIBRARIES FOR ASYMMETRIC REDUCTIONS AND C-C BOND FORMING REACTIONS
M. Mercè Coll Serrahima
DL:T. 150-2012

4.2. Carbohydrate-based pseudo-dipeptides: New ligands for the highly enantioselective Ru-catalyzed transfer hydrogenation reaction

Mercedes Coll, Oscar Pàmies, Hans Adolfsson and Montserrat Diéguez in *Chem. Commun.* **2011**, *47*, 12188 and full manuscript in preparation.

Abstract: Ruthenium-complexes of novel carbohydrate based pseudo-dipeptide ligands effectively and selectively catalyze the reduction of a broad range of aryl-alkyl ketones under ATH conditions. Excellent enantioselectivitites (>99% ee) are obtained using amino sugars as the sole source of chirality.

4.2.1. Introduction

The value of enantiopure secondary alcohols lies mainly in their use as important building blocks for the synthesis of natural, pharmaceutical and agricultural products.[1] The enantioselective reduction of prochiral ketones has emerged as an efficient and direct synthetic tool for preparing these compounds. In this context, asymmetric metal-catalyzed transfer hydrogenation (ATH) is an alternative method that is operationally simpler and significantly safer than direct hydrogenation with molecular hydrogen.[2] The most commonly used catalysts in transfer hydrogenations are based on transition metal catalysts (i.e ruthenium, rhodium, or iridium complexes) modified with monosulfonated diamines,[3,4] β-amino alcohols,[5] or 2-(aminomethyl)pyridines[6] as chiral ligands.[7] Recently, iron-based catalysts have also shown useful activity and selectivity.[8]

Adolfsson et al. have reported the use of a new type of ligand **1** —pseudo-dipeptides— (Figure 4.2.1) for the enantioselective transfer hydrogenation of a broad range of aryl-alkyl ketones.[9] These ligands are based on the combination of different *N*-Boc-protected α-amino acids and β-amino alcohols. The fundamental difference between previously described successful catalysts and these pseudo-dipeptide counterparts is the lack of a basic NH group in the latter's ligand structure. The main features of ligands **1** are that: (i) the presence of a chiral α-amino acid is crucial if significant levels of enantioselectivity are to be achieved. However, the

enantioselectivity value is dictated by the combination of substituents/configurations in both the amino acid and the amino alcohol parts;[9] and (ii) the sense of enantioselectivity is controlled by the configuration in the amino acid part. Catalysts based on L-amino acids, then, predominantly gave (*S*)-configuration products while the use of ligands based on D-amino acids resulted in the formation of the (*R*)-alcohols as the major enantiomer.[9] Despite all these important contributions, there is still a lack of a catalyst able to provide the desired secondary alcohols in enantiopure form (>99% ee) for a broad range of substrates as the enzymes do. The most successful catalysts developed to date afford the desired alcohols in a range of 95-99% ee.[2] Therefore, the development of extremely enantioselective ATH catalysts containing ligands based on simple starting materials and that have high modularity still need to be further explored.

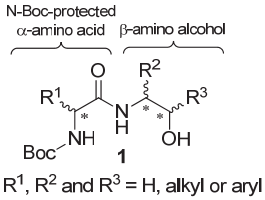
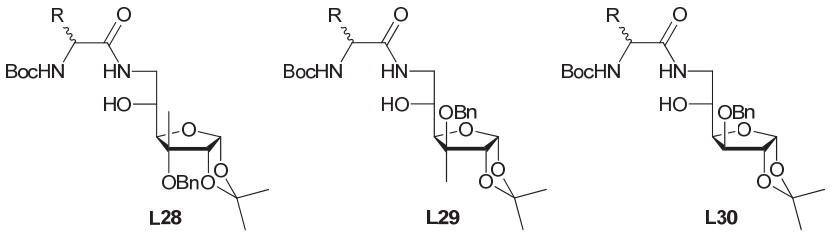


Figure 4.2.1. General structure of pseudo-dipeptide ligands **1**.

One of the simplest ways to synthesize chiral ligands is to rely on nature to provide appropriate chiral synthons. For this purpose, carbohydrates are particularly useful because they are cheap, they have several stereogenic centers and their modular constructions are easy. In this respect, carbohydrates have become an important natural source for preparing chiral ligand libraries, which have been successfully applied in several metal-catalyzed asymmetric transformations.[10,11] Despite this success, carbohydrate-based ligands have hardly been used for this transformation and in all the examples low-to-moderate enantioselectivities (<78% ee) have been reported.[12]

In this communication, we describe a new class of pseudo-dipeptide ligands (**L28-L30a-i**), derived from carbohydrates, for the highly enantioselective Ru-catalyzed transfer hydrogenation of a broad range of substrates (Figure 4.2.2). The main benefit of incorporating the sugar core is that excellent enantioselectivitites (typically >99% ee) can be obtained using the sugar amino alcohol part as a sole source of chirality. This feature allows for the use of non-enantiopure α-amino acid derivatives (even achiral or racemic ones).



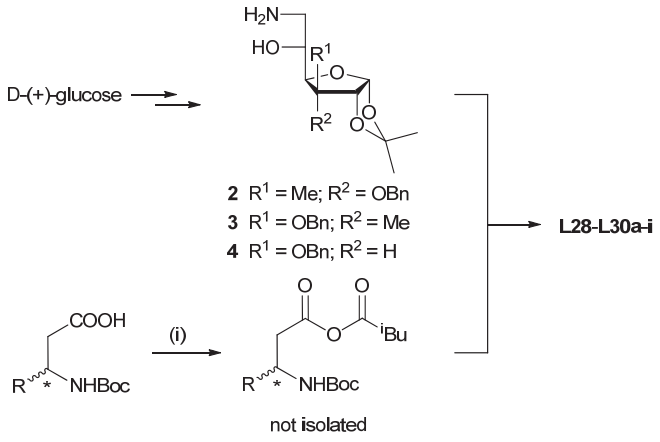
a R = (*S*)-^{i}Pr; **b** R = (*S*)-Ph; **c** R = (*S*)-Bn; **d** R = (*S*)-^{i}Bu; **e** R = (*S*)-^{t}Bu;
f R = (*S*)-Me; **g** R = H; **h** R = (*R*)-^{i}Pr; **i** R = (*R*)-Ph

Figure 4.2.2. Carbohydrate-based pseudo-dipeptide ligands **L28-L30a-i**.

4.2.2. Results and Discussions

4.2.2.1. Synthesis of the carbohydrate-based pseudo-dipeptide ligands L28-L30a-i

The synthesis of the carbohydrate-based pseudo-dipeptide ligands **L28-L30a-i** is straightforward (Scheme 4.2.1). They were efficiently prepared by coupling a series of *N*-Boc protected amino acids with the corresponding sugar amino alcohols **2-4** by using isobutyl chloroformate in the presence of *N*-methylmorpholine (Scheme 4.2.1).[9b,c] Sugar amino alcohols **2-4** are readily prepared on a large scale from inexpensive D-(+)-glucose.



Scheme 4.2.1. Synthesis of ligands **L28-L30a-i**. (i) ^{i}BuOCOCl/ NMM / THF / -15 °C.

4.2.2.2. Asymmetric transfer hydrogenation of acetophenone S1

To initially evaluate these new ligands (**L28-L30a-i**), we chose the Ru-catalyzed ATH of acetophenone **S1**. As this reaction was carried out with a wide variety of ligands bearing different donor groups, we were able to compare the efficacy of the various ligand systems. The results are summarized in Table 4.2.1.

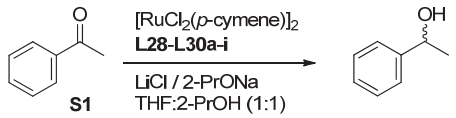
We first investigated the effect of the α-amino acid substituents on the catalytic performance with ligands **L28a-f**. We found that enantioselectivities were excellent (>99% ee) in all cases (Table 4.2.1, entries 1-5). The results indicate that varying the α-amino acid substituent does not affect enantioselectivity. However, our results also indicate that activity is affected by these α-amino acid substituents. The highest activities were obtained with catalysts based on ligands **L28a**, **c** and **f**.

Interestingly, changing the configuration of the α-amino acid from *S* (ligand **L28a**) to *R* (ligand **L28h**) inhibits the catalytic activity almost completely (Table 4.2.1, entries 1 *vs* 6 and 7). This result prompted us to study whether high levels of enantioselectivity can be maintained by introducing an achiral or racemic α-amino acid moiety into the ligand design. For this purpose we evaluated ligand **L28g**, derived from glycine, and a 1:1 mixture of **L28a** and **L28h** ligands (Table 4.2.1, entries 8 and 9), respectively. In both cases enantioselectivities were excellent (99% ee). This is unprecedented behavior which confirms that the enantioselectivity is dictated by the sugar amino alcohol part. The results contrast with the "cooperative" effect between the substituents/configurations at both the amino alcohol and the α-amino acid moieties previously observed for other successful pseudo-dipeptide ligands.[9] On the other hand, the configuration of the amino acid has an impact on the conversion, therefore, it has to be matched to the configuration of the carbohydrate part for constructing efficient ligands.

The use of ligand **L29a**, with opposite configuration at C-3 of the furanoside backbone in comparison to **L28a**, has no effect on activity and enantioselectivity (Table 4.2.1, entry 1 vs 10). This result encouraged us to study whether high ee's can also be achieved using 3-benzyl amino alcohol **4** derived ligands (**L30a** and **L30g**), which are synthesized in fewer steps than corresponding ligands derived from amino alcohols **2** and **3**. We were pleased to find out that again excellent enantioselectivities were obtained using ligands **L30a** and **L30g** (Table 4.2.1, entries 11 and 12).

We also performed the reaction at higher temperature (50 ºC) using ligand **L28a** (entry 13). Activity increased considerably (up to 98% conversion in 30 minutes), and the excellent enantioselectivity was maintained (>99% ee (*S*)).

Table 4.2.1. Ru-catalyzed asymmetric transfer hydrogenation reaction of **S1** using ligands **L28-L30a-i**.[a]



Entry	Ligand	mol% Ru	T (ºC)	% Conv (h)[b]	% ee[b]
1	**L28a**	0.25	25	80 (3)	>99 (*S*)
2	**L28b**	0.25	25	42 (3)	>99 (*S*)
3	**L28c**	0.25	25	81 (3)	>99 (*S*)
4	**L28e**	0.25	25	49 (3)	>99 (*S*)
5	**L28f**	0.25	25	80 (3)	>99 (*S*)
6	**L28h**	0.25	25	1 (3)	n.d.
7	**L28h**	1	25	6 (3)	6 (*S*)
8	**L28g**	0.25	25	56 (3)	99 (*S*)
9	**L28a+L28h**	0.25	25	48 (3)	99 (*S*)
10	**L29a**	0.25	25	78 (3)	>99 (*S*)
11	**L30a**	0.25	25	79 (3)	>99 (*S*)
12	**L30g**	0.25	25	51 (3)	99 (*S*)
13	**L28a**	0.25	50	98 (0.5)	>99 (*S*)
14[c]	**L28a**	0.25	25	21 (3)	98.7 (*S*)
15[c]	**L28h**	1	25	2 (3)	4 (*R*)

[a] Reaction conditions: **S1** (1 equiv, 0.2M in 2-propanol/THF (1:1), $[RuCl_2(p\text{-cymene})]_2$ (0.25 mol% in Ru), ligand (0.55 mol%), NaO^iPr (5 mol%), LiCl (10 mol%) and at room temperature. [b] Conversion and enantiomeric excess was determined by GC. [c] No LiCl added.

Finally, we evaluated the efficiency of these catalysts without the addition of LiCl (entries 14 and 15). The results are in line with the decrease in activity and enantioselectivity previously observed using pseudo-dipeptides **1**, which suggest a

similar coordination mode, and mechanism for the ATH reaction.[9f] The reason for the change in enantiocontrol is most likely due to interactions between the ligand and the *p*-cymene when the Ru-hydride complex is formed.

4.2.2.3. Asymmetric transfer hydrogenation of other ketones

Encouraged by the excellent results obtained up to this point, and in order to study the potential of these readily available ligands further, we evaluated them in the ATH of other ketones (**S2**-**S12**). The results are summarized in Figure 4.2.3 (for more results, see supporting information). We found that the combination of $[RuCl_2(p\text{-cymene})]_2$ and **L28a** or **L30a**, respectively, efficiently catalyze the ATH of several other aryl-alkyl ketones. The results show that the catalytic performance (activity and enantioselectivity) is not affected by the steric and electronic properties of the aryl group, except for substrates **S5**, **S9** and **S12**, which required higher catalyst loadings (1 mol% of $[RuCl_2(p\text{-cymene})]_2$) to achieve good conversions. This behavior contrasts with the electronic and steric effect on enantioselectivity observed for previous pseudo-dipeptide ligands.[9] Furthermore, enantioselectivities were excellent (up to >99 %) in all cases, surpassing the enantioselectivies obtained with previous successful pseudo-dipeptide ligands.[9]

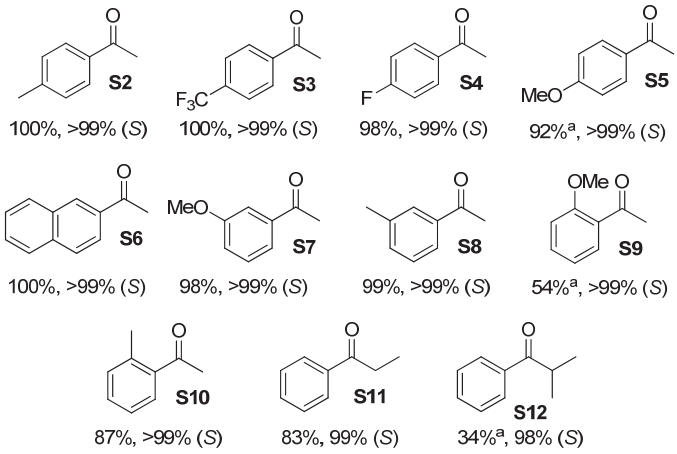


Figure 4.2.3. Selected asymmetric transfer hydrogenation results. Reaction conditions: 0.25 mol% $[RuCl_2(p\text{-cymene})]_2$, 0.55 mol% **L28a**, 1 mmol substrate, 3 h at room temperature. [a] 1 mol% of $[RuCl_2(p\text{-cymene})]_2$, 24 h.

4.2.3. Conclusions

In summary, we have successfully designed and evaluated a new pseudo-dipeptide ligand library in the Ru-catalyzed ATH of several ketones. The ligand library is based on the combination of various *N*-Boc-protected α-amino acids and a sugar amino alcohol unit. Interestingly, we have demonstrated that the introduction of a furanoside amino sugar moiety into the ligand design is highly advantageous and it efficiently transfers the chiral information to the products (ee's ranging from 98% to >99% in the reduction of a range of ketones). In contrast to previous successful pseudo-dipeptides, the enantioselectivity is exclusively controlled by the sugar moiety which enables the use of inexpensive achiral or racemic α-amino acid derivatives. Moreover, catalysts formed with the carbohydrate-based pseudo-dipeptides showed a higher degree of substrate versatility than the corresponding pseudo-dipeptides analogues **1**. These novel carbohydrate pseudo-dipeptide compounds constitute therefore an exceptional ligand system that favorably competes in terms of enantioselectivity with other successful catalytic systems including enzymatic kinetic resolution (KR) and dynamic kinetic resolution (DKR).[2,13] Because of the modular construction of these carbohydrate-based ligands, structural diversity is easy to achieve, so activities and enantioselectivities can be maximized for other substrates as required. Further studies of this kind, as well as mechanistic studies, are currently under way.

4.2.4. Experimental Section

4.2.4.1. General considerations

All reactions were carried out using standard Schlenk techniques under an atmosphere of argon. Solvents were purified and dried by standard procedures. Compounds 3-*O*-benzyl-3-*C*-methyl-1,2-*O*-isopropylidene-6-*O*-tosyl-α-D-allofuranose[14], 3-*O*-benzyl-3-*C*-methyl-1,2-*O*-isopropyilidene-α-D-glucofuranose[15] and 6-azido-6-deoxy-3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-glucofuranose[16] were prepared as previously described. ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra were recorded using a 400 MHz spectrometer. Chemical shifts are relative to that of $SiMe_4$ as internal standard. ^{1}H and ^{13}C assignments were done based on ^{1}H-^{1}H gCOSY and ^{1}H-^{13}C gHSQC experiments.

4.2.4.2. Typical procedure for the preparation of ligands L28-L30a-i

To a cooled solution (-15 °C) of the desired *N*-Boc-protected amino acid (1 mmol) in THF (2 mL) *N*-methylmorpholine (NMM, 1.15 mmol, 126 μL) and isobutylchloroformate (1.15 mmol, 150 μL) were slowly added. After 45 minutes, a solution of sugar amino alcohol (1 mmol) in THF (2 mL) was added and the resulting mixture was stirred at room temperature for 2 h. The crude mixture was purified by flash chromatography to produce the corresponding ligands as white solids.

L28a: Yield: 382 mg, 73 %. ^{1}H NMR ($CDCl_3$), δ: 0.86 (d, 3H, CH_3, ^{i}Pr, $^3J_{H-H}$= 6.8 Hz), 0.91 (d, 3H, CH_3, ^{i}Pr, $^3J_{H-H}$= 7.2 Hz), 1.33 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 1.39 (s, 9H, CH_3, ^{t}Bu), 1.57 (s, 3H, CH_3), 2.07 (m, 1H, CH, ^{i}Pr), 2.89 (b, 1H, OH), 3.39 (m, 1H, H-6'), 3.59 (m, 1H, H-6), 3.80 (m, 1H, H-5), 3.87 (m, 2H, H-4 and CH), 4.34 (d, 1H, H-2, $^3J_{2-1}$= 3.6 Hz), 4,61 (s, 2H, CH_2, Bn), 5.18 (b, 1H, NH), 5.71 (d, 1H, H-1, $^3J_{1-2}$= 3.6 Hz), 6.49 (b, 1H, NH), 7.2-7.4 (m, 5H, CH=). ^{13}C NMR ($CDCl_3$), δ: 16.6 (CH_3), 17.9 (CH_3, ^{i}Pr), 19.4 (CH_3, ^{i}Pr), 26.7 (CH_3), 26.9 (CH_3), 28.5 (CH_3, ^{t}Bu), 31.2 (CH, ^{i}Pr), 43.4 (C-6), 60.0 (CH), 67.2 (CH_2, Bn), 68.8 (C-5), 79.7 (C, ^{t}Bu), 79.9 (C-4), 82.8 (C-2), 83.4 (C-3), 104.2 (C-1), 113.2 (CMe_2), 127.8 (CH=), 127.9 (CH=), 128.4 (CH=), 138.1 (C), 155.9 (CO), 172.1 (CO). Anal. calcd (%) for $C_{27}H_{42}N_2O_8$: C 62.05, H 8.10, N 5.36; found: C 62.11, H 8.13, N 5.32.

L28b: Yield: 241 mg, 45 %. ^{1}H NMR ($CDCl_3$), δ: 1.25 (s, 3H, CH_3), 1.32 (s, 3H, CH_3), 1.37 (s, 9H, CH_3, ^{t}Bu), 1.52 (s, 3H, CH_3), 2.89 (b, 1H, OH), 3.34 (m, 1H, H-6'), 3.52 (m, 1H, H-6), 3.71 (m, 1H, H-5), 3.80 (m, 1H, H-4), 4.32 (d, 1H, H-2, $^3J_{2-1}$= 3.6 Hz), 4.57 (m, 2H, CH_2, OBn), 5.09 (m, 1H, CH), 5.60 (d, 1H, H-1, $^3J_{1-2}$= 3.6 Hz), 5.92 (b, 1H, NH), 6.27 (b, 1H, NH), 7.2-7.4 (m, 10H, CH=). ^{13}C NMR ($CDCl_3$), δ: 16.3 (CH_3), 26.5 (CH_3), 26.7 (CH_3), 28.2 (CH_3, ^{t}Bu), 43.5 (C-6), 58.3 (CH), 67.0 (CH_2, Bn), 68.3 (C-5), 79.6 (C, ^{t}Bu), 79.8 (C-4), 82.5 (C-2), 83.2 (C-3), 104.0 (C-1), 113.2 (CMe_2), 124.9 (C), 127.1 (CH=), 127.7 (CH=), 127.8 (CH=), 128.1 (CH=), 128.3 (CH=), 128.9 (CH=), 137.8 (C), 155.1 (CO), 170.3 (CO). Anal. calcd (%) for $C_{30}H_{40}N_2O_8$: C 64.73, H 7.24, N 5.03; found: C 64.78, H 7.26, N 4.99.

L28c: Yield: 422 mg, 74 %. ^{1}H NMR ($CDCl_3$), δ: 1.30 (s, 3H, CH_3), 1.32 (s, 3H, CH_3), 1.35 (s, 9H, CH_3, ^{t}Bu), 1.55 (s, 3H, CH_3), 2.72 (b, 1H, OH), 3.01 (m, 2H, CH_2), 3.23 (m, 1H, H-6'), 3.53 (m, 1H, H-6), 3.66 (m, 1H, H-5), 3.82 (m, 1H, H-4), 4.39 (m, 1H, CH), 4.32 (d, 1H, H-2, $^3J_{2-1}$= 3.6 Hz), 4.59 (m, 2H, CH_2, OBn), 5.15 (b, 1H, NH),

5.65 (d, 1H, H-1, $^3J_{1\text{-}2}$= 3.6 Hz), 6.31 (b, 1H, NH), 7.1-7.4 (m, 10H, CH=). ^{13}C NMR ($CDCl_3$), δ: 18.8 (CH_3), 26.5 (CH_3), 26.7 (CH_3), 28.2 (CH_3, ^{t}Bu), 38.9 (CH_2), 43.6 (C-6), 60.4 (CH), 67.0 (CH_2, Bn), 68.7 (C-5), 75.9 (C, ^{t}Bu), 79.8 (C-4), 82.6 (C-2), 83.3 (C-3), 104.1 (C-1), 113.1 (CMe_2), 126.7 (CH=), 127.7 (CH=), 128.3 (CH=), 128.5 (CH=), 129.3 (CH=), 136.7 (C), 137.9 (C), 155.1 (CO), 171.1 (CO). Anal. calcd (%) for $C_{31}H_{42}N_2O_8$: C 65.24, H 7.42, N 4.91; found: C 65.13, H 7.40, N 4.87.

L28e: Yield: 241 mg, 45 %. ^{1}H NMR ($CDCl_3$), δ: 0.92 (s, 9H, CH_3, ^{t}Bu), 1.31 (s, 3H, CH_3), 1.32 (s, 3H, CH_3), 1.38 (s, 9H, CH_3, ^{t}Bu), 1.55 (s, 3H, CH_3), 2.78 (b, 1H, OH), 3.41 (m, 1H, H-6'), 3.50 (m, 1H, H-6), 3.75 (m, 2H, H-5 and CH), 3.86 (m, 1H, H-4), 4.33 (d, 1H, H-2, $^3J_{2\text{-}1}$= 4.0 Hz), 4.60 (m, 2H, CH_2, Bn), 5.34 (b, 1H, NH), 5.68 (d, 1H, H-1, $^3J_{1\text{-}2}$= 4.0 Hz), 6.32 (b, 1H, NH), 7.2-7.4 (m, 5H, CH=). ^{13}C NMR ($CDCl_3$), δ: 16.4 (CH_3), 26.5 (CH_3), 26.6 (CH_3, ^{t}Bu), 26.8 (CH_3), 28.3 (CH_3, ^{t}Bu), 34.5 (C, ^{t}Bu), 43.3 (C-6), 62.3 (CH), 67.0 (CH_2, Bn), 68.6 (C-5), 79.4 (C, ^{t}Bu), 79.8 (C-4), 82.7 (C-2), 83.3 (C-3), 104.0 (C-1), 113.0 (CMe_2), 127.6 (CH=), 127.7 (CH=), 128.3 (CH=), 137.9 (C), 155.5 (CO), 171.2 (CO). Anal. calcd (%) for $C_{28}H_{44}N_2O_8$: C 62.67, H 8.26, N 5.22; found: C 62.79, H 8.34, N 5.30.

L28f: Yield: 400 mg, 81 %. ^{1}H NMR ($CDCl_3$), δ: 1.29 (d, 3H, CH_3, $^3J_{H\text{-}H}$= 6.8 Hz), 1.32 (s, 6H, CH_3), 1.39 (s, 9H, CH_3, ^{t}Bu), 1.56 (s, 3H, CH_3), 2.79 (b, 1H, OH), 3.32 (m, 1H, H-6'), 3.56 (m, 1H, H-6), 3.78 (m, 1H, H-5), 3.80 (m, 1H, H-4), 4.13 (m, 1H, CH), 4.33 (d, 1H, H-2, $^3J_{2\text{-}1}$= 3.6 Hz), 4.61 (m, 2H, CH_2, Bn), 5.37 (b, 1H, NH), 5.69 (d, 1H, H-1, $^3J_{1\text{-}2}$= 3.6 Hz), 6.60 (b, 1H, NH), 7.2-7.4 (m, 5H, CH=). ^{13}C NMR ($CDCl_3$), δ: 16.4 (CH_3), 18.8 (CH_3), 26.5 (CH_3), 26.7 (CH_3), 28.2 (CH_3, ^{t}Bu), 43.4 (C-6), 60.4 (CH), 67.0 (CH_2, Bn), 68.7 (C-5), 79.6 (C-4), 79.7 (C, ^{t}Bu), 82.6 (C-2), 83.2 (C-3), 104.0 (C-1), 113.0 (CMe_2), 127.6 (CH=), 128.3 (CH=), 137.9 (C), 155.3 (CO), 171.1 (CO). Anal. calcd (%) for $C_{25}H_{38}N_2O_8$: C 60.71, H 7.74, N 5.66; found: C 60.79, H 7.79, N 5.62.

L28g: Yield: 240 mg, 50 %. ^{1}H NMR ($CDCl_3$), δ: 1.31 (s, 6H, CH_3), 1.39 (s, 9H, CH_3, ^{t}Bu), 1.55 (s, 3H, CH_3), 2.41 (b, 1H, OH), 3.25 (m, 1H, H-6'), 3.61 (m, 1H, H-6), 3.75 (m, 2H, CH_2), 3.78 (m, 1H, H-5), 3.86 (m, 1H, H-4), 4.32 (d, 1H, H-2, $^3J_{2\text{-}1}$= 3.6 Hz), 4.58(m, 2H, CH_2, Bn), 5.38 (b, 1H, NH), 5.68 (d, 1H, H-1, $^3J_{1\text{-}2}$= 3.6 Hz), 6.70 (b, 1H, NH), 7.2-7.4 (m, 5H, CH=). ^{13}C NMR ($CDCl_3$), δ: 16.3 (CH_3), 26.5 (CH_3), 26.7 (CH_3), 28.3 (CH_3, ^{t}Bu), 43.4 (C-6), 44.0 (CH_2), 66.9 (CH_2, Bn), 68.7 (C-5), 79.7 (C-4), 79.9 (C, ^{t}Bu), 82.7 (C-2), 83.3 (C-3), 104.0 (C-1), 113.0 (CMe_2), 127.6 (CH=), 127.7

(CH=), 128.3 (CH=), 138.0 (C), 156.0 (CO), 169.9 (CO). Anal. calcd (%) for $C_{24}H_{36}N_2O_8$: C 59.98, H 7.55, N 5.83; found: C 60.01, H 7.58, N 5.85.

L28h: Yield: 402 mg, 78 %. ^{1}H NMR ($CDCl_3$), δ: 0.85 (d, 3H, CH_3, ^{i}Pr, $^3J_{H\text{-}H}$= 7.2 Hz), 0.89 (d, 3H, CH_3, ^{i}Pr, $^3J_{H\text{-}H}$= 7.2 Hz), 1.31 (s, 3H, CH_3), 1.33 (s, 3H, CH_3), 1.39 (s, 9H, CH_3, ^{t}Bu), 1.57 (s, 3H, CH_3), 2.02 (m, 1H, CH, ^{i}Pr), 2.72 (b, 1H, OH), 3.31 (m, 1H, H-6'), 3.59 (m, 1H, H-6), 3.77 (m, 1H, H-5), 3.86 (m, 2H, H-4 and CH), 4.33 (d, 1H, H-2, $^3J_{2\text{-}1}$= 3.6 Hz), 4.60 (m, 2H, CH_2, Bn), 5.19 (b, 1H, NH), 5.69 (d, 1H, H-1, $^3J_{1\text{-}2}$= 3.6 Hz), 6.45 (b, 1H, NH), 7.2-7.4 (m, 5H, CH=). ^{13}C NMR ($CDCl_3$), δ: 16.3 (CH_3), 18.7 (CH_3, ^{i}Pr), 26.5 (CH_3), 26.7 (CH_3), 28.3 (CH_3, ^{t}Bu), 30.8 (CH, ^{i}Pr), 43.3 (C-6), 58.5 (CH), 67.0 (CH_2, Bn), 68.7 (C-5), 79.9 (C, ^{t}Bu), 82.6 (C-4), 83.2 (C-2), 83.3 (C-3), 104.1 (C-1), 113.1 (CMe_2), 127.6 (CH=), 127.7 (CH=), 128.3 (CH=), 138.0 (C), 155.9 (CO), 171.9 (CO). Anal. calcd (%) for $C_{27}H_{42}N_2O_8$: C 62.05, H 8.10, N 5.36; found: C 62.13, H 8.14, N 5.33.

L29a: Yield: 415 mg, 79 %. ^{1}H NMR ($CDCl_3$), δ: 0.87 (d, 3H, CH_3, ^{i}Pr, $^3J_{H\text{-}H}$= 6.8 Hz), 0.93 (d, 3H, CH_3, ^{i}Pr, $^3J_{H\text{-}H}$= 7.2 Hz), 1.28 (s, 3H, CH_3), 1.38 (s, 9H, CH_3, ^{t}Bu), 1.48 (s, 3H, CH_3), 1.52 (s, 3H, CH_3), 2.01 (m, 1H, CH, ^{i}Pr), 3.35 (m, 1H, H-6'), 3.67 (m, 1H, H-6), 3.82 (m, 1H, H-4), 3.91 (m, 1H, H-3), 4.01 (m, 1H, CH), 4.09 (m, 1H, H-5), 4.42 (d, 1H, H-2, $^3J_{2\text{-}1}$= 3.6 Hz), 4.52 (d, 1H, CH_2, Bn, $^3J_{2\text{-}1}$= 12.4 Hz), 4.65 (d, 1H, CH_2, Bn, $^3J_{2\text{-}1}$= 12.4 Hz), 5.24 (b, 1H, NH), 5.79 (d, 1H, H-1, $^3J_{1\text{-}2}$= 3.6 Hz), 6.82 (b, 1H, NH), 7.2-7.4 (m, 5H, CH=). ^{13}C NMR ($CDCl_3$), δ: 15.4 (CH_3), 18.7 (CH_3, ^{i}Pr), 19.0 (CH_3, ^{i}Pr), 26.4 (CH_3), 27.0 (CH_3), 28.3 (CH_3, ^{t}Bu), 30.9 (CH, ^{i}Pr), 44.7 (C-6), 60.1 (CH), 65.2 (CH_2, Bn), 69.1 (C-5), 69.7 (C, ^{t}Bu), 75.7 (C-4), 83.4 (C-2), 84.6 (C-3), 104.4 (C-1), 112.0 (CMe_2), 126.7 (CH=), 127.4 (CH=), 128.3 (CH=), 138.7 (C), 155.9 (CO), 174.0 (CO). Anal. calcd (%) for $C_{27}H_{42}N_2O_8$: C 62.09, H 8.11, N 5.35; found: C 62.11, H 8.13, N 5.32.

L30a: Yield: 392 mg, 77 %. ^{1}H NMR ($CDCl_3$), δ: 0.88 (d, 3H, CH_3, ^{i}Pr, $^3J_{H\text{-}H}$= 6.8 Hz), 0.95 (d, 3H, CH_3, ^{i}Pr, $^3J_{H\text{-}H}$= 7.2 Hz), 1.27 (s, 3H, CH_3), 1.39 (s, 9H, CH_3, ^{t}Bu), 1.42 (s, 3H, CH_3), 2.11 (m, 1H, CH, ^{i}Pr), 3.36 (b, 1H, OH), 3.62 (m, 1H, H-6'), 3.82 (m, 1H, H-6), 3.91 (m, 1H, H-5), 4.02 (m, 2H, H-4 and CH), 4.56 (d, 1H, H-2, $^3J_{2\text{-}1}$= 4.0 Hz), 4.58 (d, 1H, CH_2, Bn, ^3J= 10.6 Hz), 4.65 (d, 1H, CH_2, Bn, ^3J= 10.6 Hz), 5.16 (b, 1H, NH), 5.87 (d, 1H, H-1, $^3J_{1\text{-}2}$= 4.0 Hz), 6.71 (b, 1H, NH), 7.2-7.4 (m, 5H, CH=). ^{13}C NMR ($CDCl_3$), δ: 18.7 (CH_3, ^{i}Pr), 19.2 (CH_3, ^{i}Pr), 26.2 (CH_3), 26.7 (CH_3), 28.4 (CH_3, ^{t}Bu), 30.9 (CH, ^{i}Pr), 44.1 (C-6), 60.0 (CH), 68.1 (CH_2, Bn), 71.8 (C, ^{t}Bu), 72.4 (C-5),

80.5 (C-4), 81.6 (C-2), 82.4 (C-3), 105.1 (C-1), 111.7 (CMe_2), 127.8 (CH=), 127.9 (CH=), 128.5 (CH=), 137.5 (C), 155.8 (CO), 172.0 (CO). Anal. calcd (%) for $C_{26}H_{40}N_2O_8$: C 61.44, H 7.97, N 5.56; found: C 61.40, H 7.93, N 5.51.

L30g: Yield: 294 mg, 63 %. ^{1}H NMR ($CDCl_3$), δ: 1.34 (s, 3H, CH_3), 1.39 (s, 9H, CH_3, ^{t}Bu), 1.42 (s, 3H, CH_3), 2.49 (b, 1H, OH), 3.45 (m, 1H, H-6'), 3.65 (m, 1H, H-6), 3.86 (m, 1H, H-5), 3.92 (m, 1H, H-4), 3.99 (m, 1H, CH), 4.43 (d, 1H, H-2, $^3J_{2\text{-}1}$= 3.6 Hz), 4.62 (m, 2H, CH_2, Bn), 5.21 (b, 1H, NH), 5.79 (d, 1H, H-1, $^3J_{1\text{-}2}$= 3.6 Hz), 6.73 (b, 1H, NH), 7.2-7.4 (m, 5H, CH=). ^{13}C NMR ($CDCl_3$), δ: 16.8 (CH_3), 26.4 (CH_3), 27.1 (CH_3), 28.3 (CH_3, ^{t}Bu), 43.9 (C-6), 44.3 (CH_2), 66.7 (CH_2, Bn), 68.9 (C-5), 79.4 (C-4), 79.7 (C, ^{t}Bu), 83.2 (C-2), 83.5 (C-3), 104.3 (C-1), 112.7 (CMe_2), 127.7 (CH=), 127.9 (CH=), 128.2 (CH=), 138.4 (C), 155.8 (CO), 171.2 (CO). Anal. calcd (%) for $C_{23}H_{34}N_2O_8$: C 59.24, H 7.41, N 5.97; found: C 59.21, H 7.35, N 6.00.

4.2.4.3. Synthesis of sugar amino alcohols 2-4

Synthesis of 6-azido-6-deoxy-1,2-O-isopropylidene-3-C-methyl-3-benzyl-α-allofuranose.

To a solution of 3-O-benzyl-3-C-methyl-1,2-O-isopropylidene-6-O-tosyl-α-D-allofuranose (10 mmol, 4.78 g) in DMF (100 mL), sodium azide (12 mmol, 0.78 g) was added. The solution was stirred at 90 °C overnight. Then, DMF was removed by evaporation in vacuo and water (25 mL) was added. The mixture was extracted with dichloromethane (3 x 50 mL) and the organic phase dried over $MgSO_4$. The dried extract was evaporated and purified by flash chromatography (ethyl acetate/petroleum ether: 3/1) to give the corresponding azido-alcohol as a white solid. Yield: 2.86 g, 82 %. ^{1}H NMR ($CDCl_3$), δ: 1.36 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 1.63 (s, 3H, CH_3), 2.81 (b, 1H, OH), 3.37 (dd, 1H, H-6', $^2J_{6'\text{-}6}$= 13.2 Hz, $^3J_{6'\text{-}5}$= 4.0 Hz), 3.48 (dd, 1H, H-6, $^2J_{6'\text{-}6}$= 13.2 Hz, $^3J_{6\text{-}5}$= 2.8 Hz), 3.89 (m, 1H, H-5), 3.98 (m, 1H, H-4), 4.39 (d, 1H, H-2, $^3J_{2\text{-}1}$= 3.6 Hz), 4.64 (d, 1H, CH_2, $^2J_{H\text{-}H}$= 6.8 Hz), 4.67 (d, 1H, CH_2, $^2J_{H\text{-}H}$= 6.8 Hz), 5.72 (d, 1H, H-1, $^3J_{1\text{-}2}$= 3.6 Hz), 7.2-7.4 (m, 5H, CH=).

*Synthesis of 6-amine-6-deoxy-1,2-O-isopropylidene-3-C-methyl-3-O-benzyl-α-allofuranose **2**.*

The corresponding azido-alcohol (1.74 g, 5 mmol) was dissolved in a mixture of tetrahydrofuran:water (30 mL, 4:1). Triphenylphosphine (3 g, 10.5 mmol) was then

added and the mixture was stirred at room temperature overnight. Then, tetrahydrofuran was removed by evaporation in vacuo and the residue extracted twice with diethyl ether. The aqueous phase was concentrated in vacuo to give the **2** as a white solid. Yield: 1.34 g, 83 %. ^{1}H NMR ($CDCl_3$), δ: 1.34 (s, 3H, CH_3), 1.36 (s, 3H, CH_3-C3), 1.58 (s, 3H, CH_3), 2.41 (b, 3H, NH_2, OH), 2.65 (dd, 1H, H-6', $^{2}J_{6'-6}$= 12.8 Hz, $^{3}J_{6'-5}$= 4.4 Hz), 2.91 (dd, 1H, H-6, $^{2}J_{6'-6}$= 12.8 Hz, $^{3}J_{6-5}$= 2.0 Hz), 3.63 (m, 1H, H-5), 3.78 (m, 1H, H-4), 4.15 (d, 1H, H-2, $^{3}J_{2-1}$= 3.6 Hz), 4.61 (s, 2H, CH_2), 5.67 (d, 1H, H-1, $^{3}J_{1-2}$= 3.6 Hz), 7.2-7.4 (m, 5H, CH=). ^{13}C NMR ($CDCl_3$), δ: 16.5 (CH_3), 26.6 (CH_3), 26.9 (CH_3), 45.4 (C-6), 67.1 (CH_2, Bn), 70.4 (C-5), 79.4 (C-4), 82.8 (C-2), 83.4 (C-3), 104.2 (C-1), 113.1 (CMe_2), 127.8 (CH=), 128.3 (CH=), 128.6 (CH=), 138.2 (C).

Synthesis of 3-O-benzyl-3-C-methyl-1,2-O-isopropylidene-6-O-tosyl-α-D-glucofuranose.

A solution of *p*-toluenesulfonyl chloride (0.65 g, 3.4 mmol) in dichloromethane (2.3 mL) was slowly added to a cooled solution (0 ºC) of 3-*O*-Benzyl-3-*C*-methyl-1,2-*O*-isopropylidene-α-D-glucofuranose (1.1 g, 3.4 mmol) in pyridine (2.7 mL). The reaction was allowed to stir overnight. Then, water was added and the product was extracted with dichloromethane (3 x 100 mL) and once with a solution of HCl 0.1 M (100mL). The organic layer was dried over $MgSO_4$, evaporated to dryness and purified by flash chromatography (chloroform/acetone: 9/0.5) to produce the product as a white solid. Yield: 0.9 g, 56%. ^{1}H NMR ($CDCl_3$), δ: 1.32 (s, 3H, CH_3), 1.49 (s, 3H, CH_3), 1.54 (s, 3H, CH_3), 2.44 (s, 3H, CH_3), 3.86 (m, 1H), 4.07 (dd, 1H, H-6', $^{2}J_{6'-6}$= 10.4 Hz, $^{3}J_{6'-5}$= 7.2 Hz), 4.29 (m, 1H), 4.34 (dd, 1H, H-6, $^{2}J_{6'-6}$= 10.4 Hz, $^{3}J_{6-5}$= 4.8 Hz), 4.47 (d, 1H, H-2, $^{3}J_{2-1}$= 4.0 Hz), 4.55 (d, 1H, CH_2, $^{2}J_{H-H}$= 6.4 Hz), 4.64 (d, 1H, CH_2, $^{2}J_{H-H}$= 6.4 Hz), 5.78 (d, 1H, H-1, $^{3}J_{1-2}$= 4.0 Hz), 7.34 (m, 7H, CH=), 7.77 (d, 2H, *J*= 8.0 Hz).

Synthesis of 6-azido-6-deoxy-1,2-O-isopropylidene-3-C-methyl-3-benzyl-α-glucofuranose.

A solution of 3-*O*-benzyl-3-*C*-methyl-1,2-*O*-isopropylidene-6-*O*-tosyl-α-D-allofuranose (0.9 g, 1.88 mmol) in DMF was treated with sodium azide as above described for 6-azido-6-deoxy-1,2-*O*-isopropylidene-3-*C*-methyl-3-benzyl-α-allofuranose. Yield: 0.6 g, 91%. ^{1}H NMR ($CDCl_3$), δ: 1.33 (s, 3H, CH_3), 1.53 (s, 3H, CH_3), 1.57 (s, 3H, CH_3), 3.44 (b, 1H, OH), 3.46 (dd, 1H, H-6', $^{2}J_{6'-6}$= 12.4 Hz, $^{3}J_{6'-5}$= 6.4 Hz), 3.55 (dd, 1H, H-6, $^{2}J_{6'-6}$= 12.4 Hz, $^{3}J_{6-5}$= 3.2 Hz), 3.19 (m, 1H), 4.17 (m, 1H),

4.51 (d, 1H, H-2, $^{3}J_{2\text{-}1}$= 3.6 Hz), 4.57 (d, 1H, CH_2, $^{2}J_{H\text{-}H}$= 10.8 Hz), 4.63 (d, 1H, CH_2, $^{2}J_{H\text{-}H}$= 10.8 Hz), 5.84 (d, 1H, H-1, $^{3}J_{1\text{-}2}$= 3.6 Hz), 7.30 (m, 5H, CH=).

Synthesis of 6-amine-6-deoxy-1,2-O-isopropylidene-3-C-methyl-3-benzyl-α-glucofuranose ***3.***

The corresponding azido-alcohol (0.6 g, 1.72 mmol) was treated with triphenylphosphine as above described for **2**. Yield: 240 mg, 44%. ^{1}H NMR ($CDCl_3$), δ: 1.31 (s, 3H, CH_3), 1.51 (s, 3H, CH_3), 1.55 (s, 3H, CH_3), 2.83 (b, 4H, NH_2, OH, H-6'), 3.06 (m, 1H, H-6), 3.91 (m, 1H, H-4), 4.05 (m, 1H, H-3), 4.47 (d, 1H, H-2, $^{3}J_{2\text{-}1}$= 4.0 Hz), 4.57 (m, 2H, CH_2), 5.84 (d, 1H, H-1, $^{3}J_{1\text{-}2}$= 4.0 Hz), 7.32 (m, 5H, CH=). ^{13}C NMR ($CDCl_3$), δ: 15.7 (CH_3), 26.6 (CH_3), 27.3 (CH_3), 44.5 (C-6), 65.4 (CH_2, Bn), 68.2 (C-5), 83.3 (C-2), 85.0 (C-4), 85.3 (C-3), 104.7 (C-1), 112.2 (CMe_2), 127.0 (CH=), 127.6 (CH=), 128.6 (CH=), 138.8 (C).

Synthesis of 6-amine-6-deoxy-1,2-O-isopropylidene-3-C-methyl-3-benzyl-α-glucofuranose ***4.***

The corresponding azido-alcohol (2.4 g, 7.15 mmol) was treated with triphenylphosphine as above described for **2**. Yield: 1.79 g, 81%. For characterization details, see ref. 17.

4.2.4.4. Typical procedure for the ATH of ketones.

The desired ligand (0.0055 mmol), catalyst precursor ($[RuCl_2(p\text{-cymene})_2]_2$) (0.0025 mmol), and LiCl (4.2 mg, 0.1 mmol) were treated under vacuum for 10 min. Under argon, substrate (1 mmol), propan-2-ol (2 mL) and THF (2.5 mmol) were sequentially added. The reaction was initiated by adding ^{i}PrONa (0.1M, 0.5 mL, 0.05 mmol) to the solution. After completion of the reaction the solution was filtered through a plug of silica and eluted with Et_2O, and the solvents were evaporated. The products were analyzed by GC (CP Chirasil DEX CB).[9b,c,18]

4.2.5. Acknowledgements

We thank the Swedish Research Council and The Carl Trygger Foundation, the Spanish (CTQ2010-15835) and Catalan (2009SGR116) Governments, and the ICREA Foundation for financial support.

4.2.6. References

[1] *Modern Reduction Methods* (Eds: Andersson, P. G.; Munslow, I. J.), Wiley-VCH, Weinheim, **2008**.

[2] See for example: a) Wang, C.; Wu, X.; Xiao, J. *Chem. Asian J.* **2008**, *3*, 1750; b) Gladiali, S.; Alberico, E. *Chem. Soc. Rev.* **2006**, *35*, 226; c) Everaere, K.; Mortreux, A.; Carpentier, J.-F. *Adv. Synth. Catal.* **2003**, *345*, 67; d) Ohkuma, T.; Noyori, R. in *Comprehensive Asymmetric Catalysis I–III*, Vol. 1 (Eds: Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H.), Springer, Berlin, **1999**, p. 199; e) Palmer, M. J.; Wills, M. *Tetrahedron: Asymmetry* **1999**, *10*, 2045.

[3] Hashiguchi, S.; Fujii, A.; Takehara, J.; Ikariya, T.; Noyori, R. J. *Am. Chem. Soc.* **1995**, *117*, 7562.

[4] Selected recent examples: a) Cheung, F. K.; Lin, C.; Minissi, F.; Crivillé, A. L.; Graham, M. A.; Fox, D. J.; Wills, M. *Org. Lett.* **2007**, *9*, 4659; b) Cortez, N. A.; Aguirre, G.; Parra-Hake, M.; Somanathan, R. *Tetrahedron Lett.* **2007**, *48*, 4335; c) Canivet, J.; Süss-Fink, G. *Green Chem.* **2007**, *9*, 391; d) Li, L.; Wu, J.; Wang, F.; Liao, J.; Zhang, H.; Lian, C.; Zhu, J.; Deng, J. *Green Chem.* **2007**, *9*, 23; e) Matharu, D. S.; Morris, D. J.; Clarkson, G. J.; Wills, M. *Chem. Commun.* **2006**, 3232; f) Hayes, A. M.; Morris, D. J.; Clarkson, G. J.; Wills, M. *J. Am. Chem. Soc.* **2005**, *127*, 7318; g) Wang, F.; Liu, H.; Cun, L.; Zhu, J.; Deng, J.; Jiang, Y. *J. Org. Chem.* **2005**, *70*, 9424; h) Wu, X.; Vinci, D.; Ikariya, T.; Xiao, J. *Chem. Commun.* **2005**, 4447; i) Hannedouche, J.; Clarkson, G. J.; Wills, M. *J. Am. Chem. Soc.* **2004**, *126*, 986; j) Ma, Y. ; Liu, H. ; Chen, L. ; Cui, X. ; Zhu, J. ; Deng, J. *Org. Lett.* **2003**, *5*, 2103.

[5] See for example: a) Nordin, S. J.; Roth, P.; Tarnai, T.; Alonso, D. A.; Brandt, P.; Andersson, P. G. *Chem. Eur. J.* **2001**, *7*, 1431; b) Alonso, D. A.; Nordin, S. J.; Roth, P.; Tarnai, T.; Andersson, P. G.; Thommen, M.; Pittelkow, U. *J. Org. Chem.* **2000**, *65*, 3116; c) Schlatter, A.; Woggon, W.-D. *Adv. Synth. Catal.* **2008**, *350*, 995; d) Schlatter, A.; Kundu, M. K.; Woggon, W.-D. *Angew. Chem. Int. Ed.* **2004**, *43*, 6731.

[6] Baratta, W.; Bosco, M.; Chelucci, G.; Del Zotto, A.; Siega, K.; Toniutti, M.; Zangrando, E.; Rigo, P. *Organometallics* **2006**, *25*, 4611.

[7] For a recent example of a phosphine-based catalyst, see; Reetz, M. T.; Li, X. *J. Am. Chem. Soc.* **2006**, *128*, 1044.

[8] a) Casey, C. P.; Guan, H. *J. Am. Chem. Soc.* **2007**, *129*, 5816; b) Zhou, S.; Fleischer, S.; Junge, K.; Das, S.; Addis, D.; Beller, M. *Angew. Chem. Int. Ed.* **2010**, *49*, 8121; c) Naik, A.; Maji, T.; Reiser, O. *Chem. Commun.* **2010**, *46*, 4475; d) Mikhailine, A.; Lough, A. L.; Morris, R. H. *J. Am. Chem. Soc.* **2009**, *131*, 1394.

[9] a) Pastor, I. M.; Västilä, P.; Adolfsson, H. *Chem. Commun.* **2002**, 2046; b) Pastor, I. M.; Västilä, P.; Adolfsson, H. *Chem. Eur. J.* **2003**, *9*, 4031; c) Bøgevig, A.; Pastor, I. M.; Adolfsson, H. *Chem. Eur. J.* **2004**, *10*, 294; d) Västilä, P.; Wettergren, J.; Adolfsson, H. *Chem. Commun.* **2005**, 4039; e) Västilä, P.; Zaitsev, A. B.; Wettergren, J.; Privalov, T.; Adolfsson, H. *Chem. Eur. J.* **2006**, *12*, 3218; f) Wettergren, J.; Buitrago, E.; Ryberg, P.; Adolfsson, H. *Chem. Eur. J.* **2009**, *15*, 5709.

[10] For recent reviews, see: a) Diéguez, M.; Pàmies, O.; Claver, C. *Chem. Rev.* **2004**, *104*, 3189; b) Boysen, M. M. K. *Chem. Eur. J.* **2007**, *13*, 8648; c) Benessere, V.; Del Litto, R.; De Roma, A.; Ruffo, F. *Coord. Chem. Rev.* **2010**, *254,* 390; d) Woodward, S.; Diéguez, M. ; Pàmies, O. *Coord. Chem. Rev.* **2010**, *254*, 2007.

[11] One of the limitations of using sugars as precursors for ligands is that often only one of the enantiomers is readily available. However, this limitation can be overcome by the rational design of pseudo-enantiomeric ligands. See ref. 10d.

[12] a) Guillarme, S.; Mai Nguyen, T. X.; Saluzzo, C. *Tetrahedron: Asymmetry* **2008**, *19*, 1450; b) Huynh, K.-D.; Ibrahim, H.; Toffano, M.; Vo-Thanh, G. *Tetrahedron: Asymmetry* **2010**, *21*, 1542.

[13] See for example: Martín-Matute, B.; Bäckvall, J.-E. *Curr. Op. Chem. Bio.* **2007**, *11*, 226.

[14] Redlich, H; Lenfers, J. B.; Bruns, W. *Liebigs Ann. Chem.* **1985**, 1570.

[15] Nishiyama, S.; Toshima, H.; Kanari, H.; Yamamura, S. *Tetrahedron* **1988**, *44*, 6315.

[16] Wang, J.; Li, J.; Tuttle, D.; Takemoto, J. Y.; Chang, C.-W. T. *Org. Lett.* **2002**, *4*, 3997.

[17] Yamashita, M.; Takahashi, C.; Seo, K. *Heterocycles* **1993**, *36*, 651.

[18] Wettergren, J.; Bøgevig, A.; Portier, M.; Adolfsson, H. *Adv. Synth. Catal.* **2006**, *348*, 1277.

4.2.7. Supporting information

1. Ru-catalyzed asymmetric transfer hydrogenation reaction using ligands **L28f** and **L28g**.

Table 4.2.2. Ru-catalyzed asymmetric transfer hydrogenation reaction using ligands **L28f** and **L28g**.[a]

Entry	Substrate	Ligand	% Conv (h)[b]	% ee[b]
1	**S2**	**L28f**	100 (3)	>99 (*S*)
2[c]	**S2**	**L28g**	98 (3)	99 (*S*)
3	**S3**	**L28f**	99 (3)	99 (*S*)
4[c]	**S3**	**L28g**	99 (3)	99 (*S*)
5	**S6**	**L28f**	100 (3)	99 (*S*)
6[c]	**S6**	**L28g**	100 (3)	>99 (*S*)
7	**S7**	**L28f**	99 (3)	99 (*S*)
8[c]	**S7**	**L28g**	95 (3)	99 (*S*)
9	**S10**	**L28f**	78 (3)	99 (*S*)
10[c]	**S10**	**L28g**	69 (3)	98 (*S*)

[a] Reaction conditions: substrate (1 equiv, 0.2M in 2-propanol/THF (1:1), $[RuCl_2(p\text{-cymene})]_2$ (0.25 mol% in Ru), ligand (0.55 mol%), NaO^iPr (5 mol%), LiCl (10 mol%) and at room temperature. [b] Conversion and enantiomeric excess was determined by GC. [c] Using 1 mol% of Ru.

4.3. Modular furanoside pseudo-dipeptides and thioamides, readily available ligand libraries for metal-catalyzed transfer hydrogenation reactions. Scope and limitations

Mercedes Coll, Katrin Ahlford, Oscar Pàmies, Hans Adolfsson, and Montserrat Diéguez
submitted for publication to *Adv. Synth. Catal*.

Abstract. Two new highly modular carbohydrate-based, pseudo-dipeptide and thioamide ligand libraries have been synthesized for the Rh- and Ru-catalyzed asymmetric transfer hydrogenation (ATH) of prochiral ketones. These series of ligands can be prepared efficiently from easily accessible D-(+)-xylose and D-(+)-glucose. The ligand libraries contain two main ligand structures (pseudo-dipeptide and thioamide) that have been designed by making systematic modifications to one of the most successful ligand families developed for the ATH (see Section 4.2). As well as studying the effect of these two ligand structures on the catalytic performance, we also evaluated the effect of modifying several of the ligand parameters. We found that the effectiveness of the ligands at transferring the chiral information in the product can be tuned by correctly choosing the ligand components (ligand structure and ligand parameters). Excellent enantioselectivities (ee's up to 99%) were therefore obtained in both enantiomers of the alcohol products using a wide range of substrates.

4.3.1. Introduction

Fine chemicals and natural product chemistry rely on enantiomerically pure compounds. The discovery of synthetic routes for preparing these compounds is one of the most persistently pursued goals in chemistry. Asymmetric catalysis is one of the most attractive approaches, because it can provide very high reactivity and selectivity, and is environmentally friendly.[1] In this respect, the enantioselective reduction of prochiral ketones has acquired greater importance, since the resulting enantioenriched secondary alcohols are key intermediates for the preparation of a large number of biologically active compounds.[2] Asymmetric transfer hydrogenation (ATH) has proven to be an efficient, mild and versatile method for this particular transformation, in which

the use of hazardous molecular hydrogen or highly reactive hydride reagents can be avoided.[3] Nowadays, most transfer hydrogenations are performed using transition metal complexes, mainly based on ruthenium, rhodium or iridium.[3] Recently, the use of iron-based catalysts has also shown interesting results, but their scope is still low compared to the Ru-catalysts.[4] In the mid 1990s, Noyori and coworkers found that ruthenium η^6-arene complexes in combination with vicinal amino alcohol or diamine ligands served as efficient catalysts for the reduction of ketones and ketimines, respectively, under ATH conditions.[5] Since then, many types of chiral ligands have been developed, some of which have been successfully applied in selective transfer hydrogenation.[6] In this context, Adolfsson's group reported that amino acid-derived pseudo-dipeptides **1**[6i,7] and thioamides **2**[6j,8] (Figure 4.3.1) in combination with Ru or Rh half-sandwich complexes are excellent catalysts for the ATH of aryl-alkyl ketones. These ligands are based on the combination of different *N*-Boc-protected α-amino acids and β-amino alcohols (for type **1**) or on thioamides (for type **2**), respectively. Both showed the advantage of possessing a modular ligand building block: the amino acid part.

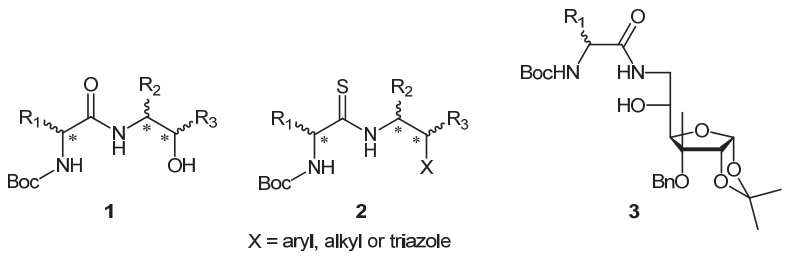


Figure 4.3.1. General structure of pseudo-dipeptide ligands **1,** thioamide ligands **2** and sugar-based pseudo-dipeptide ligands **3**.

Despite all these important contributions, ligands based on simple starting materials and that have high modularity still need to be further explored. For this purpose, carbohydrates are particularly advantageous thanks to their low price and easy modular constructions.[9] Although they have been successfully used in other enantioselective reactions, they have only very recently shown their huge potential as a source of highly effective chiral ligands in this process.[10,11] In this context and based on previous successful ligands **1**, we have recently reported new pseudo-dipeptide ligands **3** (Figure 4.3.1) in which the β-amino alcohol part is replaced by a readily available sugar β-amino alcohol moiety. These new carbohydrate-based pseudo-dipeptide ligands

3 were the first successful sugar-based ligands applied in the Ru-catalyzed asymmetric transfer hydrogenation of several ketones.[10] Despite this success, the use of other carbohydrate-based pseudo-dipeptide ligands or carbohydrate-based thioamides has yet to be reported. Therefore, a systematic study of the possibilities offered by carbohydrate-based pseudo-dipeptides and thioamides as new ligands for ATH reactions was persued. To this end, in this paper we prepared and evaluated two new carbohydrate-based libraries of 36 potential pseudo-dipeptides and 36 potential thioamide ligands (Figure 4.3.2 and 4.3.3). The first set (ligands **L31**-**L34a-i**) is based on the previous sugar-based pseudo-dipeptide ligands **3**, in which a 1,3-amino alcohol sugar core was used instead of a classical 1,2-amino alcohol motif (Figure 4.3.2).

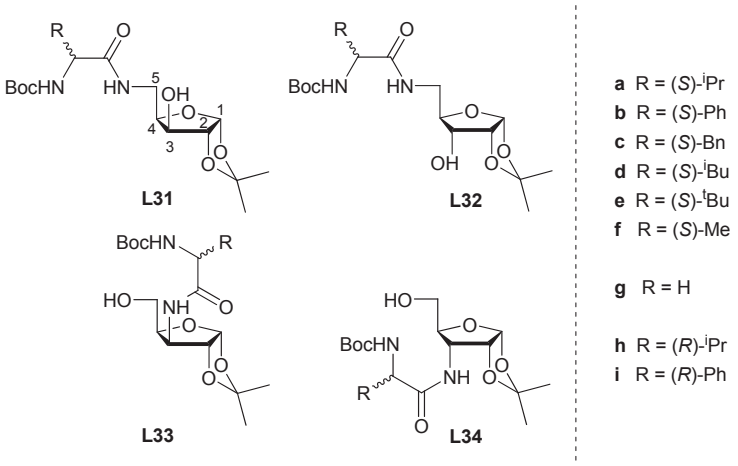


Figure 4.3.2. Furanoside pseudo-dipeptide ligand library **L31-L34a-i**.

In the second set (carbohydrate-thioamide **L35-L38a-i** ligands), the peptide bond in the previous ligands **L31- L34a-i** was converted to a thioamide group (Figure 4.3.3). As well as being prepared from commercially available D-(+)-glucose or D-(+)-xylose, both ligand libraries also have the advantage of a flexible ligand scaffold that enables various ligand parameters to be easily tuned so that the catalyst performance can be maximized. With these libraries, then, we investigated the effect of systematically varying the position of the amino acids/thioamide groups at either C-5 (ligands **L31**/**L32** and **L35**/**L36**) or C-3 (ligands **L33**/**L34** and **L37**/**L38**) of the furanoside backbone, the configuration at C-3 of the furanoside backbone and substituents/configurations (**a-i**) in the amino acid/thioamide moieties. By carefully

selecting the ligand components we achieved both enantiomers of the desired alcohols in high enantioselectivities and activities for a wide range of substrates.

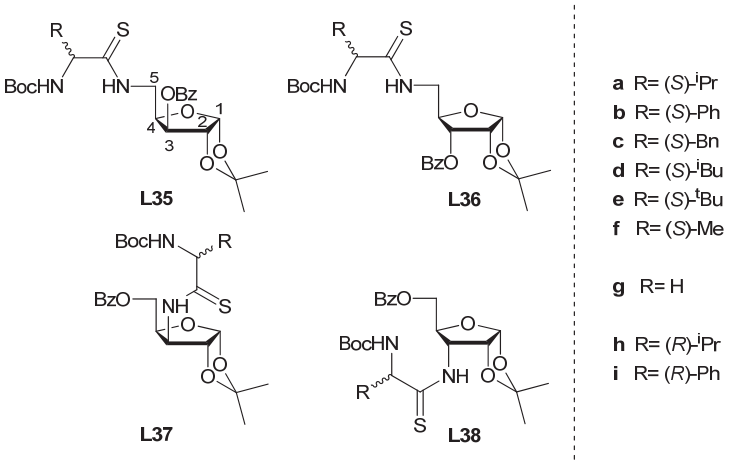


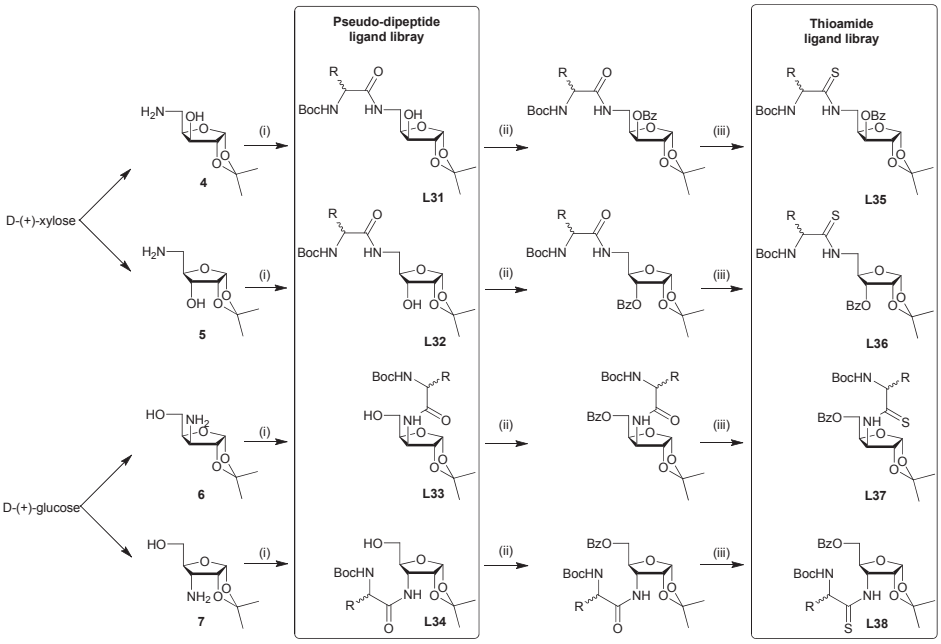
Figure 4.3.3. Furanoside-based thioamide ligand library **L35-L38a-i**.

4.3.2. Results and Discussion

4.3.2.1. Synthesis of pseudo-dipeptide L31-L34a-i and thioamide L35-L38a-i ligand libraries

The sequence for synthesizing pseudo-dipeptide **L31-L34a-i** and thioamide **L35-L38a-i** ligand libraries is illustrated in Scheme 4.3.1. These ligand libraries were efficiently prepared from the corresponding easily accessible 1,3-amino alcohol sugar derivatives (**4-7**, Scheme 4.3.1). Compounds **4-7** were easily made in few steps from the corresponding D-(+)-xylose or D-(+)-glucose.[12] These compounds (**4-7**) were chosen as intermediates for preparing ligands because the various elements that make it possible to study the position in which the α-amino acid/thioamide is coupled (at either C-5 or C-3) and the configuration of C-3 of the sugar amino alcohol can be easily incorporated. Initially, we synthesized the pseudo-dipeptide ligand library **L31-L34a-i** by coupling a series of *N*-Boc protected amino acids with the corresponding amino alcohols **4-7** using isobutyl chloroformate in the presence of *N*-methylmorpholine (Scheme 4.3.1, step i).[6i] In this step the desired diversity in the substituents and configuration of the amino acid part was also attained (**a-i**). Then, we synthesized thioamide ligands **L35-L38a-h** from

the previously obtained pseudo-dipeptide ligands **L31-L34a-i** in a two step procedure. The first step was the benzoylation of the hydroxyl group attached at either C-3 (**L31** and **L32**) or C-5 (**L33** and **L34**) of the furanoside backbone (Scheme 4.3.1, step ii). The second step is the formation of the desired thioamide ligands **L35-L38a-i** by treating the corresponding benzoyl protected pseudo-dipeptide compounds with Lawesson's reagent (Scheme 4.3.1, step iii).[6j] It should be pointed out that under the conditions described in this section Lawesson's reagent was unable to produce the desired thioamides when *tert*-butyl groups were present in the α-amino acid moiety.



Scheme 4.3.1. Synthesis of pseudo-dipeptide ligand library **L31-L34a-i** and thioamide ligand library **L35-L38a-i.** (i) ^{i}BuOCOCl/ NMM / THF / -15 °C. (ii) BzCl / Py / CH_2Cl_2 / 0 °C to rt. (iii) Lawesson's reagent / THF /60 °C.

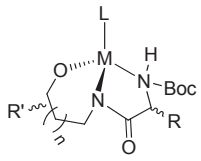
All the ligands were isolated in moderate-to-good yields by purification on neutral silica gel. They were stable at room temperature and characterized by ^{1}H and ^{13}C NMR spectroscopy. The spectral assignments (see experimental section) were based on information from ^{1}H–^{1}H and ^{13}C–^{1}H correlation measurements and were as expected for these C_1 ligands.

4.3.2.2. Asymmetric transfer hydrogenation

4.3.2.2.1. Asymmetric transfer hydrogenation of acetophenone S1

In a first set of experiments, we used the Ru- and Rh-catalyzed transfer hydrogenation of acetophenone **S1** to study the potential of both ligand libraries. **S1** was chosen as a model substrate because the reaction was performed with a wide range of ligands, which enabled the efficiency of the various ligand systems to be compared directly.[3-5] In all cases, the catalysts were generated *in situ* from the corresponding ligand and either $[RuCl_2(p\text{-cymene})]_2$ or $[RhCl_2Cp^*]_2$.

Initially we investigated the pseudo-dipeptide ligand library **L31**-**L34a-i**. The results are summarized in Table 4.3.1. Activities and enantioselectivities were low for both Ru- and Rh-catalytic systems. Comparing entries 2-4 we can conclude that the catalyst deactivates quickly under reaction conditions. This behavior can be explained by the previous mechanistic studies with pseudo-dipeptide ligands **1**,[7g] which proposed compound **8** as the key species responsible for the catalytic activity (Figure 4.3.4). In this compound, pseudo-dipeptide ligands are coordinated to the metal through all of the ligand functionalities. Therefore, the alcohol functionality and the peptide nitrogen of the ligand coordinate as anions (note that the reaction proceeds under basic conditions) and the carbamate binds in a neutral fashion (Figure 4.3.4). Our pseudo-dipeptide ligand library **L31**-**L34a-i** differs from previous successful pseudo-dipeptide ligands **1** in the fact that 1,3-amino alcohols are used instead of previously described 1,2-amino alcohols. This change should result in the formation of a reaction intermediate **8** in which the coordination of the alcohol as an alkoxide forms a six-membered chelate, which is less favored than when 1,2-amino alcohols are used (which form a more stable five-membered chelate), thus favoring catalyst decomposition after only a few turnovers (Figure 4.3.4).[13]



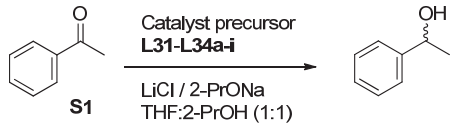
8

M = Ru or Rh
L = arene ligand

Amino alcohol type	n	Coordination of the O to M (chelate ring size)
1,2	0	favoured (5-member)
1,3	1	less favoured (6-member)

Figure 4.3.4. Proposed key reaction intermediate **8** in the ATH of ketones using pseudo-dipeptide ligands **1** and **L31-L34a-i**, respectively.

Table 4.3.1. Selected results for the Ru- and Rh-catalyzed asymmetric transfer hydrogenation reaction of **S1** using pseudo-dipeptide ligands **L31-L34a-i**.[a]



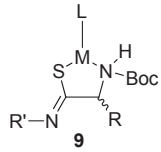
S1

Entry	Ligand	Catalyst precursor	T (ºC)	% Conv (h)[b]	% ee[b]
1	**L31a**	$[RuCl_2(p\text{-cymene})_2]_2$	25	3 (2)	18 (*R*)
2	**L31a**	$[RuCl_2(p\text{-cymene})_2]_2$	50	11 (1)	12 (*R*)
3				13 (3)	12 (*R*)
4				14 (10)	11 (*R*)
5	**L32a**	$[RuCl_2(p\text{-cymene})_2]_2$	25	3 (2)	16 (*S*)
6	**L32a**	$[RuCl_2(p\text{-cymene})_2]_2$	50	3 (1)	14 (*S*)
7	**L33a**	$[RuCl_2(p\text{-cymene})_2]_2$	25	1 (2)	3 (*S*)
8	**L34a**	$[RuCl_2(p\text{-cymene})_2]_2$	25	6 (2)	0
9	**L31b**	$[RuCl_2(p\text{-cymene})_2]_2$	50	12 (1)	11 (*R*)
10	**L31f**	$[RuCl_2(p\text{-cymene})_2]_2$	50	9 (1)	12 (*R*)
11	**L31h**	$[RuCl_2(p\text{-cymene})_2]_2$	50	10 (1)	4 (*S*)
12	**L31a**	$[RhCl_2Cp^*]_2$	25	5 (24)	14 (*R*)
13	**L32a**	$[RhCl_2Cp^*]_2$	25	3 (24)	6 (S)

[a] Reaction conditions: **S1** (1 equiv, 0.2M in 2-propanol/THF: 1/1), $[RuCl_2(p\text{-cymene})]_2$ (0.25 mol%) or $[RhCl_2Cp^*]_2$ (0.25 mol%), ligand (0.55 mol%), NaO^iPr (5 mol%), LiCl (10 mol%) and at room temperature. [b] Conversion and enantiomeric excess was determined by GC (CP Chirasil DEX CB).

In our efforts to improve catalytic performance and take advantage of our modular ligand systems we went on to develop and screen the thioamide ligand library **L35-L38a-i**. Recently, thioamide-based ligands **2** (Figure 4.3.1) have demonstrated their potential utility in the ATH of several aryl-alkyl ketones, affording the desired

alcohols in a range of 59-97% ee.[6j,8] Our new ligand library **L35-L38a-i** was designed on the basis of previous mechanistic studies with successful thioamide ligands **2** that showed that this type of ligand coordinates to the metal in a bidentate fashion, through the carbamate nitrogen and the thioamide sulfur atoms, to form a five-membered ring (Figure 4.3.5).[8a] In order to obtain the same coordination pattern we developed the thioamide ligands **L35-L38a-i** in which the hydroxyl group is protected to prevent its coordination to the metal in the form of alkoxide. The enantioselectivity, then, is expected to be high.



9

M = Ru or Rh
L = arene ligand

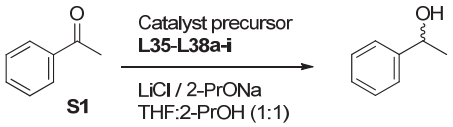
Figure 4.3.5. Proposed key reaction intermediate **9** in the ATH of ketones using thioamide ligands **2**.

The results using ligands **L35-L38a-i** are summarized in Table 4.3.2. With ligands **L35-L37a**, we first investigated the effect of the catalyst precursor. We found it had an important effect on both the activity and enantioselectivity of the reaction (Table 4.3.2, entries 1-8). Results were therefore best with the catalyst precursor $[RhCl_2Cp^*]_2$. The other ligands were then screened using $[RhCl_2Cp^*]_2$ as the optimum source of metal.

We then moved on to investigate the effect of the ligand parameters on the catalytic performance. The results indicate that enantioselectivity is highly affected by the position of the thioamide group at either C-5 or C-3 of the furanoside backbone, the configuration of C-3 and the substituents/configurations in the thioamide moiety.

Interestingly, we found a cooperative effect between the position of the thioamide group and the configuration of carbon atom C-3 of the furanoside backbone (Table 4.3.2, entries 2, 4, 6 and 8). The results indicate that the matched combination is achieved with ligands **L37**, which have the thioamide moiety attached to C-3 and an (*S*)-configuration of carbon atom C-3 (entry 6).

Table 4.3.2. Selected results for the Ru- and Rh-catalyzed asymmetric transfer hydrogenation reaction of **S1** using thioamide ligands **L35-L38a-i**.[a]



Entry	Ligand	Catalyst precursor	% Conv (h)[b]	% ee[b]
1	**L35a**	$[RuCl_2(p\text{-cymene})_2]_2$	39 (2)	82 (*R*)
2	**L35a**	$[RhCl_2Cp^*_2]_2$	64 (1)	86 (*R*)
3	**L36a**	$[RuCl_2(p\text{-cymene})_2]_2$	24 (2)	80 (*R*)
4	**L36a**	$[RhCl_2Cp^*_2]_2$	59 (1)	92 (*R*)
5	**L37a**	$[RuCl_2(p\text{-cymene})_2]_2$	10 (2)	79 (*R*)
6	**L37a**	$[RhCl_2Cp^*_2]_2$	72 (1)	97 (*R*)
7	**L38a**	$[RuCl_2(p\text{-cymene})_2]_2$	29 (2)	91 (*R*)
8	**L38a**	$[RhCl_2Cp^*_2]_2$	53 (1)	94 (*R*)
9	**L35b**	$[RhCl_2Cp^*_2]_2$	67 (1)	70 (*R*)
10	**L35c**	$[RhCl_2Cp^*_2]_2$	65 (1)	76 (*R*)
11	**L35d**	$[RhCl_2Cp^*_2]_2$	59 (1)	88 (*R*)
12	**L35f**	$[RhCl_2Cp^*_2]_2$	74 (1)	69 (*R*)
13	**L35g**	$[RhCl_2Cp^*_2]_2$	44 (1)	5 (*S*)
14	**L35h**	$[RhCl_2Cp^*_2]_2$	63 (1)	91 (*S*)
15	**L35i**	$[RhCl_2Cp^*_2]_2$	64 (1)	67 (*S*)
16	**L37b**	$[RhCl_2Cp^*_2]_2$	52 (1)	90 (*R*)
17	**L37d**	$[RhCl_2Cp^*_2]_2$	55 (1)	98 (*R*)
18	**L37h**	$[RhCl_2Cp^*_2]_2$	25 (1)	93 (*S*)
19[c]	**L37a**	$[RhCl_2Cp^*_2]_2$	59 (1)	93 (*R*)
20[c]	**L38a**	$[RhCl_2Cp^*_2]_2$	45 (1)	88 (*R*)

[a] Reaction conditions: **S1** (1 equiv, 0.2M in 2-propanol/THF: 1/1), $[RuCl_2(p\text{-cymene})]_2$ (0.25 mol%) or $[RhCl_2Cp^*]_2$ (0.25 mol%), ligand (0.55 mol%), NaO^iPr (5 mol%), LiCl (10 mol%) and at room temperature. [b] Conversion and enantiomeric excess was determined by GC (CP Chirasil DEX CB). [c] No LiCl was added.

We next studied the effect of the substituents and configuration of the thioamide moiety with ligands **L35a-i**. Systematic variation of the electronic and steric properties of thioamide substituents indicated that enantioselectivities were mainly controlled by the steric properties of these substituents and were higher when more sterically

demanding substituents were present (i.e. ^{i}Bu≈^{i}Pr>Bn>Ph≈Me). Little effect of the thioamide substituents on activity was observed. In addition the presence of a chiral thioamide substituent is crucial if levels of enantioselectivity are to be high (Table 4.3.2, entries 2, 9-12 *vs* 13). We also found that the sense of enantioselectivity is governed by the absolute configuration of the substituent in the thioamide moiety (Table 4.3.2, entries 2 *vs* 14 and 6 *vs* 18). Both enantiomers of the reduction products can therefore be accessed in high enantioselectivity simply by changing the absolute configuration of the thioamide substituent.

The best results were therefore obtained with ligands **L37a** and **L37d** (Table 4.3.2, entries 6 and 17, ee's up to 98%). Interestingly, catalytic systems Rh-**L37a** and Rh-**L37b** provided higher enantioselectivities than those obtained using previously described Rh-**2** catalysts (ee's up to 96%).[8c]

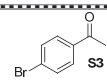
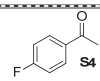
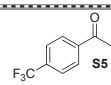
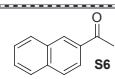
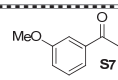
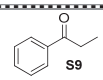
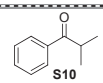
Finally, we also evaluated the efficiency of these catalysts without the addition of LiCl (entries 19 and 20). The results are in line with the decrease in activity and enantioselectivity previously observed using thioamide ligands **2**, which, as expected, agrees with a similar coordination mode and mechanism for the asymmetric transfer hydrogenation reaction. The higher ee's obtained using our sugar-based ligands (see also results in Table 4.3.3, *vide infra*) are therefore most likely due to interactions between the ligand and the arene group when the Rh-hydride complex is formed.

4.3.2.2.2. Asymmetric transfer hydrogenation of different aryl-alkyl ketones

To further study the potential of these readily available ligands, we evaluated them in the ATH of other ketones **S2-S10**. The results are summarized in Table 4.3.3. In general, the trends were the same as for the ATH of **S1**. Results were best with ligands **L37a** and **L37d**. Again, both enantiomers of the secondary alcohol product were accessible in high enantioselectivities (ee's up to 99%, i.e. Table 4.3.3, entries 3-5 and 10-15). We found that activities were best when electron-withdrawing groups at the *para* position were present (entries 6-12 *vs* 3-5). However, enantioselectivity was hardly affected by the presence of electron-withdrawing or electron-donating groups at the *para* position of the phenyl group (entries 1-12). This behaviour contrast with the electronic effect on enantioselectivity observed for previous thioamide ligands.[6j,8] Therefore, several *para*-substituted aryl ketones, including those containing 2-naphthyl

groups, can be efficiently reduced using Rh-**L37a** and Rh-**L37d** catalytic systems (ee's ranging from 97% to 99%).

Table 4.3.3. Results for the Rh-catalyzed asymmetric transfer hydrogenation reaction of several aryl-alkyl ketones using thioamide ligands **L35-L38a-i**.[a]

Entry	Substrate	Ligand	% Conv (h)[b]	% ee[b]
1	 S1	**L37a**	85 (3)	97 (*R*)
2		**L37d**	72 (3)	98 (*R*)
3	 S2	**L37a**	68 (3)	98 (*R*)
4		**L37d**	60 (3)	98 (*R*)
5		**L37h**	49 (3)	94 (*S*)
6	 S3	**L37a**	94 (2)	97 (*R*)
7		**L37d**	78 (2)	97 (*R*)
8	 S4	**L37a**	95 (2)	97 (*R*)
9		**L37d**	85 (2)	98 (*R*)
10	 S5	**L37a**	90 (1)	96 (*R*)
11		**L37d**	91 (2)	97 (*R*)
12		**L37h**	88 (3)	95 (*S*)
13	 S6	**L37a**	87 (3)	99 (*R*)
14		**L37d**	65 (3)	99 (*R*)
15		**L37h**	59 (3)	97 (*S*)
16	 S7	**L37a**	87 (24)	95 (*R*)
17		**L37d**	69 (24)	95 (*R*)
18		**L37h**	54 (24)	93 (*S*)
19	 S8	**L37a**	18 (24)	37 (*S*)
20		**L37d**	12 (24)	34 (*S*)
21	 S9	**L37a**	76 (24)	96 (*R*)
22		**L37d**	71 (24)	97 (*R*)
23	 S10	**L37a**	68 (24)	98 (*R*)
24		**L37d**	67 (24)	98 (*R*)

[a] Reaction conditions: ketone (1 equiv, 0.2M in 2-propanol/THF: 1/1), $[RhCl_2Cp^*]_2$ (0.25 mol%), ligand (0.55 mol%), NaO^iPr (5 mol%), LiCl (10 mol%) and at room temperature. [b] Conversion and enantiomeric excess was determined by GC (CP Chirasil DEX CB).

The catalytic performance (activity and enantioselectivity) of the reaction was influenced by steric factors on the aryl substituent. Although enantioselectivity was

hardly affected by the presence of *meta*-substituents in the phenyl group (entries 16 and 17), both activity and enantioselectivity decreased considerably when *ortho*-substituted aryl ketones were used (entries 19 and 20). On the other hand, enantioselectivities are not affected by the steric bulk of the alkyl substituent (entries 1 and 2 *vs* 21-24).

In summary, the modular ligand design (position of the thioamide group, configuration at C-3 of the furanoside backbone and the substituents/configurations of the thioamide moieties) has been shown to be highly successful, both in finding highly selective ligands for almost each substrate, and identifying three general ligands **L37a**, **L37d** and **L37h** with good performance over the entire range of substrates (ee's up to 99%). It should be pointed out that these catalysts are also very tolerant to the electronic nature of the aryl ring and to the steric bulk of the alkyl group. Interestingly, when these latter results are compared with the enantioselectivity obtained with their corresponding non-sugar based thioamide ligands **2**,[14] we can conclude that introducing a sugar amino alcohol moiety is advantageous. These results are among the best that have been reported.[3]

4.3.3. Conclusions

Two new highly modular carbohydrate-based, pseudo-dipeptide and thioamide ligand libraries have been synthesized for the Rh- and Ru-catalyzed asymmetric transfer hydrogenation of several ketones. Both ligand libraries have the advantage that they can be efficiently prepared from commercial α-amino acids, D-(+)-xylose and D-(+)-glucose, inexpensive natural chiral feedstocks. These ligand libraries contain two main ligand structures (pseudo-dipeptides and thioamides) that have been designed by systematically modifying one of the most successful ligand families developed for this process (see Section 4.2). As well as studying the effect of these two ligand structures on the catalytic performance, we also evaluated the effect of modifying several ligand parameters (the position of the amino acids/thioamide groups at either C-5 or C-3 of the furanoside backbone, the configuration at C-3 of the furanoside backbone and substituents/configurations in the amino acids/thioamide moieties). By carefully selecting the ligand components, we have developed the first carbohydrate-based thioamide ligand library that provides high enantioselectivity in a broad range of aryl-alkyl ketones (ee's up to 99%). It should be noted that both enantiomers of alcohol products can be obtained with high enantioselectivities by simply changing the absolute

configuration of the thioamide substituent. In contrast to previous successful thioamides, enantioselectivity is hardly affected by the presence of electron-withdrawing or electron-donating groups, therefore, a range of *para*- and *meta*-substituted aryl-alkyl ketones were efficiently reduced. We have therefore demonstrated that the introduction of a furanoside aminosugar moiety into the ligand design is advantageous and it efficiently transfers the chiral information to the products (ee's ranging from 95% to 99% in the reduction of a range of *para*- and *meta*-substituted aryl-alkyl ketones). These results, which are among the best that have been reported for this process, open up a new class of readily available ligands for the highly enantioselective ATH.

4.3.4. Experimental Section

4.3.4.1. General conditions

All reactions were carried out using standard Schlenk techniques under an argon atmosphere. Solvents were purified and dried by standard procedures. Sugar amino alcohols **4-7** were prepared as previously described.[12] ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra were recorded using a 400 MHz spectrometer. Chemical shifts are relative to that of $SiMe_4$ (^{1}H and ^{13}C) as internal standard. ^{1}H and ^{13}C assignments were made on the basis of ^{1}H-^{1}H gCOSY and ^{1}H-^{13}C gHSQC.

4.3.4.2. Typical procedure for the preparation of pseudo-dipeptide ligands L„31-L„34a-i

To a cooled solution (-15 °C) of the desired *N*-Boc-protected amino acid (1 mmol) in THF (2 mL), *N*-methylmorpholine (NMM, 1.15 mmol, 126 μL) and isobutylchloroformate (1.15 mmol, 150 μL) were slowly added. After 45 minutes, a solution of the desired amino alcohol (1 mmol, 189.2 mg), previously azeotropically dried with toluene, in THF (2 mL) was added and the resulting mixture was stirred at room temperature for 2 h. The crude mixture was purified by flash chromatography to produce the corresponding ligands as white solids.

L31a: Yield: 315 mg, 81 %. ^{1}H NMR ($CDCl_3$), δ: 0.91 (d, 3H, CH_3, ^{i}Pr, $^{3}J_{H-H}$= 7.2 Hz), 0.94 (d, 3H, CH_3, ^{i}Pr, $^{3}J_{H-H}$= 7.2 Hz), 1.29 (s, 3H, CH_3), 1.43 (s, 9H, CH_3, ^{t}Bu), 1.46 (s, 3H, CH_3), 2.13 (m, 1H, CH, ^{i}Pr), 3.24 (m, 1H, H-5), 3.81 (m, 1H, H-5'), 3.87 (m, 1H, CH), 3.95 (d, 1H, H-3, $^{3}J_{3-4}$= 2.4 Hz), 4.03 (m, 1H, H-4), 4.56 (d, 1H, H-2, $^{3}J_{2-1}$= 3.6 Hz), 4.99 (m, 1H, NH), 5.89 (d, 1H, H-1, $^{3}J_{1-2}$= 3.6 Hz), 6.72 (m, 1H, NH). ^{13}C NMR ($CDCl_3$), δ: 19.3 (CH_3, ^{i}Pr), 26.0 (CH_3), 26.8 (CH_3), 28.3 (CH_3, ^{t}Bu), 30.3 (CH, ^{i}Pr), 37.1 (C-5), 60.2 (CH), 73.7 (C-3), 78.7 (C, ^{t}Bu), 79.8 (C-4), 84.7 (C-2), 104.8 (C-1), 111.5 (CMe_2), 151.2 (CO), 174.1 (CO). Anal. calcd (%) for $C_{18}H_{32}N_2O_7$: C 55.65, H 8.30, N 7.21; found: C 55.69, H 8.34, N 7.18.

L31b: Yield: 334 mg, 79 %. ^{1}H NMR ($CDCl_3$), δ: 1.26 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 1.40 (s, 9H, CH_3, ^{t}Bu), 3.22 (m, 1H, H-5), 3.78 (m, 2H, H-5' and H-3), 3.92 (m, 1H, H-4), 4.48 (d, 1H, H-2, $^{3}J_{2-1}$= 3.6 Hz), 5.23 (m, 1H, CH), 5.70 (m, 1H, NH), 5.82 (d, 1H, H-1, $^{3}J_{1-2}$= 3.6 Hz), 7.00 (m, 1H, NH), 7.34 (m, 5H, CH=). ^{13}C NMR ($CDCl_3$), δ: 26.3 (CH_3), 26.9 (CH_3), 28.5 (CH_3, ^{t}Bu), 37.5 (C-5), 58.7 (CH), 74.0 (C-3), 79.8 (C-4), 80.8 (C, ^{t}Bu), 84.9 (C-2), 104.9 (C-1), 111.7 (CMe_2), 127.2 (CH=), 128.9 (CH=), 129.3 (CH=), 137.3 (C), 155.4 (CO), 172.9 (CO). Anal. calcd (%) for $C_{21}H_{30}N_2O_7$: C 59.70, H 7.16, N 6.63; found: C 59.74, H 7.18, N 6.59.

L31c: Yield: 375 mg, 86 %. ^{1}H NMR ($CDCl_3$), δ: 1.28 (s, 3H, CH_3), 1.38 (s, 9H, CH_3, ^{t}Bu), 1.42 (s, 3H, CH_3), 3.02 (m, 2H, CH_2, Bn), 3.13 (m, 1H, H-5), 3.70 (m, 1H, H-5'), 3.95 (m, 2H, H-3 and H-4), 4.32 (m, 1H, CH), 4.55 (d, 1H, H-2, $^{3}J_{2-1}$= 3.6 Hz), 5.16 (m, 1H, NH), 5.82 (d, 1H, H-1, $^{3}J_{1-2}$= 3.6 Hz), 6.69 (m, 1H, NH), 7.1-7.3 (m, 5H, CH=). ^{13}C NMR ($CDCl_3$), δ: 26.0 (CH_3), 26.7 (CH_3), 28.3 (CH_3, ^{t}Bu), 37.2 (C-5), 38.3 (CH_2), 55.9 (CH), 73.7 (C-3), 79.6 (C-4), 80.6 (C, ^{t}Bu), 84.8 (C-2), 104.8 (C-1), 111.5 (CMe_2), 127.1 (CH=), 128.7 (CH=), 129.2 (CH=), 136.2 (C), 155.5 (CO), 173.6 (CO). Anal. calcd (%) for $C_{22}H_{32}N_2O_7$: C 60.54, H 7.39, N 6.42; found: C 60.52, H 7.37, N 6.47.

L31d: Yield: 350 mg, 87 %. ^{1}H NMR ($CDCl_3$), δ: 0.92 (m, 6H, CH_3, ^{i}Bu), 1.29 (s, 3H, CH_3), 1.42 (s, 9H, CH_3, ^{t}Bu), 1.45 (s, 3H, CH_3), 1.47 (m, 1H, CH_2, ^{i}Bu), 1.64 (m, 2H, CH and CH_2, ^{i}Bu), 3.22 (m, 1H, H-5), 3.78 (m, 1H, H-5'), 3.94 (d, 1H, H-3, $^{3}J_{3-4}$= 2.4 Hz), 4.01 (m, 1H, H-4), 4.05 (m, 1H, CH), 4.56 (d, 1H, H-2, $^{3}J_{2-1}$= 3.6 Hz), 4.92 (m, 1H, NH), 5.89 (d, 1H, H-1, $^{3}J_{1-2}$= 3.6 Hz), 6.86 (m, 1H, NH). ^{13}C NMR ($CDCl_3$), δ: 21.9 (CH_3, ^{i}Bu), 22.8 (CH_3, ^{i}Bu), 24.7 (CH_2, ^{i}Bu), 26.0 (CH_3), 26.8 (CH_3), 28.3 (CH_3, ^{t}Bu), 37.0 (C-5), 40.5 (CH, ^{i}Bu), 53.1 (CH), 75.6 (C-3), 79.8 (C-4), 80.3 (C, ^{t}Bu), 84.7 (C-2),

104.8 (C-1), 111.5 (CMe_2), 155.8 (CO), 175.0 (CO). Anal. calcd (%) for $C_{19}H_{34}N_2O_7$: C 56.70, H 8.51, N 6.96; found: C 56.69, H 8.53, N 6.94.

L31e: Yield: 306 mg, 76 %. ^{1}H NMR ($CDCl_3$), δ: 0.92 (s, 9H, CH_3, ^{t}Bu), 1.24 (s, 3H, CH_3), 1.38 (s, 9H, CH_3, ^{t}Bu), 1.40 (s, 3H, CH_3), 3.21 (m, 1H, H-5), 3.69 (m, 1H, H-5'), 3.82 (m, 1H, CH), 3.94 (d, 1H, H-3, $^3J_{3\text{-}4}$= 2.0 Hz), 4.02 (m, 1H, H-4), 4.51 (d, 1H, H-2, $^3J_{2\text{-}1}$= 3.6 Hz), 5.30 (m, 1H, NH), 5.84 (d, 1H, H-1, $^3J_{1\text{-}2}$= 3.6 Hz), 7.03 (m, 1H, NH). ^{13}C NMR ($CDCl_3$), δ: 26.0 (CH_3), 26.7 (CH_3, ^{t}Bu), 26.8 (CH_3), 28.3 (CH_3, ^{t}Bu), 34.5 (C, ^{t}Bu), 37.1 (C-5), 62.2 (CH), 73.7 (C-3), 79.7 (C-4), 80.1 (C, ^{t}Bu), 84.8 (C-2), 104.7 (C-1), 111.5 (CMe_2), 155.9 (CO), 173.3 (CO). Anal. calcd (%) for $C_{19}H_{34}N_2O_7$: C 56.70, H 8.51, N 6.96; found: C 56.67, H 8.52, N 6.95.

L31f: Yield: 249 mg, 69 %. ^{1}H NMR ($CDCl_3$), δ: 1.24 (s, 3H, CH_3), 1.29 (d, 3H, CH_3, $^3J_{H\text{-}H}$= 7.2 Hz), 1.38 (s, 9H, CH_3, ^{t}Bu), 1.40 (s, 3H, CH_3), 3.18 (m, 1H, H-5), 3.74 (m, 1H, H-5'), 3.90 (d, 1H, H-3, $^3J_{3\text{-}4}$= 2.4 Hz), 3.96 (m, 1H, H-4), 4.09 (m, 1H, CH), 4.51 (d, 1H, H-2, $^3J_{2\text{-}1}$= 3.6 Hz), 5.00 (m, 1H, NH), 5.84 (d, 1H, H-1, $^3J_{1\text{-}2}$= 3.6 Hz), 6.91 (m, 1H, NH). ^{13}C NMR ($CDCl_3$), δ: 17.9 (CH_3), 26.0 (CH_3), 26.7 (CH_3), 28.3 (CH_3, ^{t}Bu), 37.0 (C-5), 50.1 (CH), 73.7 (C-3), 79.8 (C-4), 80.2 (C, ^{t}Bu), 84.7 (C-2), 104.8 (C-1), 111.5 (CMe_2), 155.6 (CO), 175.0 (CO). Anal. calcd (%) for $C_{16}H_{28}N_2O_7$: C 53.32, H 7.83, N 7.77; found: C 53.34, H 7.85, N 7.74.

L31g: Yield: 250 mg, 75 %. ^{1}H NMR ($CDCl_3$), δ: 1.28 (s, 3H, CH_3), 1.42 (s, 9H, CH_3, ^{t}Bu), 1.44 (s, 3H, CH_3), 3.27 (m, 1H, H-5), 3.75 (m, 3H, H-5', CH_2), 4.05 (d, 1H, H-3, $^3J_{3\text{-}4}$= 2.4 Hz), 4.05 (m, 1H, H-4), 4.54 (d, 1H, H-2, $^3J_{2\text{-}1}$= 3.6 Hz), 5.43 (m, 1H, NH), 5.88 (d, 1H, H-1, $^3J_{1\text{-}2}$= 3.6 Hz), 7.07 (m, 1H, NH). ^{13}C NMR ($CDCl_3$), δ: 26.0 (CH_3), 26.7 (CH_3), 28.2 (CH_3, ^{t}Bu), 37.3 (C-5), 44.1 (CH_2), 73.9 (C-3), 79.6 (C-4), 80.6 (C, ^{t}Bu), 84.8 (C-2), 104.7 (C-1), 111.5 (CMe_2), 156.2 (CO), 171.7 (CO). Anal. calcd (%) for $C_{15}H_{26}N_2O_7$: C 52.01, H 7.57, N 8.09; found: C 52.06, H 7.56, N 8.07.

L31h: Yield: 307 mg, 79 %. ^{1}H NMR ($CDCl_3$), δ: 0.90 (d, 3H, CH_3, ^{i}Pr, $^3J_{H\text{-}H}$= 7.2 Hz), 0.93 (d, 3H, CH_3, ^{i}Pr, $^3J_{H\text{-}H}$= 7.2 Hz), 1.28 (s, 3H, CH_3), 1.41 (s, 9H, CH_3, ^{t}Bu), 1.44 (s, 3H, CH_3), 2.03 (m, 1H, CH, ^{i}Pr), 3.20 (m, 1H, H-5), 3.78 (m, 1H, H-5'), 3.95 (m, 1H, CH), 3.98 (d, 1H, H-3, $^3J_{3\text{-}4}$= 2.4 Hz), 4.02 (m, 1H, H-4), 4.55 (d, 1H, H-2, $^3J_{2\text{-}1}$= 4.0 Hz), 5.23 (m, 1H, NH), 5.87 (d, 1H, H-1, $^3J_{1\text{-}2}$= 4.0 Hz), 7.21 (m, 1H, NH). ^{13}C NMR ($CDCl_3$), δ: 18.2 (CH_3, ^{i}Pr), 19.5 (CH_3, ^{i}Pr), 26.3 (CH_3), 26.9 (CH_3), 28.5 (CH_3, ^{t}Bu), 31.0 (CH, ^{i}Pr), 37.4 (C-5), 60.0 (CH), 74.0 (C-3), 80.0 (C-4), 80.5 (C, ^{t}Bu), 85.0

(C-2), 104.9 (C-1), 111.7 (CMe_2), 156.2 (CO), 174.3 (CO). Anal. calcd (%) for $C_{18}H_{32}N_2O_7$: C 55.65, H 8.30, N 7.21; found: C 55.71, H 8.36, N 7.16.

L31i: Yield: 321 mg, 76 %.^{1}H NMR ($CDCl_3$), δ: 1.25 (s, 3H, CH_3), 1.40 (s, 9H, CH_3, ^{t}Bu), 1.42 (s, 3H, CH_3), 3.43 (m, 1H, H-5), 3.66 (m, 1H, H-5'), 3.73 (m, 1H, H-3), 3.89 (m, 1H, H-4), 4.51 (d, 1H, H-2, $^3J_{2\text{-}1}$= 3.6 Hz), 5.27 (m, 1H, CH), 5.72 (m, 1H, NH), 5.76 (d, 1H, H-1, $^3J_{1\text{-}2}$= 3.6 Hz), 6.89 (m, 1H, NH), 7.42 (m, 5H, CH=). ^{13}C NMR ($CDCl_3$), δ: 26.4 (CH_3), 27.1 (CH_3), 28.6 (CH_3, ^{t}Bu), 37.8 (C-5), 58.1 (CH), 74.4 (C-3), 79.9 (C-4), 80.3 (C, ^{t}Bu), 84.4 (C-2), 104.3 (C-1), 112.1 (CMe_2), 127.4 (CH=), 128.8 (CH=), 129.2 (CH=), 137.4 (C), 155.7 (CO), 172.7 (CO). Anal. calcd (%) for $C_{21}H_{30}N_2O_7$: C 59.70, H 7.16, N 6.63; found: C 59.72, H 7.17, N 6.61.

L32a: Yield: 330 mg, 85 %. ^{1}H NMR ($CDCl_3$), δ: 0.86 (d, 3H, CH_3, ^{i}Pr, $^3J_{H\text{-}H}$= 7.2 Hz), 0.91 (d, 3H, CH_3, ^{i}Pr, $^3J_{H\text{-}H}$= 7.2 Hz), 1.30 (s, 3H, CH_3), 1.39 (s, 9H, CH_3, ^{t}Bu), 1.52 (s, 3H, CH_3), 2.08 (m, 1H, CH, ^{i}Pr), 3.54 (m, 2H, H-5 and H-5'), 3.68 (m, 1H, H-3), 3.87 (m, 1H, H-4), 3.93 (m, 1H, CH), 4.53 (dd, 1H, H-2, $^3J_{2\text{-}1}$= 4.0 Hz, $^3J_{2\text{-}3}$= 3.6 Hz), 5.22 (m, 1H, NH), 5.69 (d, 1H, H-1, $^3J_{1\text{-}2}$= 4.0 Hz), 6.72 (m, 1H, NH). ^{13}C NMR ($CDCl_3$), δ: 17.8 (CH_3, ^{i}Pr), 19.4 (CH_3, ^{i}Pr), 26.4 (CH_3), 26.6 (CH_3), 28.4 (CH_3, ^{t}Bu), 30.8 (CH, ^{i}Pr), 39.7 (C-5), 60.2 (CH), 72.9 (C-3), 78.5 (C-4), 79.0 (C-2), 80.1 (C, ^{t}Bu), 103.8 (C-1), 112.9 (CMe_2), 156.0 (CO), 172.9 (CO). Anal. calcd (%) for $C_{18}H_{32}N_2O_7$: C 55.65, H 8.30, N 7.21; found: C 55.70, H 8.35, N 7.20.

L33a: Yield: 280 mg, 72 %. ^{1}H NMR ($CDCl_3$), δ: 0.93 (m, 6H, CH_3, ^{i}Pr), 1.29 (s, 3H, CH_3), 1.42 (s, 9H, CH_3, ^{t}Bu), 1.50 (s, 3H, CH_3), 2.06 (m, 1H, CH, ^{i}Pr), 3.80 (m, 3H, H-5, H-5' and CH), 4.31 (m, 1H, H-4), 4.41 (m, 1H, H-3), 4.53 (d, 1H, H-2, $^3J_{2\text{-}1}$= 4.0 Hz), 5.16 (m, 1H, NH), 5.86 (d, 1H, H-1, $^3J_{1\text{-}2}$= 4.0 Hz), 7.42 (m, 1H, NH). ^{13}C NMR ($CDCl_3$), δ: 18.4 (CH_3, ^{i}Pr), 19.5 (CH_3, ^{i}Pr), 26.4 (CH_3), 26.8 (CH_3), 28.5 (CH_3, ^{t}Bu), 30.4 (CH, ^{i}Pr), 57.1 (C-3), 59.8 (CH), 60.6 (C-5), 78.0 (C-4), 80.5 (C, ^{t}Bu), 84.7 (C-2), 104.5 (C-1), 112.2 (CMe_2), 156.4 (CO), 173.0 (CO). Anal. calcd (%) for $C_{18}H_{32}N_2O_7$: C 55.65, H 8.30, N 7.21; found: C 55.66, H 8.32, N 7.22.

L33b: Yield: 346 mg, 82 %. ^{1}H NMR ($CDCl_3$), δ: 1.24 (s, 3H, CH_3), 1.40 (s, 9H, CH_3, ^{t}Bu), 1.47 (s, 3H, CH_3), 3.05 (m, 1H, H-5), 4.08 (m, 2H, H-5' and H-3), 4.28 (m, 1H, H-4), 4.57 (m, 1H, CH), 4.60 (d, 1H, H-2, $^3J_{2\text{-}1}$= 3.6 Hz), 5.19 (m, 1H, NH), 5.88 (d, 1H, H-1, $^3J_{1\text{-}2}$= 3.6 Hz), 7.34 (m, 5H, CH=), 7.51 (m, 1H, NH). ^{13}C NMR ($CDCl_3$), δ: 26.4 (CH_3), 26.9 (CH_3), 28.5 (CH_3, ^{t}Bu), 57.8 (C-3), 59.2 (CH), 60.0 (C-5), 77.7 (C-4), 80.6 (C, ^{t}Bu), 84.4 (C-2), 104.5 (C-1), 112.2 (CMe_2), 127.3 (CH=), 128.7

(CH=), 129.2 (CH=), 137.6 (C), 155.6 (CO), 171.6 (CO). Anal. calcd (%) for $C_{21}H_{30}N_2O_7$: C 59.70, H 7.16, N 6.63; found: C 59.76, H 7.19, N 6.61.

L33d: Yield: 322 mg, 80 ^{1}H NMR ($CDCl_3$), δ: 0.93 (m, 6H, CH_3, ^{i}Bu), 1.30 (s, 3H, CH_3), 1.42 (s, 9H, CH_3, ^{t}Bu), 1.48 (s, 3H, CH_3), 1.51 (m, 1H, CH_2, ^{i}Bu), 1.64 (m, 2H, CH and CH_2, ^{i}Bu), 3.76 (m, 2H, H-5 and CH), 3.80 (m, 1H, H-5'), 4.29 (m, 1H, H-4), 4.39 (m, 1H, H-3), 4.51 (d, 1H, H-2, $^3J_{2\text{-}1}$= 4.0 Hz), 5.11 (m, 1H, NH), 5.79 (d, 1H, H-1, $^3J_{1\text{-}2}$= 4.0 Hz), 7.37 (m, 1H, NH). ^{13}C NMR ($CDCl_3$), δ: 21.8 (CH_3, ^{i}Bu), 22.7 (CH_3, ^{i}Bu), 24.7 (CH_2, ^{i}Bu), 26.4 (CH_3), 26.9 (CH_3), 28.4 (CH_3, ^{t}Bu), 40.4 (CH, ^{i}Bu), 57.0 (C-3), 59.7 (CH), 60.3 (C-5), 78.2 (C-4), 80.6 (C, ^{t}Bu), 84.9 (C-2), 103.9 (C-1), 112.4 (CMe_2), 156.2 (CO), 174.1 (CO). Anal. calcd (%) for $C_{19}H_{34}N_2O_7$: C 56.70, H 8.51, N 6.96; found: C 56.67, H 8.52, N 6.95.

L33h: Yield: 319 mg, 82 %. ^{1}H NMR ($CDCl_3$), δ: 0.90 (d, 3H, CH_3, $^3J_{H\text{-}H}$= 7.2 Hz), 0.97 (d, 3H, CH_3, $^3J_{H\text{-}H}$= 7.2 Hz), 1.29 (s, 3H, CH_3), 1.43 (s, 9H, CH_3, ^{t}Bu), 1.49 (s, 3H, CH_3), 2.11 (m, 1H, CH, ^{i}Pr), 2.77 (m, 1H, H-5), 3.83 (d, 1H, H-3, $^3J_{3\text{-}4}$= 1.2 Hz), 3.89 (m, 2H, H-5' and H-4), 4.32 (m, 1H, CH), 4.55 (d, 1H, H-2, $^3J_{2\text{-}1}$= 3.6 Hz), 5.18 (m, 1H, NH), 5.88 (d, 1H, H-1, $^3J_{1\text{-}2}$= 3.6 Hz), 7.52 (m, 1H, NH). ^{13}C NMR ($CDCl_3$), δ: 17.8 (CH_3, ^{i}Pr), 19.3 (CH_3, ^{i}Pr), 26.1 (CH_3), 26.6 (CH_3), 28.3 (CH_3, ^{t}Bu), 30.5 (CH, ^{i}Pr), 57.4 (C-3), 60.1 (CH and C-5), 77.2 (C-4), 80.0 (C, ^{t}Bu), 84.6 (C-2), 104.4 (C-1), 112.0 (CMe_2), 156.0 (CO), 172.7 (CO). Anal. calcd (%) for $C_{18}H_{32}N_2O_7$: C 55.65, H 8.30, N 7.21; found: C 55.69, H 8.33, N 7.19.

L34a: Yield: 334 mg, 86 %. ^{1}H NMR ($CDCl_3$), δ: 0.88 (d, 3H, CH_3, ^{i}Pr, $^3J_{H\text{-}H}$= 7.2 Hz), 0.93 (d, 3H, CH_3, ^{i}Pr, $^3J_{H\text{-}H}$= 7.2 Hz), 1.31 (s, 3H, CH_3), 1.40 (s, 9H, CH_3, ^{t}Bu), 1.49 (s, 3H, CH_3), 2.11 (m, 1H, CH, ^{i}Pr), 3.64 (dd, 1H, H-5, $^2J_{5\text{-}5'}$= 13.2 Hz, $^3J_{5\text{-}4}$= 2.8 Hz), 3.74 (m, 1H, H-4), 3.81 (dd, 1H, H-5, $^2J_{5\text{-}5'}$= 13.2 Hz, $^3J_{5\text{-}4}$= 2.4 Hz), 3.93 (m, 1H, CH), 4.20 (m, 1H, -3), 4.59 (dd, 1H, H-2, $^3J_{2\text{-}1}$= 4.0 Hz, $^3J_{2\text{-}3}$= 3.6 Hz), 5.10 (m, 1H, NH), 5.84 (d, 1H, H-1, $^3J_{1\text{-}2}$= 4.0 Hz), 6.59 (m, 1H, NH). ^{13}C NMR ($CDCl_3$), δ: 17.6 (CH_3, ^{i}Pr), 19.2 (CH_3, ^{i}Pr), 26.3 (CH_3), 26.4 (CH_3), 28.2 (CH_3, ^{t}Bu), 30.5 (CH, ^{i}Pr), 51.3 (C-3), 59.8 (CH), 60.5 (C-5), 78.8 (C-2), 80.1 (C, ^{t}Bu), 80.4 (C-4), 104.1 (C-1), 112.5 (CMe_2), 155.8 (CO), 172.8 (CO). Anal. calcd (%) for $C_{18}H_{32}N_2O_7$: C 55.65, H 8.30, N 7.21; found: C 55.72, H 8.36, N 7.16.

4.3.4.3. Typical procedure for the benzoylation of L31-L34a-i

A solution of benzoyl chloride (1.1 mmol, 130 μL) in dichloromethane (0.4 mL) was slowly added to a cooled solution (0 °C) of the desired pseudo-dipeptide (1 mmol) in pyridine (1 mL). The reaction was stirred overnight. Then ice was added and the product was extracted with dichloromethane (3 x 20 mL), dried over $MgSO_4$, evaporated to dryness and purified by flash chromatography (pentane/ethyl acetate: 2/1) to produce the corresponding benzoylated product as white solids.

N-(tert-Butoxycarbonyl)-L-valine-(5-amide-3-O-benzoyl-1,2-O-isopropylidene-α-D-xylofuranose): Yield: 374 mg, 76 %. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 0.89 (d, 3H, CH_3, J = 6.8 Hz), 0.95 (d, 3H, CH_3, J = 6.8 Hz), 1.33 (s, 3H, CH_3), 1.44 (s, 9H, CH_3), 1.53 (s, 3H, CH_3), 2.16 (m, 1H, CH), 3.58 (t, 2H, H-5, H-5', $^3J_{5,5'-4}$ = 6.4 Hz), 3.95 (t, 1H, CH-NH, J_{CH-NH} = 6.8 Hz), 4.43 (dt, 1H, H-4, $^3J_{4-5,5'}$ = 6.6 Hz, $^3J_{4-3}$ = 2.8 Hz), 4.68 (d, 1H, H-2, $^3J_{2-1}$ = 3.6 Hz), 5.09 (d, 1H, NHBoc, J_{NH-CH} = 9.2 Hz), 5.42 (d, 1H, H-3, $^3J_{3-4}$ = 2.8 Hz), 6.00 (d, 1H, H-1, $^3J_{1-2}$ = 3.6 Hz), 6.41 (b, 1H, NH), 7.44-8.15 (m, 5H, CH=). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 17.9 (CH_3), 19.5 (CH_3), 26.4 (CH_3), 26.8 (CH_3), 28.5 (CH_3), 31.1 ($CHMe_2$), 37.9 (C-5), 60.0 (CH), 77.0 (C-3), 78.2 (C-4), 83.8 (C-2), 104.9 (C-1), 112.6 (CMe_2), 128.6-134.0 (CH=), 156.0 (CMe_3), 165.7 (CO), 171.9 (CO).

N-(tert-Butoxycarbonyl)-L-phenylglycine-(5-amide-3-O-benzoyl-1,2-O-isopropylidene-α-D-xylofuranose): Yield: 337 mg, 64 %. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 1.31 (s, 3H,CH_3), 1.40 (s, 9H, CH_3), 1.51 (s, 3H, CH_3), 3.44 (m, 1H, H-5'), 3.63 (m, 1H, H-5), 4.37 (sp, 1H, H-4), 4.63 (d, 1H, H-2, $^3J_{2-1}$ = 4 Hz), 5.18 (a, 1H, CH-NH), 5.26 (d, 1H, H-3, $^3J_{3-4}$ = 2.8 Hz), 5.92 (a, 1H, NHBoc), 5.95 (d, 1H, H-1, $^3J_{1-2}$ = 4 Hz), 6.42 (a, 1H, NH), 7.27-8.11 (m, 10H, CH=). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 26.4 (CH_3), 26.8 (CH_3), 28.4 (CH_3), 38.4 (C-5), 58.7 (CH-NH), 76.9 (C-3), 78.1 (C-4), 83.6 (C-2), 104.8 (C-1), 112.5 (CMe_2), 127.3-133.9 (CH=), 138.4 (CAr), 155.3 (CMe_3) 165.6 (CO), 170.6 (CO).

N-(tert-Butoxycarbonyl)-L-phenylalanine-(5-amide-3-O-benzoyl-1,2-O-isopropylidene-α-D-xylofuranose): Yield: 260 mg, 48 %. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 1.33 (s, 3H,CH_3), 1.40 (s, 9H, CH_3), 1.56 (s, 3H, CH_3),3.04 (m, 2H, H-8, H-8'), 3.38 (m, 1H, H-5'), 3.59 (m, 1H, H-5), 4.24 (m, 1H, H-4), 4.37 (a, 1H, CH-NH), 4.63 (d, 1H, H-2, $^3J_{2-1}$ = 4 Hz), 5.14 (m, 1H, H-3), 5.27 (a, 1H, NHBoc), 5.95 (d, 1H, H-1, $^3J_{1-2}$ = 3.6 Hz), 6.37

(a, 1H, NH), 7.20-8.11 (m, 10H, CH=). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 26.3 (CH_3), 26.8 (CH_3), 28.4 (CH_3), 37.6 (C-5), 39.0 (CH_2), 56.2 (CH-NH), 76.8 (C-3), 77.9 (C-4), 83.7 (C-2), 104.8 (C-1), 112.5 (CMe_2), 127.1-133.9 (CH=), 136.8 (CAr), 155.6 (CMe_3) 165.7 (CO), 171.7 (CO).

N-(tert-Butoxycarbonyl)-L-leucine-(5-amide-3-O-benzoyl-1,2-O-isopropylidene-α-D-xylofuranose): Yield: 213 mg, 42 %. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 0.94 (dd, 6H, CH_3, J = 8 Hz, J = 4 Hz), 1.34 (s, 3H,CH_3), 1.45 (s, 9H, CH_3), 1.55 (s, 3H, CH_3), 1.66 (m, 3H, CH_2, CH), 3.59 (t, 2H, H-5, H-5', ^3J = 6 Hz), 4.13 (a, 1H, CH-NH), 4.32 (dt, 1H, H-4, $^3J_{4\text{-}5,5'}$ = 6.5 Hz, $^3J_{4\text{-}3}$ = 3 Hz), 4.69 (d, 1H, H-2, $^3J_{2\text{-}1}$ = 3.6 Hz), 4.84 (a, 1H, NHBoc), 5.42 (d, 1H, H-3, $^3J_{3\text{-}4}$ = 2.8 Hz), 6.01 (d, 1H, H-1, $^3J_{1\text{-}2}$ = 3.6 Hz), 6.48 (t, 1H, NH, J = 6 Hz), 7.45-8.12 (m, 5H, CH=). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 22.1 (CH_3), 23.2 (CH_3), 25.0 (CH_2), 26.4 (CH_3), 26.8 (CH_3), 28.5 (CH_3), 38.2 (C-5), 41.6 ($CHMe_2$), 56.8 (CH-NH), 77.4 (C-3), 78.2 (C-4), 83.8 (C-2), 104.9 (C-1), 112.6 (CMe_2), 128.7-133.9 (CH=), 150.4 (CMe_3), 165.5 (CO), 172.9 (CO).

N-(tert-Butoxycarbonyl)-L-tert-leucine-(5-amide-3-O-benzoyl-1,2-O-isopropylidene-α-D-xylofuranose): Yield: 400 mg, 79 %. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 0.98 (s, 9H, CH_3), 1.30 (s, 3H,CH_3), 1.41 (s, 9H, CH_3), 1.51 (s, 3H, CH_3), 3.51 (m, 1H, H-5'), 3.62 (m, 1H, H-5), 3.91 (d, 1H, CH-NH, J = 9.6 Hz), 4.43 (m, 1H, H-4), 4.66 (d, 1H, H-2, $^3J_{2\text{-}1}$ = 4 Hz), 5.40 (d, 1H, H-3, $^3J_{3\text{-}4}$ = 2.4 Hz), 5.45 (m, 1H, NHBoc), 5.98 (d, 1H, H-1, $^3J_{1\text{-}2}$ = 4 Hz), 6.46 (m, 1H, NH), 7.41-8.16 (m, 5H, CH=). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 26.4 (CH_3), 26.7 (CH_3), 26.8 (CH_3), 28.4 (CH_3), 37.8 (C-5), 62.5 (CH-NH), 77.0 (C-3), 78.1 (C-4), 83.7 (C-2), 104.8 (C-1), 112.5 (CMe_2), 128.4-134.7 (CH=), 156.0 (CMe_3), 165.7 (CO), 169.9 (CMe_3), 171.4 (CO).

N-(tert-Butoxycarbonyl)-L-alanine-(5-amide-3-O-benzoyl-1,2-O-isopropylidene-α-D-xylofuranose): Yield: 293 mg, 63 %. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 1.31 (s, 3H,CH_3), 1.34 (d, 3H, CH_3, J = 7.2 Hz), 1.43 (s, 9H, CH_3), 1.52 (s, 3H, CH_3), 3.59 (m, 2H, H-5, H-5'), 4.19 (a, 1H, CH-NH), 4.44 (dt, 1H, H-4, $^3J_{4\text{-}5,5'}$ = 6.4 Hz, $^3J_{4\text{-}3}$ = 2.6 Hz), 4.67 (d, 1H, H-2, $^3J_{2\text{-}1}$ = 3.6 Hz), 5.20 (a, 1H, NHBoc), 5.42 (d, 1H, H-3, $^3J_{3\text{-}4}$ = 2.4 Hz), 5.99 (d, 1H, H-1, $^3J_{1\text{-}2}$ = 4 Hz), 6.74 (t, 1H, NH, J = 5.6 Hz), 7.42-8.11 (m, 5H, CH=). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 18.6 (CH_3), 26.3 (CH_3), 26.8 (CH_3), 28.4 (CH_3), 38.0 (C-5), 50.3 (CH), 76.9 (C-3), 78.1 (C-4), 83.7 (C-2), 104.9 (C-1), 112.5 (CMe_2), 128.5-133.9 (CH=), 155.7 (CMe_3), 165.7 (CO), 171.4 (CO).

N-(tert-Butoxycarbonyl)-L-glycine-(5-amide-3-O-benzoyl-1,2-O-isopropylidene-α-D-xylofuranose): Yield: 198 mg, 44 %. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 1.32 (s, 3H,CH_3), 1.45 (s, 9H, CH_3), 1.53 (s, 3H, CH_3), 3.59 (m, 2H, H-5, H-5'), 3.78 (m, 2H, CH_2-NH), 4.43 (dt, 1H, H-4, $^{3}J_{4\text{-}5,5'}$ = 6.4 Hz, $^{3}J_{4\text{-}3}$ = 3.2 Hz), 4.68 (d, 1H, H-2, $^{3}J_{2\text{-}1}$ = 3.6 Hz), 5.16 (t, 1H, NHBoc, *J* = 5.6 Hz), 5.43 (d, 1H, H-3, $^{3}J_{3\text{-}4}$ = 2.8 Hz), 5.99 (d, 1H, H-1, $^{3}J_{1\text{-}2}$ = 3.6 Hz), 6.52 (a, 1H, NH), 7.43-8.02 (m, 5H, CH=). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 26.1 (CH_3), 26.6 (CH_3), 28.3 (CH_3), 37.7 (C-5), 44.2 (CH_2-NH), 76.8 (C-3), 77.9 (C-4), 83.6 (C-2), 104.5 (C-1), 112.4 (CMe_2), 128.0-133.8 (CH=), 165.5 (CO), 169.6 (CO).

N-(tert-Butoxycarbonyl)-D-valine-(5-amide-3-O-benzoyl-1,2-O-isopropylidene-α-D-xylofuranose): Yield: 305 mg, 62 %. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 0.91 (d, 6H, CH_3, *J* = 6.8 Hz), 1.30 (s, 3H, CH_3), 1.41 (s, 9H, CH_3), 1.49 (s, 3H, CH_3), 2.06 (m, 1H, CH), 3.53 (m, 1H, H-5'), 3.66 (m, 1H, H-5), 3.96 (t, 1H, CH-NH, $J_{CH\text{-}NH}$ = 7.8 Hz), 4.59 (sp, 1H, H-4), 4.65 (d, 1H, H-2, $^{3}J_{2\text{-}1}$ = 4 Hz), 5.43 (d, 1H, H-3, $^{3}J_{3\text{-}4}$ = 2.4 Hz), 5.46 (d, 1H, NHBoc, *J* = 8.4 Hz), 5.96 (d, 1H, H-1, $^{3}J_{1\text{-}2}$ = 4 Hz), 6.81 (a, 1H, NH), 7.40-8.09 (m, 5H, CH=). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 18.1 (CH_3), 19.3 (CH_3), 26.3 (CH_3), 26.7 (CH_3), 28.4 (CH_3), 31.1 ($CHMe_2$), 38.0 (C-5), 60.2 (CH), 76.9 (C-3), 77.9 (C-4), 83.7 (C-2), 104.8 (C-1), 112.5 (CMe_2), 128.4-133.8 (CH=), 156.2 (CMe_3), 165.6 (CO), 170.4 (CO).

N-(tert-Butoxycarbonyl)-D-phenylglycine-(5-amide-3-O-benzoyl-1,2-O-isopropylidene-α-D-xylofuranose): Yield: 337 mg, 64 %. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 1.31 (s, 3H,CH_3), 1.40 (s, 9H, CH_3), 1.48 (s, 3H, CH_3), 3.45 (m, 1H, H-5'), 3.64 (m, 1H, H-5), 4.36 (dt, 1H, H-4, $^{3}J_{4\text{-}5,5'}$ = 6.5 Hz, $^{3}J_{4\text{-}3}$ = 2.8 Hz), 4.65 (d, 1H, H-2, $^{3}J_{2\text{-}1}$ = 4 Hz), 5.16 (a, 1H, CH-NH), 5.39 (d, 1H, H-3, $^{3}J_{3\text{-}4}$ = 3.2 Hz), 5.88 (d, 1H, NHBoc, *J* = 7.2 Hz), 5.94 (d, 1H, H-1, $^{3}J_{1\text{-}2}$ = 3.2 Hz), 6.42 (t, 1H, NH, *J* = 5.6 Hz), 7.27-8.10 (m, 10H, CH=). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 26.4 (CH_3), 26.8 (CH_3), 28.4 (CH_3), 38.1 (C-5), 58.6 (CH-NH), 76.9 (C-3), 77.8 (C-4), 83.6 (C-2), 104.8 (C-1), 112.5 (CMe_2), 127.3-133.9 (CH=), 138.3 (CAr), 155.3 (CMe_3) 165.8 (CO), 170.2 (CO).

N-(tert-Butoxycarbonyl)-L-valine-(5-amide-3-O-benzoyl-1,2-O-isopropylidene-α-D-ribofuranose): Yield: 374 mg, 76 %. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 0.89 (d, 3H, CH_3, *J* = 8 Hz), 0.95 (d, 3H, CH_3, *J* = 4 Hz), 1.33 (s, 3H, CH_3), 1.45 (s, 9H, CH_3), 1.56 (s, 3H, CH_3), 2.15 (m, 1H, CH), 3.52 (m, 1H, H-5'), 3.76 (m, 1H, H-5), 3.93 (t, 1H, CH-NH, $J_{CH\text{-}NH}$ = 6 Hz), 4.36 (sp, 1H, H-4), 4.71 (dd, 1H, H-3, $^{3}J_{3\text{-}2}$ = 8 Hz , $^{3}J_{3\text{-}4}$ = 4 Hz),

4.94 (t, 1H, H-2, $^{3}J_{2\text{-}1,3}$ = 6 Hz), 5.00 (a, 1H, NHBoc), 5.85 (d, 1H, H-1, $^{3}J_{1\text{-}2}$ = 4 Hz), 6.26 (a, 1H, NH), 7.43-8.09 (m, 5H, CH=). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 17.5 (CH_3), 19.5 (CH_3), 26.7 (CH_3), 28.5 (CH_3), 31.0 ($CHMe_2$), 39.7 (C-5), 60.1 (CH), 73.7 (C-3), 76.4 (C-4), 77.7 (C-2), 104.3 (C-1), 113.4 (CMe_2), 128.6-133.7 (CH=), 149.8 (CMe_3), 166.1 (CO), 172.0 (CO).

N-(tert-Butoxycarbonyl)-L-valine-(3-amide-5-O-benzoyl-1,2-O-isopropylidene-α-D-xylofuranose): Yield: 251 mg, 51 %. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 0.86 (d, 3H, CH_3, *J* = 4 Hz), 0.95 (d, 3H, CH_3, *J* = 8 Hz), 1.33 (s, 3H, CH_3), 1.45 (s, 9H, CH_3), 1.55 (s, 3H, CH_3), 2.21 (m, 1H, CH), 3.86 (t, 1H, CH-NH, $J_{CH\text{-}NH}$ = 8 Hz), 4.49 (m, 1H, H-3), 4.52 (d, 1H, H-2, $^{3}J_{2\text{-}1}$ = 4 Hz), 4.60 (m, 1H, H-4), 4.66 (dd, 2H, H-5, H-5', $^{2}J_{5\text{-}5'}$ = 8 Hz , $^{3}J_{5\text{-}5'\text{-}4}$ = 4 Hz), 4.86 (a, 1H, NHBoc), 5.90 (d, 1H, H-1, $^{3}J_{1\text{-}2}$ = 4 Hz), 6.41 (d, 1H, NH, *J* = 8 Hz), 7.44-8.11 (m, 5H, CH=). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 17.8 (CH_3), 19.6 (CH_3), 26.3 (CH_3), 26.7 (CH_3), 28.4 (CH_3), 29.8 ($CHMe_2$), 55.7 (C-5), 59.6 (CH), 62.0 (C-3), 76.1 (C-4), 84.6 (C-2), 104.7 (C-1), 112.5 (CMe_2), 128.6-133.4 (CH=), 146.9 (CMe_3), 166.2 (CO), 171.7 (CO).

N-(tert-Butoxycarbonyl)-L-phenylglycine-(3-amide-5-O-benzoyl-1,2-O-isopropylidene-α-D-xylofuranose): Yield: 342 mg, 65 %. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 1.27 (s, 3H,CH_3), 1.41 (s, 9H, CH_3), 1.52 (s, 3H, CH_3), 4.39 (s, 1H, H-2), 4.53 (d, 1H, H-3, $^{3}J_{3\text{-}4}$ = 6 Hz), 4.58 (m, 1H, H-4), 4.63 (dd, 2H, H-5, H-5', $^{2}J_{5\text{-}5'}$ = 8.8 Hz, $^{3}J_{5,5'\text{-}4}$ = 3.2 Hz), 5.19 (a, 1H, CH-NH), 5.71 (a, 1H, NHBoc), 5.77 (s, 1H, H-1), 6.66 (a, 1H, NH), 7.29-8.12 (m, 10H, CH=). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 26.3 (CH_3), 26.7 (CH_3), 28.4 (CH_3), 56.2 (C-5), 59.2 (CH-NH), 62.0 (C-3), 76.2 (C-4), 84.4 (C-2), 104.6 (C-1), 112.5 (CMe_2), 127.3-133.7 (CH=), 137.5 (CAr), 155.6 (CMe_3) 166.3 (CO), 170.7 (CO).

N-(tert-Butoxycarbonyl)-L-leucine-(3-amide-5-O-benzoyl-1,2-O-isopropylidene-α-D-xylofuranose): Yield: 288 mg, 57 %. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 0.86 (d, 3H, CH_3, *J* = 4 Hz), 0.95 (d, 3H, CH_3, *J* = 8 Hz), 1.33 (s, 3H, CH_3), 1.45 (s, 9H, CH_3), 1.55 (s, 3H, CH_3), 1.66 (m, 3H, CH_2, CH), 3.86 (t, 1H, CH-NH, $J_{CH\text{-}NH}$ = 8 Hz), 4.49 (m, 1H, H-3), 4.52 (d, 1H, H-2, $^{3}J_{2\text{-}1}$ = 4 Hz), 4.60 (m, 1H, H-4), 4.66 (dd, 2H, H-5, H-5', $^{2}J_{5\text{-}5'}$ = 8 Hz , $^{3}J_{5\text{-}5'\text{-}4}$ = 4 Hz), 4.86 (a, 1H, NHBoc), 5.90 (d, 1H, H-1, $^{3}J_{1\text{-}2}$ = 4 Hz), 6.41 (d, 1H, NH, *J* = 8 Hz), 7.44-8.11 (m, 5H, CH=). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 22.1 (CH_3), 23.2 (CH_3), 26.3 (CH_3), 27.2 (CH_3), 28.4 (CH_3), 32.8 ($CHMe_2$), 55.7 (C-5), 59.6 (CH),

62.0 (C-3), 76.1 (C-4), 84.6 (C-2), 104.7 (C-1), 112.5 (CMe_2), 128.6-133.4 (CH=), 146.9 (CMe_3), 166.2 (CO), 171.7 (CO).

N-(tert-Butoxycarbonyl)-D-valine-(3-amide-5-O-benzoyl-1,2-O-isopropylidene-α-D-xylofuranose): Yield: 290 mg, 59 %. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 0.88 (d, 6H, CH_3, J = 6.8 Hz), 1.30 (s, 3H, CH_3), 1.44 (s, 9H, CH_3), 1.53 (s, 3H, CH_3), 2.03 (m, 1H, CH), 3.88 (t, 1H, CH-NH, J_{CH-NH} = 8 Hz), 4.42 (m, 1H, H-3), 4.50 (d, 1H, H-2, $^3J_{2-1}$ = 4 Hz), 4.60 (m, 1H, H-4), 4.68 (dd, 2H, H-5, H-5', $^2J_{5-5'}$ = 9.4 Hz , $^3J_{5-5'-4}$ = 3.4 Hz), 5.27 (d, 1H, NHBoc, J = 7.6 Hz), 5.93 (d, 1H, H-1, $^3J_{1-2}$ = 3.6 Hz), 6.79 (d, 1H, NH, J = 8.4 Hz), 7.41-8.12 (m, 5H, CH=). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 17.8 (CH_3), 19.3 (CH_3), 26.1 (CH_3), 26.5 (CH_3), 28.3 (CH_3), 30.6 ($CHMe_2$), 55.6 (C-5), 60.4 (CH), 62.1 (C-3), 75.9 (C-4), 84.5 (C-2), 104.6 (C-1), 112.2 (CMe_2), 128.4-133.4 (CH=), 156.2 (CMe_3), 166.1 (CO), 172.1 (CO).

N-(tert-Butoxycarbonyl)-L-valine-(3-amide-5-O-benzoyl-1,2-O-isopropylidene-α-D-ribofuranose): Yield: 399 mg, 81 %. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 0.95 (d, 3H, CH_3, J = 8 Hz), 1.00 (d, 3H, CH_3, J = 4 Hz), 1.38 (s, 3H, CH_3), 1.47 (s, 9H, CH_3), 1.59 (s, 3H, CH_3), 2.17 (m, 1H, CH), 3.99 (a, 1H, CH-NH), 4.09 (m, 1H, H-4), 4.3 (dd, 1H, H-5', $^2J_{5-5'}$ = 12 Hz , $^3J_{5-5'-4}$ = 4 Hz), 4.46 (m, 1H, H-3), 4.65 (t, 1H, H-2, $^3J_{2-1,3}$ = 4 Hz), 4.74 (dd, 1H, H-5, $^2J_{5-5'}$ = 12 Hz , $^3J_{5-5'-4}$ = 4 Hz), 5.09 (a, 1H, NHBoc), 5.91 (d, 1H, H-1, $^3J_{1-2}$ = 4 Hz), 6.36 (d, 1H, NH, J = 12 Hz), 7.44-8.12 (m, 5H, CH=). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 17.8 (CH_3), 19.6 (CH_3), 26.5 (CH_3), 26.8 (CH_3), 28.5 (CH_3), 31.0 ($CHMe_2$), 52.0 (C-3), 59.9 (CH), 63.6 (C-5), 78.5 (C-4), 78.9 (C-2), 104.7 (C-1), 117.7 (CMe_2), 128.5-133.2 (CH=), 149.8 (CMe_3), 166.4 (CO), 171.9 (CO).

4.3.4.4. Typical procedure for the preparation of thioamide ligands L35-L38a-i

To a cooled solution of the desired benzoylated product (1 mmol) in THF (4 mL) Lawesson's reagent (0.8 mmol, 317 mg) was added. The reaction was stirred overnight at 60 °C. Then, the reaction mixture was evaporated and chromatographed (pentane/ethyl acetate: 3/1) to produce the corresponding thioamides as white solids.

L35a: Yield: 232 mg, 57 %. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 0.93 (dd, 6H, CH_3, $^2J_{5-5'}$ = 10.6 Hz, $^3J_{5,5'-4}$ = 6.8 Hz), 1.33 (s, 3H, CH_3), 1.44 (s, 9H, CH_3), 1.53 (s, 3H,

CH_3), 2.28 (m, 1H, CH), 3.97 (m, 1H, H-5'), 4.02 (m, 1H, H-5), 4.08 (m, 1H, CH-NH), 4.63 (sp, 1H, H-4), 4.70 (d, 1H, H-2, $^3J_{2\text{-}1}$ = 4 Hz), 5.26 (a, 1H, NHBoc), 5.42 (d, 1H, H-3, $^3J_{3\text{-}4}$ = 2.8 Hz), 6.01 (d, 1H, H-1, $^3J_{1\text{-}2}$ = 4 Hz), 7.45-8.04 (m, 5H, CH=), 8.25 (m, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 17.9 (CH_3), 19.8 (CH_3), 26.4 (CH_3), 26.8 (CH_3), 28.5 (CH_3), 33.5 ($CHMe_2$), 43.8 (C-5), 55.7 (CH), 76.4 (C-4), 77.2 (C-3), 83.7 (C-2), 104.9 (C-1), 112.7 (CMe_2), 128.8-134.2 (CH=), 155.8 (CMe_3), 165.8 (CO), 205.2 (CS).

L35b: Yield: 287 mg, 66 %. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 1.32 (s, 3H,CH_3), 1.42 (s, 9H, CH_3), 1.51 (s, 3H, CH_3), 3.83 (m, 1H, H-5'), 4.11 (m, 1H, H-5), 4.59 (m, 1H, H-4), 4.66 (d, 1H, H-2, $^3J_{2\text{-}1}$ = 4 Hz), 5.31 (d, 1H, H-3, $^3J_{3\text{-}4}$ = 2.4 Hz), 5.47 (a, 1H, CH-NH), 5.97 (d, 1H, H-1, $^3J_{1\text{-}2}$ = 3.6 Hz), 6.16 (d, 1H, NHBoc, *J* = 6.4 Hz), 7.27-8.12 (m, 10H, CH=), 8.41 (a, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 26.4 (CH_3), 26.8 (CH_3), 28.4 (CH_3), 44.2 (C-5), 64.0 (CH-NH), 76.4 (C-4), 77.1 (C-3), 83.6 (C-2), 104.8 (C-1), 112.7 (CMe_2), 127.1-133.9 (CH=), 139.5 (CAr), 154.9 (CMe_3) 165.7 (CO), 202.9 (CS).

L35c: Yield: 361 mg, 81%. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 1.34 (s, 3H,CH_3), 1.42 (s, 9H, CH_3), 1.57 (s, 3H, CH_3), 3.10 (m, 1H, H-8'), 3.20 (m, 1H, H-8), 3.67 (m, 1H, H-5'), 4.00 (m, 1H, H-5), 4.31 (m, 1H, H-4), 4.56 (a, 1H, CH-NH), 4.64 (d, 1H, H-2, $^3J_{2\text{-}1}$ = 4 Hz), 5.01 (m, 1H, H-3), 5.43 (a, 1H, NHBoc), 5.94 (d, 1H, H-1, $^3J_{1\text{-}2}$ = 4 Hz), 7.23-8.09 (m, 10H, CH=), 7.80 (a, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 26.4 (CH_3), 26.9 (CH_3), 28.5 (CH_3), 42.4 (CH_2), 43.3 (C-5), 60.6 (CH-NH), 76.3 (C-4), 77.4 (C-3), 83.8 (C-2), 104.8 (C-1), 112.8 (CMe_2), 127.3-134.1 (CH=), 136.8 (CAr), 155.2 (CMe_3) 165.9 (CO), 204.2 (CS).

L35d: Yield: 96 mg, 23 %. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 0.94 (dd, 6H, CH_3, *J* = 6.2 Hz, *J* = 1.8 Hz), 1.33 (s, 3H,CH_3), 1.44 (s, 9H, CH_3), 1.54 (s, 3H, CH_3), 1.58-1.74 (m, 3H, CH_2, CH), 3.93 (m, 1H, H-5'), 4.06 (m, 1H, H-5), 4.39 (m, 1H, CH-NH), 4.62 (sp, 1H, H-4), 4.70 (d, 1H, H-2, $^3J_{2\text{-}1}$ = 4 Hz), 5.13 (d, 1H, NHBoc, *J* = 7.6 Hz), 5.42 (d, 1H, H-3, $^3J_{3\text{-}4}$ = 2.8 Hz), 6.01 (d, 1H, H-1, $^3J_{1\text{-}2}$ = 4 Hz), 7.45-8.04 (m, 5H, CH=), 8.36 (a, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 22.1 (CH_3), 23.1 (CH_3), 25.1 (CH_2), 26.4 (CH_3), 26.8 (CH_3), 28.5 (CH_3), 44.0 (C-5), 44.8 ($CHMe_2$), 59.6 (CH-NH), 76.5 (C-4), 77.2 (C-3), 83.8 (C-2), 104.9 (C-1), 112.7 (CMe_2), 128.3-134.0 (CH=), 155.7 (CMe_3), 165.7 (CO), 206.3 (CS).

L35f: Yield: 299 mg, 78 %. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 1.33 (s, 3H,CH_3), 1.42 (s, 3H, CH_3), 1.44 (s, 9H, CH_3), 1.54 (s, 3H, CH_3), 3.95 (m, 1H, H-5'), 4.05 (m, 1H, H-5), 4.43 (m, 1H, CH-NH), 4.61 (sp, 1H, H-4), 4.70 (d, 1H, H-2, $^{3}J_{2\text{-}1}$ = 4 Hz), 5.15 (a, 1H, NHBoc), 5.43 (d, 1H, H-3, $^{3}J_{3\text{-}4}$ = 4 Hz), 6.01 (d, 1H, H-1, $^{3}J_{1\text{-}2}$ = 4 Hz), 7.45-8.03 (m, 5H, CH=), 8.28 (a, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 21.9 (CH_3), 26.4 (CH_3), 26.9 (CH_3), 28.5 (CH_3), 44.0 (C-5), 52.5 (CH), 76.5 (C-3), 77.4 (C-4), 83.8 (C-2), 104.9 (C-1), 112.7 (CMe_2), 128.8-134.0 (CH=), 157.7 (CMe_3), 165.8 (CO), 206.2 (CS).

L35g: Yield: 295 mg, 79 %. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 1.32 (s, 3H,CH_3), 1.45 (s, 9H, CH_3), 1.52 (s, 3H, CH_3), 3.95 (m, 1H, H-5'), 4.09 (m, 1H, H-5), 4.15 (d, 2H, H-7, H-7', $^{2}J_{7\text{-}7'}$ = 7.2 Hz), 4.62 (sp, 1H, H-4), 4.69 (d, 1H, H-2, $^{3}J_{2\text{-}1}$ = 4 Hz), 5.31 (a, 1H, NHBoc), 5.44 (d, 1H, H-3, $^{3}J_{3\text{-}4}$ = 3.2 Hz), 5.99 (d, 1H, H-1, $^{3}J_{1\text{-}2}$ = 3.6 Hz), 7.43-8.01 (m, 5H, CH=), 8.55 (a, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 26.4 (CH_3), 26.8 (CH_3), 28.4 (CH_3), 43.8 (C-5), 52.3 (CH_2-NH), 76.5 (C-4), 77.2 (C-3), 83.7 (C-2), 104.9 (C-1), 112.6 (CMe_2), 128.7-133.9 (CH=), 165.6 (CO), 200.8 (CS).

L35h: Yield: 260 mg, 64 %. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 0.93 (d, 6H, CH_3, J = 6 Hz), 1.31 (s, 3H, CH_3), 1.43 (s, 9H, CH_3), 1.49 (s, 3H, CH_3), 2.19 (m, 1H, CH), 3.84 (m, 1H, H-5'),4.09 (t, 1H, CH-NH, $J_{CH\text{-}NH}$ = 7.6 Hz), 4.17 (m, 1H, H-5), 4.65 (sp, 1H, H-4), 4.67 (d, 1H, H-2, $^{3}J_{2\text{-}1}$ = 4 Hz), 5.32 (a, 1H, NHBoc), 5.42 (d, 1H, H-3, $^{3}J_{3\text{-}4}$ = 2.4 Hz), 5.96 (d, 1H, H-1, $^{3}J_{1\text{-}2}$ = 3.6 Hz), 7.44-8.01 (m, 5H, CH=), 8.48 (a, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 18.3 (CH_3), 19.6 (CH_3), 26.5 (CH_3), 26.8 (CH_3), 28.5 (CH_3), 33.6 ($CHMe_2$), 44.0 (C-5), 66.7 (CH), 76.3 (C-4), 76.9 (C-3), 83.7 (C-2), 104.8 (C-1), 112.6 (CMe_2), 128.8-133.9 (CH=), 156.1 (CMe_3), 165.7 (CO), 205.1 (CS).

L35i: Yield: 321 mg, 74 %. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 1.32 (s, 3H,CH_3), 1.43 (s, 9H, CH_3), 1.47 (s, 3H, CH_3), 3.87 (t, 1H, H-5', J =7 Hz), 3.98 (t, 1H, H-5, J = 5.8 Hz), 4.54 (m, 1H, H-4), 4.68 (d, 1H, H-2, $^{3}J_{2\text{-}1}$ = 3.6 Hz), 5.40 (d, 1H, H-3, $^{3}J_{3\text{-}4}$ = 2.4 Hz), 5.47 (a, 1H, CH-NH), 5.95 (d, 1H, H-1, $^{3}J_{1\text{-}2}$ = 3.6 Hz), 6.12 (a, 1H, NHBoc), 7.27-8.10 (m, 10H, CH=), 8.37 (a, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 26.4 (CH_3), 26.8 (CH_3), 28.4 (CH_3), 44.1 (C-5), 63.9 (CH-NH), 76.3 (C-4), 76.9 (C-3), 83.6 (C-2), 104.8 (C-1), 112.7 (CMe_2), 127.0-134.0 (CH=), 139.4 (CAr), 155.1 (CMe_3) 165.8 (CO), 202.9 (CS).

L36a: Yield: 93 mg, 23 %. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 0.92 (d, 3H, CH_3, J = 8 Hz), 0.95 (d, 3H, CH_3, J = 4 Hz), 1.34 (s, 3H, CH_3), 1.46 (s, 9H, CH_3), 1.56 (s, 3H,

CH_3), 2.33 (m, 1H, CH), 3.98 (m, 1H, H-5'), 4.17 (m, 1H, H-5), 4.20 (a, 1H, CH-NH), 4.52 (sp, 1H, H-4), 4.73 (dd, 1H, H-3, $^3J_{3-2}$ = 10 Hz , $^3J_{3-4}$ = 6 Hz), 4.98 (t, 1H, H-2, $^3J_{2-1,3}$ = 4 Hz), 5.18 (a, 1H, NHBoc), 5.87 (d, 1H, H-1, $^3J_{1-2}$ = 4 Hz), 7.45-8.09 (m, 5H, CH=), 8.11 (a, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 17.6 (CH_3), 20.0 (CH_3), 26.7 (CH_3), 28.5 (CH_3), 33.2 ($CHMe_2$), 45.8 (C-5), 67.4 (CH), 74.0 (C-3), 75.5 (C-4), 77.6 (C-2), 104.5 (C-1), 113.6 (CMe_2), 128.6-133.7 (CH=), 155.8 (CMe_3), 166.0 (CO), 205.3 (CS).

L37a: Yield: 49 mg, 12 %. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 0.79 (d, 3H, CH_3, *J* = 8 Hz), 0.93 (d, 3H, CH_3, *J* = 4 Hz), 1.34 (s, 3H, CH_3), 1.44 (s, 9H, CH_3), 1.57 (s, 3H, CH_3), 2.44 (m, 1H, CH), 4.09 (t, 1H, CH-NH, J_{CH-NH} = 8 Hz), 4.57 (m, 1H, H-3), 4.62 (d, 1H, H-2, $^3J_{2-1}$ = 4 Hz), 4.68 (m, 1H, H-4), 5.02 (d, 1H, NHBoc, *J* = 8 Hz), 5.25 (dd, 2H, H-5, H-5', $^2J_{5-5'}$ = 8 Hz , $^3J_{5-5'-4}$ = 4 Hz), 5.88 (d, 1H, H-1, $^3J_{1-2}$ = 4 Hz), 7.44-8.06 (m, 5H, CH=), 8.40 (a, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 17.5 (CH_3), 19.3 (CH_3), 26.3 (CH_3), 26.7 (CH_3), 28.4 (CH_3), 32.0 ($CHMe_2$), 61.3 (C-5), 61.7 (C-3), 68.3 (CH), 75.7 (C-4), 83.7 (C-2), 104.6 (C-1), 112.7 (CMe_2), 128.6-134.3 (CH=), 156.1 (CMe_3), 166.1 (CO), 205.3 (CS).

L37b: Yield: 103 mg, 19 %. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 1.29 (s, 3H,CH_3), 1.44 (s, 9H, CH_3), 1.54 (s, 3H, CH_3), 4.51 (d, 1H, H-2, $^3J_{2-1}$ =3.2 Hz), 4.62 (d, 1H, H-3, $^3J_{3-4}$ = 5.2 Hz), 4.68 (m, 1H, H-4), 5.20 (dd, 1H, H-5, H-5', $^2J_{5-5'}$ = 8.2 Hz, $^3J_{5,5'-4}$ = 3.4 Hz), 5.51 (d, 1H, CH-NH), 5.69 (a, 1H, NHBoc), 5.75 (d, 1H, H-1, $^3J_{1-2}$ = 3.6 Hz), 7.25-8.11 (m, 10H, CH=), 8.45 (a, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 26.4 (CH_3), 26.7 (CH_3), 28.4 (CH_3), 61.6 (C-5), 61.7 (C-3), 65.8 (CH), 75.5 (C-4), 83.5 (C-2), 104.6 (C-1), 112.8 (CMe_2), 127.0-133.8 (CH=), 138.5 (CAr), 155.3 (CMe_3) 166.2 (CO), 203.2 (CS).

L37d: Yield: 67 mg, 16%. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 0.96 (dd, 6H, CH_3, *J* = 6.2 Hz, *J* = 1.8 Hz), 1.35 (s, 3H,CH_3), 1.42 (s, 9H, CH_3), 1.51 (s, 3H, CH_3), 1.6-1.8 (m, 3H, CH_2, CH), 4.06 (t, 1H, CH-NH, J_{CH-NH} = 8 Hz), 4.61 (m, 1H, H-3), 4.65 (m, 2H, H-2 and H-4), 5.01 (d, 1H, NHBoc, *J* = 8 Hz), 5.26 (dd, 2H, H-5, H-5', $^2J_{5-5'}$ = 8 Hz , $^3J_{5-5'-4}$ = 4 Hz), 5.92 (d, 1H, H-1, $^3J_{1-2}$ = 4 Hz), 7.44-8.06 (m, 5H, CH=), 8.42 (a, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 22.1 (CH_3), 23.1 (CH_3), 25.1 (CH_2), 26.4 (CH_3), 26.8 (CH_3), 32.0 ($CHMe_2$), 61.2 (C-5), 61.9 (C-3), 68.6 (CH), 75.9 (C-4), 83.3 (C-2), 104.1 (C-1), 112.2(CMe_2), 128.6-134.3 (CH=), 156.1 (CMe_3), 166.3 (CO), 205.6 (CS).

L37h: Yield: 85 mg, 21 %. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 0.83 (d, 3H, CH_3, *J* = 6.8 Hz), 0.91 (d, 3H, CH_3, *J* = 6.4 Hz), 1.32 (s, 3H, CH_3), 1.44 (s, 9H, CH_3), 1.56 (s, 3H, CH_3), 2.87 (m, 1H, CH), 3.48 (t, 1H, CH-NH, J_{CH-NH} = 5 Hz), 3.67 (t, 1H, NHBoc, J = 5 Hz), 4.51 (m, 1H, H-3), 4.59 (d, 1H, H-2, $^{3}J_{2-1}$ = 3.6 Hz), 4.69 (m, 1H, H-4), 5.26 (dd, 2H, H-5, H-5', $^{2}J_{5-5'}$ = 8.2 Hz , $^{3}J_{5-5'-4}$ = 3.8 Hz), 5.94 (d, 1H, H-1, $^{3}J_{1-2}$ = 3.6 Hz), 7.44-8.14 (m, 5H, CH=), 8.54 (a, 1H, NH).

L38a: Yield: 154 mg, 38 %. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 0.95 (dd, 6H, CH_3, *J* = 10.6 Hz, *J* = 6.6 Hz), 1.36 (s, 3H, CH_3), 1.44 (s, 9H, CH_3), 1.59 (s, 3H, CH_3), 2.29 (m, 1H, CH), 4.11 (t, 1H, CH-NH, J_{CH-NH} = 7.8 Hz), 4.23 (m, 1H, H-4), 4.34 (dd, 1H, H-5', $^{2}J_{5-5'}$ = 12.6 Hz , $^{3}J_{5-5'-4}$ = 5.8 Hz), 4.76 (t, 1H, H-2, $^{3}J_{2-1,3}$ = 1 Hz), 4.78 (dd, 1H, H-5, $^{2}J_{5-5'}$ = 5.4 Hz , $^{3}J_{5-5'-4}$ = 2 Hz), 5.20 (m, 1H, H-3), 5.28 (a, 1H, NHBoc), 5.93 (d, 1H, H-1, $^{3}J_{1-2}$ = 4 Hz), 7.41-8.08 (m, 5H, CH=). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 17.8 (CH_3), 19.7 (CH_3), 26.3 (CH_3), 26.6 (CH_3), 28.3 (CH_3), 33.2 ($CHMe_2$), 56.5 (C-3), 63.7 (C-5), 67.1 (CH), 78.1 (C-4), 78.3 (C-2), 104.6 (C-1), 113.1 (CMe_2), 128.1-133.0 (CH=), 155.6 (CMe_3), 166.2 (CO), 205.7 (CS).

4.3.4.5. Typical procedure for the ATH of ketones

The desired ligand (0.0055 mmol), catalyst precursor ($[RuCl_2(p\text{-cymene})_2]_2$ or $[RhCl_2Cp^*_2]_2$) (0.0025 mmol), and LiCl (4.2 mg, 0.1 mmol) were treated under vacuum for 10 min. Under argon, substrate (1 mmol), propan-2-ol (2 mL) and THF (2.5 mmol) were sequentially added. The reaction was initiated by adding ^{i}PrONa (0.1M, 0.5 mL, 0.05 mmol) to the solution. After completion of the reaction the solution was filtered through a plug of silica and eluted with Et_2O, and the solvents were evaporated. The products were analyzed by GC (CP Chirasil DEX CB).[7a,b,d]

4.3.5. Acknowledgements

We would like to thank the Swedish Research Council, the Knut and Alice Wallenberg foundation, the Spanish Government for providing grants CTQ2010-15835, and 2008PGIR/07 to O. Pàmies and 2008PGIR/08 to M. Diéguez, 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.

4.3.6. References

[1] See for example: a) *Asymmetric Catalysis in Industrial Scale: Challenges, Approaches and Solutions*; Eds. Blaser, H. U.; Schmidt, E. Wiley:Weinheim, Germany, **2003**; b) Ed. Ojima, I. in *Catalytic Asymmetric Synthesis*; Wiley-VCH: New York, **2000**; c) Brown, J. M. in *Comprehensive Asymmetric Catalysis*; Eds.; Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. Springer-Verlag: Berlin, **1999**; Vol. I, pp 121-182; d) Noyori, R. in *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, **1994**; e) *Applied Homogeneous Catalysis with Organometallic Compounds*, 2nd edition, Eds.: Cornils, B.; Herrmann, W. A. Wiley-VCH, Weinheim, **2002**.

[2] Farina, V.; Reeves, J. T.; Senanayake, C. H.; Song, J. J. *Chem. Rev.* **2006**, *106*, 2734.

[3] See for example: a) Wang, C.; Wu, X.; Xiao, J. *Chem. Asian J.* **2008**, *3*, 1750; b) Gladiali, S.; Alberico, E. *Chem. Soc. Rev.* **2006**, *35*, 226; c) Everaere, K.; Mortreux, A.; Carpentier, J.-F. *Adv. Synth. Catal.* **2003**, *345*, 67; d) Ohkuma, T.; Noyori R. in *Comprehensive Asymmetric Catalysis* I–III, Vol. 1. Eds.: Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. Springer, Berlin, **1999**, p. 199; e) Palmer, M. J.; Wills, M. *Tetrahedron: Asymmetry* **1999**, *10*, 2045; f) Noyori, R.; Hashiguchi, S. *Acc. Chem. Res.* **1997**, *30*, 97; g) Zassinovich, G.; Mestroni, G.; Gladiali, S. *Chem. Rev.* **1992**, *92*, 1051.

[4] a) Casey, C. P.; Guan, H. *J. Am. Chem. Soc.* **2007**, *129*, 5816; b) Zhou, S.; Fleischer, S.; Junge, K.; Das, S.; Addis, D.; Beller, M. *Angew. Chem. Int. Ed.* **2010**, *49*, 8121; c) Mikhailine, A. A.; Morris, R. H. *Inorg. Chem.* **2010**, *49*, 11039; d) Naik, A.; Maji, T.; Reiser, O. *Chem. Commun.* **2010**, *46*, 4475; e) Mikhailine, A.; Lough, A. L.; Morris, R. H. *J. Am. Chem. Soc.* **2009**, *131*, 1394.

[5] Hashiguchi, S.; Fujii, A.; Takahara, J.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 7562; b) Fujii, A.; Hashiguchi, S.; Uematsu, N.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 2521.

[6] See, for example: a) Nordin, S. J.; Roth, P.; Tarnai, T.; Alonso, D. A.; Brandt, P.; Andersson, P. G. *Chem. Eur. J.* **2001**, *7*, 1431; b) Alonso, D. A; Nordin, S. J.; Roth, P.; Tarnai, T.; Andersson, P. G; Thommen, M.; Pittelkow, U. *J. Org. Chem.* **2000**, *65*, 3116; c) Alonso, D. A.; Guijarro, D.; Pinho, P.; Temme, O.; Andersson, P. G. *J. Org. Chem.* **1998**, *63*, 2749; d) Schlatter, A.; Woggon, W.-D. *Adv. Synth. Catal.* **2008**, *350*, 995; e) Schlatter, A.; Kundu, M. K.; Woggon, W.-D. *Angew. Chem., Int. Ed.* **2004**, *43*, 6731; f) Reetz, M. T.; Li, X. *J. Am. Chem. Soc.* **2006**, *128*, 1044; g) Jiang, Y.; Jiang, Q.; Zhang, X. *J. Am. Chem. Soc.* **1998**, *120*, 3817; h) Matharu, D. S.; Morris, D. J.;

Kawamoto, A. M.; Clarkson, G. J.; Wills, M. *Org. Lett.* **2005**, *7*, 5489; i) Pastor, I. M.; Västilä, P.; Adolfsson, H. *Chem. Commun.* **2002**, 2046; j) Zaitsev, A. B.; Adolfsson, H. *Org. Lett.* **2006**, *8*, 5129.

[7] a) Pastor, I. M.; Västilä, P.; Adolfsson, H. *Chem. Eur. J.* **2003**, *9*, 4031; b) Bøgevig, A.; Pastor, I. M.; Adolfsson, H. *Chem. Eur. J.* **2004**, *10*, 294; c) Västilä, P.; Wettergren, J.; Adolfsson, H. *Chem. Commun.* **2005**, 4039; d) Wettergren, J.; Bøgevig, A.; Portier, M.; Adolfsson, H. *Adv. Synth. Catal.* **2006**, *348*, 1277; e) Västilä, P.; Zaitsev, A. B.; Wettergren, J.; Privalov, T.; Adolfsson, H. *Chem. Eur. J.* **2006**, *12*, 3218; f) Wettergren, J.; Zaitsev, A. B.; Adolfsson, H. *Adv. Synth. Catal.* **2007**, *349*, 2556; g) Wettergren, J.; Buitrago, E.; Ryberg, P.; Adolfsson, H. *Chem. Eur. J.* **2009**, *15*, 5709.

[8] a) Ahlford, K.; Ekström, J.; Zaitsev, A. B.; Ryberg, P.; Eriksson, L.; Adolfsson, H. *Chem. Eur. J.* **2009**, *15*, 11197; b) Tinnis, F.; Adolfsson, H. *Org. Biomol. Chem.* **2010**, *8*, 4536; c) Ahlford, K.; Livendahl, M.; Adolfsson, H. *Tetrahedron Let.* **2009**, *50*, 6321.

[9] a) Diéguez, M. ; Pàmies, O. ; Claver, C. *Chem. Rev.* **2004**, *104*, 3189; b) Diéguez, M.; Pàmies, O.; Ruiz, A.; Díaz, Y.; Castillón, S.; Claver, C. *Coord. Chem. Rev.* **2004**, *248*, 2165; c) Diéguez, M.; Ruiz, A.; Claver, C. *Dalton Trans.,* **2003**, 2957; d) Castillón, S.; Díaz, Y.; Claver, C. *Chem. Soc. Rev.* **2005**, *34*, 702; e) Diéguez, M.; Claver, C.; Pàmies, O. *Eur. J. Org. Chem.* **2007**, 4621; f) Boysen, M. M. K. *Chem. Eur. J.* **2007**, *13*, 8648; g) Benessere, V.; Del Litto, R.; De Roma, A.; Ruffo, F. *Coord. Chem. Rev.* **2010**, *254*, 390; h) Woodward, S.; Diéguez, M.; Pàmies, O. *Coord. Chem. Rev.* **2010**, *254*, 2007.

[10] For a recent successful application of ligands **3**, see: Coll, M.; Pàmies, O.; Adolfsson, H.; Diéguez, M. *Chem. Commun.* **2011**, *47*, 12188.

[11] There are few other examples on the use of carbohydrate-based ligands in this transformation with low-to-moderate enantioselectivities (<78% ee). See: a) Guillarme, S.; Mai Nguyen, T. X.; Saluzzo, C. *Tetrahedron: Asymmetry* **2008**, *19*, 1450; b) Huynh, K.-D.; Ibrahim, H.; Toffano, M.; Vo-Thanh, G. *Tetrahedron: Asymmetry* **2010**, *21*, 1542.

[12] Raluy, E.; Pàmies, O.; Diéguez, M. *Adv. Synth. Catal.* **2009**, *351*, 1648 and references cited therein.

[13] Hancock, R. O. *J. Chem. Educ.* **1992**, *69*, 615.

[14] The related non-sugar based thioamide ligands **2** afforded 79% ee for **S2**, 92% ee for **S3**, 81% ee for **S4**, 89% ee for **S5**, 94% ee for **S6**, 92% ee for **S7**, 97% ee for **S9** and 97% for **S10**. There is no data reported for substrate **S8**. See references: 6j and 8.

CHAPTER 5

Asymmetric Pd-catalyzed allylic substitution

UNIVERSITAT ROVIRA I VIRGILI
SUGAR-BASED LIGAND LIBRARIES FOR ASYMMETRIC REDUCTIONS AND C-C BOND FORMING REACTIONS
M. Mercè Coll Serrahima
DL:T. 150-2012

5. Asymmetric Pd-catalyzed allylic substitution

5.1. Background

As we discussed in the introduction, most of the successful chiral ligands developed to date for asymmetric allylic substitution have been designed using two main strategies. The first one, developed by Trost and coworkers, was to increase the ligand's bite angle in order to create a chiral cavity in which the allyl system is embedded. This idea opened up the successful application of ligands with large bite angles for the allylic substitution of sterically undemanding substrates.[1,2] The second 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.[1,3] This made it possible to successfully use a wide range of heterodonor ligands in allylic substitution reactions. In this context, mixed phosphorus-nitrogen ligands have played a dominant role among the heterodonor ligands. Recently, a group of less electron-rich phosphorus compounds–phosphite and phosphoroamidite containing ligands–have also demonstrated their potential utility in this process.[4] In this context, our group has successfully reported the use of several phosphite-nitrogen and phosphoroamidite containing ligand families that overcomes the most common limitations of this process, such as low reaction rates and high substrate specificity.[4]

Less attention has been paid to catalysts containing heterodonor phosphorus-thioether ligands in asymmetric allylic substitution.[1h] However, phosphine-thioether and phosphinite-thioether ligands have also demonstrated their potential utility in this process.[1h] Despite the above mentioned advantages in this process of phosphite/phosphoroamide moieties in ligand design very little attention has been paid to mixed phosphite/phosphoroamidite-thioether ligands. Only one family of phosphite-thioether ligands, with a furanoside backbone, has been applied in this process but with moderate success (Figure 1.1.13; Chapter 1, introduction).[5] To our knowledge phosphoroamidite-thioether ligands have never been applied in Pd-catalyzed asymmetric allylic substitution reactions. This encourages further research into phosphite-thioether and phosphoroamidite-thioether ligands to study the scope of this type of compounds as a new class of ligands for this process.

In this chapter, we therefore report the application of the furanoside phosphite-thioether, phosphinite-thioether and phosphoroamidite-thioether ligands previously reported in Chapter 3 in the Pd-catalyzed asymmetric allylic substitution of several substrates. Systematic variation of the ligand parameters indicates that the catalytic performance is affected by the position of the thioether group at either C-5 or C-3, the configuration of C-3, the substituents/configuration in the thioether and biaryl phosphite moieties, the replacement of the phosphite moiety by a phosphinite or a phosphoroamidite group. For sterically hindered substrates, enantioselectivities (ee's up to 92%) were best with phosphinite-thioether ligands, whereas for unhindered substrates, the best enantioselectivities (ee's up to 82%) were obtained with phosphite-thioether ligands. Interestingly, we were able to identify pseudo-enantiomeric ligands.

5.1.1. References

[1] For reviews, see: a) Tsuji, J. Palladium Reagents and Catalysis, *Innovations in Organic Synthesis*; Wiley: New York, **1995**; b) Trost, B. M.; van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395; c) Johannsen, M.; Jorgensen, K. A. *Chem. Rev.* **1998**, *98*, 1689; d) Pfaltz, A.; Lautens, M. in *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds.; Springer-Verlag: Berlin, **1999**; Vol. 2, Chapter 24; e) Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000**, *33*, 336; f) Masdeu-Bultó, A. M.; Diéguez, M.; Martin, E.; Gómez, M. *Coord. Chem. Rev.* **2003**, *242*, 159; g) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921; h) Martin, E.; Diéguez, M. *C. R. Chemie* **2007**, *10*, 188; i) Lu, Z.; Ma, S. *Angew. Chem. Int. Ed.* **2008**, *47*, 258.

[2] See, for example: a) Trost, B. M.; Bunt, R. C. *J. Am. Chem. Soc.* **1994**, *116*, 4089; b) Trost, B. M.; Krueger, A. C.; Bunt, R. C.; Zambrano, J. *J. Am. Chem. Soc*. **1996**, *118*, 6520.

[3] See, for instance: a) Dawson, G. J.; Frost, C. G.; Williams, J. M. J. *Tetrahedron Lett.* **1993**, *34*, 3149; b) von Matt, P.; Pfaltz, A. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 566; c) Sennhenn, P.; Gabler, B.; Helmchen, G. *Tetrahedron Lett.* **1994**, *35*, 8595.

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

[5] Pàmies, O.; Van Strijdonck, G. P. F.; Diéguez, M.; Deerenberg, S.; Net, G.; Ruiz, A.; Claver, C.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *J. Org. Chem*. **2001**, *66*, 8867.

5.2. Novel P,S ligands for Pd-catalyzed asymmetric allylic substitution reactions

Mercedes Coll, Oscar Pàmies and Montserrat Diéguez *preliminary results*.

Abstract: We have also tested the previously described furanoside thioether-phosphite (**L6-L20a-h**), thioether-phosphinite (**L6-L20i**) and thioether-phosphoroamidite (**L21-L26a-f**) ligand library in the Pd-catalyzed allylic substitution reactions of acyclic and cyclic allylic substrates. The library has been designed to rapidly screen the ligands to uncover their important structural features and to determine the scope of furanoside heterodonor P,S-ligands in these catalytic reactions. Our results indicated that selectivity depended strongly on the ligand parameters and the substrate structure. For sterically hindered substrates **S1** and **S2**, enantioselectivities (ee's up to 92%) were best with thioether-phosphinite ligands, whereas for unhindered substrates **S3-S6**, the best enantioselectivities (ee's up to 82%) were obtained with thioether-phosphite ligands. Interestingly, we were able to identify pseudo-enantiomeric ligands.

5.2.1. Introduction

The development of methods for enantioselective formation of carbon-carbon and carbon-heteroatom bonds is one of the key issues in organic synthesis. A versatile method for achieving this is asymmetric palladium-catalyzed allylic substitution with several stabilized nucleophiles.[1] Many chiral ligands, bidentate nitrogen and phosphorus donors (both homo- and heterodonors), have been successfully applied.[1] Mixed phosphorus-nitrogen ligands have played a dominant role among the heterodonor ligands.[1] To a lesser extent, phosphorus-thioether 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 phosphine-thioether[2] and phosphinite-thioether[3] have been studied and have prove to be effective.

Less attention has been paid to catalysts containing phosphite-thioether ligands[4] 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,5] There are only three phosphite-thioether ligands applied in this process but with moderate success (Figure 5.2.1).

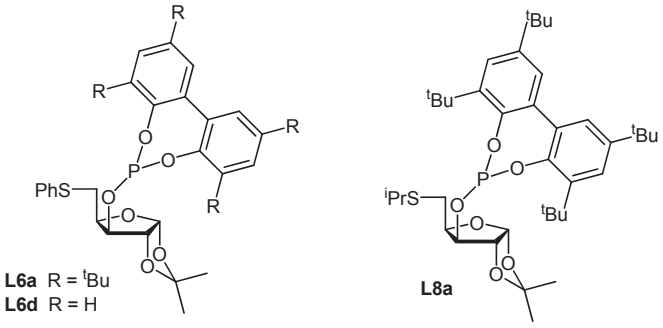


Figure 5.2.1. Previously applied phosphite-thioether ligands.

Therefore a study of the possibilities offered by phosphite-thioether as new ligands for this process is still needed. For this purpose, in this chapter we have made further modifications to the previously reported phosphite-thioether ligands (Figure 5.2.1) by introducing new substituents with different electronic and steric properties at thioether moiety (ligands **L7** and **L9-L12**; Figure 5.2.2), by including new furanoside backbones (ligands **L13-L16**, **L17-L18** and **L19-L20**; Figure 5.2.2) and new substituents/configurations at the biaryl phosphite group (**b-h**; Figure 5.2.2). We also compared the effectiveness of these phosphite-thioether ligands with the results obtained using related phosphinite-thioether (**L6-L20i**) and phosphoroamidite-thioether[6] (**L21-L26a-f**) ligands. To do so, we have also expanded our previous work on phosphinite-thioether ligands (**L6-L12i**)[3e,f] by synthesizing new related phosphinite-thioether ligands (**L13i-L20i**). With ligands **L6i-L20i** we contemplate the four possible combinations of varying the position of the thioether group (at either C-5 or C-3 of the furanoside backbone) and the configuration of C-3.

We report, then, the application of a furanoside thioether-phosphorous ligand library **L6-L26a-i** (Figure 5.2.2) in the asymmetric Pd-catalyzed allylic substitution reactions. These ligands have the advantages of carbohydrate and phosphite/phosphinite/phosphoroamidite ligands; that is, they are available at low cost from readily available feedstocks, have high resistance to oxidation, and have straightforward modular constructions.[7,8]

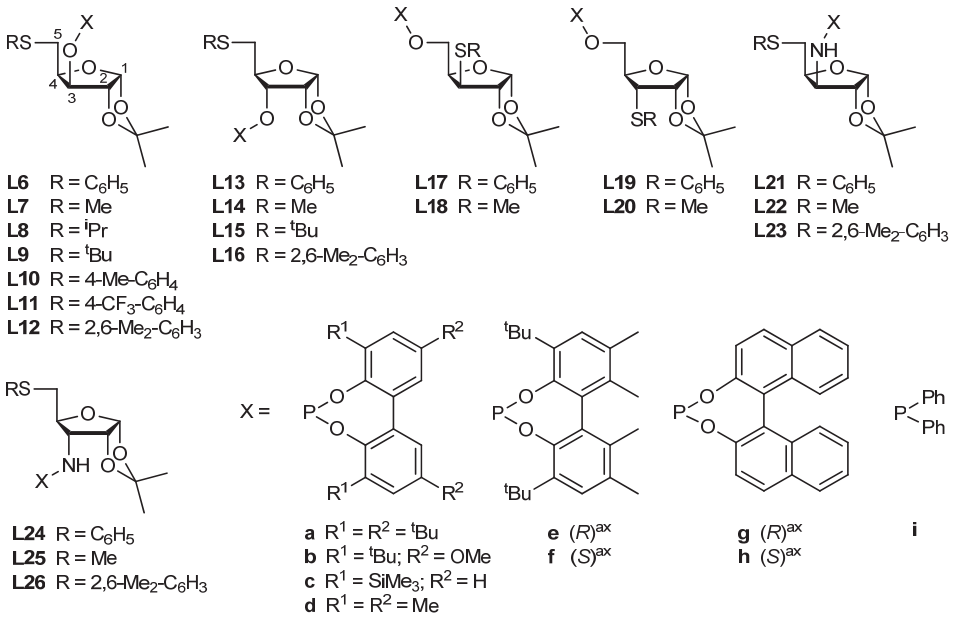
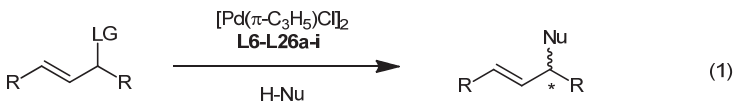


Figure 5.2.2. Furanoside heterodonor P,S-ligand library **L6-L26a-i**.

5.2.2. Results and Discussion

5.2.2.1. Allylic substitution of disubstituted linear substrates

In this section, we report the use of the chiral P,S-ligands **L6-L26a-i** in the Pd-catalyzed allylic substitution (equation 1) of linear substrates with different steric properties: *rac*-1,3-diphenyl-3-acetoxyprop-1-ene **S1** (widely used as a model substrate), *rac*-(*E*)-ethyl-2,5-dimethyl-3-hex-4-enylcarbonate **S2** and *rac*-1,3-dimethyl-3-acetoxyprop-1-ene **S3**. In all the cases, the catalysts were generated *in situ* from π-allyl-palladium chloride dimer $[PdCl(\eta^3\text{-}C_3H_5)]_2$, the corresponding ligand and the corresponding nucleophile. Two nucleophiles were used. For the allylic alkylation, the nucleophile was generated from dimethyl malonate in the presence of *N,O*-bis(trimethylsilyl)-acetamide (BSA), while for the allylic amination, benzylamine was used as the nucleophile.



(1)

S1 R = C_6H_5; LG= OAc
S2 R = iPr; LG= OCO2Et
S3 R = Me; LG= OAc

1 R = C_6H_5; H-Nu = H-CH(COOMe)2
2 R = C_6H_5; H-Nu = H-NHCH2C_6H_5
3 R = iPr; H-Nu = H-CH(COOMe)2
4 R = Me; H-Nu = H-CH(COOMe)2

5.2.2.1.1. Allylic substitution of rac-1,3-diphenyl-3-acetoxyprop-1-ene S1 using dimethyl malonate and benzylamine as nucleophiles (equation 1)

For an initial evaluation of the furanoside heterodonor P-S-ligand library (**L6-L26a-i**), we chose the Pd-catalyzed allylic substitution of **S1** (equation 1; R = Ph, LG = OAc), which is widely used as a model substrate. We used dimethyl malonate and benzylamine as nucleophiles.

Initially, we determined the optimal reaction conditions by conducting a series of experiments in which the solvent and the ligand-to-palladium ratio were varied. The results are shown in Table 5.2.1. The solvent effect on catalytic performance was studied using four solvents (tetrahydrofurane (THF), dichloromethane (DCM), toluene and dimethylformamide (DMF)) and **L6a** and **L21a** as ligands (Table 5.2.1, entries 1-8). The best combination of activity and enantioselectivity was achieved with dichloromethane. The enantiomeric excesses obtained with tetrahydrofurane and toluene were comparable to those of dichloromethane, but the activities were the lowest. On the other hand, dimethylformamide yielded high relative conversions, but their ee's were the lowest of the four solvents. Varying the ligand-to-palladium ratio showed that excess ligand was not needed to obtain good enantioselectivities and activities (Table 5.2.1; entries 1, 9 and 10 for **L6a** and entries 5, 11 and 12 for **L21a**). At higher ligand-to-palladium ratios, we observed a small decrease in the enantioselectivity. This is due to the fact that at a ligand-to-palladium ratio of 2 there is a mixture of Pd-species in which the thioether-phosphite/phosphinite acts as both bi- and mono-dentated ligand. The presence of small amounts of Pd-species containing two ligands coordinated in a mono-dentated may account for the drop on enantioselectivity observed.[5f,9]

Table 5.2.1. Pd-catalyzed allylic alkylation of **S1** using ligands **L6a** and **L21a**. Effect of the solvent and ligand-to-palladium ratio.[a]

Entry	Ligand	Solvent	L/Pd	% Conv (t/h)[b]	% ee[c]
1	**L6a**	DCM	1.1	100 (3)	58 (*R*)
2	**L6a**	THF	1.1	84 (3)	56 (*R*)
3	**L6a**	Toluene	1.1	69 (3)	57 (*R*)
4	**L6a**	DMF	1.1	100 (3)	36 (*R*)
5	**L21a**	DCM	1.1	55 (3)	19 (*S*)
6	**L21a**	THF	1.1	22 (3)	16 (*S*)
7	**L21a**	Toluene	1.1	12 (3)	17 (*S*)
8	**L21a**	DMF	1.1	100 (3)	8 (*S*)
9	**L6a**	DCM	0.75	95 (3)	58 (*R*)
10	**L6a**	DCM	2	100 (3)	53 (*R*)
11	**L21a**	DCM	0.75	50 (3)	19 (*S*)
12	**L21a**	DCM	2	59 (3)	14 (*S*)

[a] All reactions were run at room temperature. 0.5 mol% $[PdCl(\eta^3\text{-}C_3H_5)]_2$. 1 mmol **S1**. 3 mmol BSA. 3 mmol dimethyl malonate. KOAc as base. [b] Conversion determined by ^{1}H-NMR. Reaction time shown in parenthesis. [c] Enantiomeric excesses of **1** determined by HPLC on a Chiralcel-OD column. Absolute configuration drawn in parentheses.

For the purpose of comparison, the rest of the ligands were tested under optimitzed conditions (i.e. a ligand-to-palladium ratio of 1.1 and dichloromethane as solvent). Table 5.2.2 shows the results when dimethyl malonate were used as nucleophile. These results indicate that catalytic performance (activities and enantioselectivities) is 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 or a phosphoroamidite group.

Table 5.2.2. Selected results for the Pd-catalyzed allylic alkylation of **S1** using ligands **L6-L26a-i**.

Entry	Ligand	% Conv (t/h)[b]	% ee[c]	Entry	Ligand	% Conv (t/h)[b]	% ee[c]
1	**L6a**	100 (3)	58 (*R*)[d]	17	**L6b**	99 (3)	57 (*R*)
2	**L7a**	100 (3)	65 (*R*)	18	**L6c**	100 (3)	58 (*R*)
3	**L8a**	100 (3)	54 (*R*)[d]	19	**L6d**	94 (3)	3 (*S*)[d]
4	**L9a**	93 (3)	49 (*R*)	20	**L6e**	100 (3)	24 (*R*)
5	**L10a**	100 (3)	57 (*R*)	21	**L6f**	100 (3)	57 (*R*)
6	**L11a**	100 (3)	52 (*R*)	22	**L6g**	100 (3)	10 (*S*)
7	**L12a**	96 (3)	53 (*R*)	23	**L6h**	100 (3)	9 (*R*)
8	**L13a**	100 (3)	53 (*S*)	24	**L7f**	100 (3)	67 (*R*)
9	**L14a**	100 (3)	63 (*S*)	25	**L14f**	100 (3)	64 (*S*)
10	**L17a**	100 (3)	12 (*R*)	26	**L9i**	100 (0.5)	87 (*S*)[e]
11	**L19a**	100 (3)	9 (*S*)	27	**L13i**	100 (0.5)	70 (*S*)
12	**L21a**	55 (3)	19 (*S*)	28	**L16i**	100 (0.5)	83 (*S*)
13	**L22a**	65 (3)	18 (*S*)	29	**L17i**	100 (0.5)	82 (*R*)
14	**L23a**	46 (3)	15 (*S*)	30	**L19i**	100 (0.5)	64 (*R*)
15	**L24a**	89 (3)	8 (*S*)	31	**L27a**	100 (3)	32 (*R*)
16	**L25a**	93 (3)	8 (*S*)				

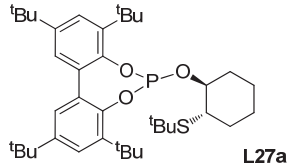
[a] All reactions were run at room temperature. 0.5 mol% $[PdCl(\eta^3\text{-}C_3H_5)]_2$. 1 mmol **S1**. 3 mmol BSA. 3 mmol dimethyl malonate. KOAc as base. CH_2Cl_2 as solvent. [b] Conversion determined by ^{1}H-NMR. Reaction time shown in parenthesis. [c] Enantiomeric excesses of **1** determined by HPLC on a Chiralcel-OD column. Absolute configuration drawn in parentheses. [d] Data from ref. 4. [e] Data from ref. 3e.

We first studied the effect of the position of the thioether group at either C-5 or C-3 of the furanoside backbone and the configuration of C-3 using ligands **L6-L20**. Ligands **L6-L16**, that contains the thioether group at the C-5 position, produced better enantioselectivities than ligands **L17-L20**, with the thioether group at C-3 position (i.e. Table 5.2.2, entries 1 and 8 *vs* 10 and 11). Interestingly, both enantiomers of the alkylation product can be attained by changing the configuration of carbon atom C-3 of the furanoside backbone (i.e. Table 5.2.2, entries 2 *vs* 9). Ligands **L6-L12** act therefore as pseudo-enantiomers of ligands **L13-L16**.

Results also showed that enantioselectivity is dependent on both the steric and electronic properties of the substituents in the thioether moiety (Table 5.2.2, entry 2 *vs* 1, 3-7). Therefore, either bulky or electron-withdrawing substituents in this position decreased enantioselectivities. Enantioselectivities were best with ligands **L7a** and **L14a**, which contain a methyl-thioether group (Table 5.2.2, entries 2 and 9).

We next studied the effects of the biaryl phosphite moiety using ligands **L6a-h** (Table 5.2.2). It was observed that this moiety affected both activities and enantioselectivities of the reaction. The presence of bulky substituents at the *ortho* positions is necessary if enantioselectivity is to be high (Table 5.2.2, entries 1, 17 and 18 *vs* 19, 22 and 23). We also found a cooperative effect between the configuration of the bulky biaryl moiety and the configuration of the ligand backbone on enantioselectivity. This led to a matched combination for ligand **L6f**, which contains an (*S*)-biaryl moiety. Also, by comparing the results obtained using ligands **L6a-c** with the related chiral biphenyl ligands **L6e** and **L6f** (Table 5.2.2, entry 1, 17 and 18 *vs* 20 and 21), we can conclude that the atropoisomeric biphenyl moiety in ligands **L6a-c** adopts an (*S*)-configuration when coordinated in the Pd-π-allyl intermediate species.

To sum up, the best results using the phosphite-thioether ligands were therefore obtained with pseudo-enantiomeric ligand pairs **L7a** and **L7f** and **L14a** and **L14f** (ee's up to 67%) which contain the optimal combination of ligand parameters. For comparison purposes, we also screened cyclohexane-based phosphite-thioether ligand **L27a**, which is based on one of the most successful ligand backbones developed for this process (Figure 5.2.3).[3a,b] Although the combination of the Evan's cyclohexane-backbone with the phosphinite group led to excellent results (ee's up to 98%),[3a,b] this backbone is much less effective in transferring the chiral information when combined with a phosphite group than the furanoside backbone (Table 5.2.2, entry 4 *vs* 31).



L27a

Figure 5.2.3. Thioether-phosphite ligand **L27a** based on Evan's cyclohexane backbone**.**

We also investigated the effect of replacing the phosphite moiety by phosphinite group (ligands **L6-L20i**). We found that the introduction of a phosphinite group led to

higher activities and enantioselectivities (ee's up to 86%; Table 5.2.2, entries 26-30). Interestingly, the results using phosphinite-thioether ligands followed a different trend than those observed for the phosphite counterparts. The main differences are: (a) the presence of bulky thioether substituents has a positive effect on enantioselectivity (i.e. Table 5.2.2, entries 27 *vs* 28); and (b) pseudo-enantiomeric ligands are obtained by changing the position of the thioether moiety from C-5 to C-3 (ligands **L9i** and **L17i**) rather than by changing the configuration of C-3. Therefore, both enantiomers of the alkylation product can also be obtained in high enantioselectivity. On the other hand, the replacement of the phosphite moiety by a phosphoroamidite group (ligands **L21-L26**) led to lower activities and enantioselectivities (i.e., Table 5.2.2, entry 1 *vs* 12).

Finally, we also evaluated the furanoside heterodonor P,S-ligand library (**L6-L26a-i**) in the allylic substitution of **S1** using benzylamine as nucleophile (equation 1).

Table 5.2.3. Selected results for the Pd-catalyzed allylic amination of **S1**.[a]

Entry	Ligand	% Conv. (t/h)[b]	% ee[c]
1	**L6a**	58 (12)	67 (*S*)
2	**L12a**	49 (12)	59 (*S*)
3	**L13a**	65 (12)	56 (*R*)
4	**L17a**	72 (12)	16 (*S*)
5	**L19a**	61 (12)	12 (*R*)
6	**L20a**	24 (12)	21 (*R*)
7	**L6d**	33 (12)	4 (*R*)
8	**L6e**	57 (12)	23 (*S*)
9	**L6f**	56 (12)	68 (*S*)
10	**L6i**	84 (12)	92 (*R*)
11	**L13i**	91 (12)	75 (*R*)
12	**L17i**	79 (12)	89 (*S*)

[a] All reactions were run at room temperature. 0.5 mol% $[PdCl(\eta^3\text{-}C_3H_5)]_2$. CH_2Cl_2 as solvent. 0.5 mmol **S1**. 1.5 mmol BSA. [b] Conversion determined by ^{1}H-NMR. Reaction time in parenthesis. [c] Enantiomeric excesses of **2** determined by HPLC on a Chiralcel-OJ column. Absolute configuration drawn in parentheses.

This situation is different from that described before for the alkylation of **S1** because a new stereogenic C-N bond is created rather than a C-C bond. The most remarkable results are shown in Table 5.2.3. In general, they follow the same trends as for the allylic alkylation of **S1**. However, the enantiomeric excesses were slightly higher (ee's up to 92% at room temperature), although as expected, the activities were lower than in the alkylation reaction. The best enantioselectivity was therefore obtained with pseudo-enantiomeric ligands **L6i** and **L17i** (Table 5.2.3, entries 10 and 12). The stereoselectivity of the amination was the same as for the alkylation reaction, though the CIP descriptor was inverted because of the change in the priority of the groups.

5.2.2.1.2. Allylic alkylation of rac-(E)-ethyl-2,5-dimethyl-3-hex-4-enylcarbonate S2 using dimethyl malonate as nucleophile (equation 1)

We also screened the furanoside heterodonor P,S-ligand library **L6-L26a-i** in the allylic alkylation process of **S2** using dimethyl malonate as the nucleophile (equation 1, R = ^{i}Pr, LG = OCO_2Et). This substrate is more sterically demanding than substrate **S1**, which we used before. The most noteworthy results are shown in Table 5.2.4. As expected the activities were lower than in the alkylation reaction of **S1**. The stereoselectivity of the alkylation of **S2** was the same as for the alkylation reaction of **S1**, though the CIP descriptor was inverted because the priority of the groups had been changed.

In general, the results using the thioether-phosphite/phosphoroamidite ligands **L6-L26a-h** follow the same trends as for the allylic alkylation of **S1**. Therefore, the best enantioselectivities (up to 62%) were obtained using pseudo-enantiomeric ligands **L7a,f** and **L14a,f** (i.e. Table 5.2.4, entries 2, 9, 17 and 18). Although for phosphinite-thioether ligands, the trends are also similar, it is interesting to point out that the positive effect exerted on enantioselectivity by the presence of bulky thioether substituents is more pronounce for **S2** than for **S1** (i.e. Table 5.2.4, entry 19 *vs* 20). The best enantioselectivities (ee's up to 90%) were therefore obtained using 5-deoxy-xylofuranoside ligand **L9i**, containing a bulky *tert*-butyl thioether substituent.

Table 5.2.4. Selected results for the Pd-catalyzed allylic alkylation of **S2** using ligands **L6-L26a-i**.

Entry	Ligand	% Conv (t/h)[b]	% ee[c]	Entry	Ligand	% Conv (t/h)[b]	% ee[c]
1	**L6a**	100 (18)	59 (*S*)	13	**L6c**	100 (18)	59 (*S*)
2	**L7a**	100 (18)	61 (*S*)	14	**L6d**	100 (18)	5 (*S*)[d]
3	**L8a**	100 (18)	53 (*S*)	15	**L6e**	100 (18)	19 (*S*)
4	**L9a**	100 (18)	51 (*S*)	16	**L6f**	100 (18)	60 (*S*)
5	**L10a**	100 (18)	58 (*S*)	17	**L7f**	100 (18)	62 (*S*)
6	**L11a**	100 (18)	61 (*S*)	18	**L14f**	100 (18)	61 (*R*)
7	**L12a**	100 (18)	48 (*S*)	19	**L6i**	100 (18)	52 (*R*)[d]
8	**L13a**	100 (18)	57 (*R*)	20	**L9i**	100 (18)	90 (*R*)[d]
9	**L14a**	100 (18)	59 (*R*)	21	**L13i**	100 (18)	48 (*R*)
10	**L17a**	100 (18)	18 (*S*)	22	**L15i**	100 (18)	64 (*R*)
11	**L19a**	100 (18)	5 (*R*)	23	**L17i**	100 (18)	49 (*S*)
12	**L20a**	59 (18)	21 (*S*)	24	**L19i**	100 (18)	16 (*S*)

[a] All reactions were run at room temperature. 1 mol% $[PdCl(\eta^3\text{-}C_3H_5)]_2$. 3 mol BSA. 3 mol dimethyl malonate. KOAc as base. CH_2Cl_2 as solvent. [b] Conversion percentage of **S2** determined by ^{1}H-NMR. [c] Enantiomeric excesses of **3** determined by ^{1}H-NMR using $Eu(hfc)_3$. Absolute configuration drawn in parentheses. [d] Data from ref. 3f.

5.2.2.1.3. Allylic alkylation of rac-1,3-dimethyl-3-acetoxyprop-1-ene S3 using dimethyl malonate as nucleophile (equation 1)

We also evaluated the furanoside heterodonor P,S-ligand library **L6-L26a-i** in the allylic alkylation of the linear substrate **S3** (equation 1, R = Me, LG = OAc). This substrate is less sterically demanding than substrates **S1** and **S2**, which we had used before. The enantioselectivity for **S3** is therefore more difficult to control than with hindered substrates such as **S1** and **S2**. If ee's are to be high, the ligand must create a small chiral pocket (the chiral cavity where the allyl is embedded) around the metal center, mainly because of the presence of less sterically demanding methyl *syn* substituents. Therefore, few catalytic systems have provided high enantioselectivities.[1]

The results of using ligands **L6-L26a-i** are summarized in Table 5.2.5. Again, enantioselectivities were 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 and the replacement of the phosphite moiety by a phosphinite or a phosphoroamidite group. However, the effect of some of these parameters was different from the effect observed in the alkylation of **S1** and **S2**. Thus, while the effects of the position of the thioether group, the configuration of C-3, and the substituents/configurations of the biaryl phosphite moieties on enantioselectivity are similar to the effect in the alkylation of **S1** and **S2**, the effects of the thioether substituent and of introducing a phosphinite moiety instead of a phosphite group are different. Therefore, unlike the alkylation of **S1** and **S2**, enantioselectivity is affected by the steric and electronic properties of the thioether substituent (Table 5.2.5, entries 1-7). Moreover, the replacement of the phosphite moiety by a phosphinite group has a negative effect on enantioselectivity (Table 5.2.5, entry 1 *vs* 18). Enantioselectivities (up to 55%) were therefore best with pseudo-enantiomeric ligands **L6a**,**f** and **L13a**,**f** which contain the optimal combination of ligand parameters.

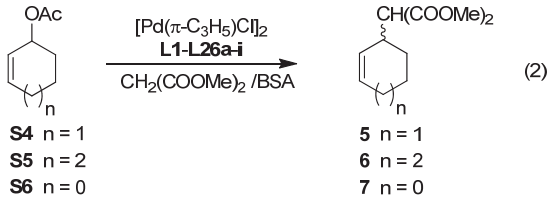
Table 5.2.5. Selected results for the Pd-catalyzed allylic alkylation of **S3** using ligands **L6-L26a-i**.

Entry	Ligand	% Conv (t/h)[b]	% ee[c]	Entry	Ligand	% Conv (t/h)[b]	% ee[c]
1	**L6a**	95 (3)	55 (*R*)	12	**L21a**	76 (3)	18 (*R*)
2	**L7a**	100 (3)	47 (*R*)	13	**L6c**	100 (3)	54 (*R*)
3	**L8a**	100 (3)	39 (*R*)	14	**L6d**	100 (3)	2 (*R*)[d]
4	**L9a**	93 (3)	4 (*R*)	15	**L6e**	100 (3)	16 (*R*)
5	**L10a**	100 (3)	55 (*R*)	16	**L6f**	100 (3)	54 (*R*)
6	**L11a**	100 (3)	51 (*R*)	17	**L13f**	100 (3)	52 (*S*)
7	**L12a**	96 (3)	16 (*R*)	18	**L6i**	100 (0.5)	7 (*R*)[d]
8	**L13a**	100 (3)	51 (*S*)	19	**L13i**	100 (0.5)	32 (*S*)
9	**L14a**	100 (3)	49 (*S*)	20	**L17i**	100 (0.5)	32 (*R*)
10	**L17a**	100 (3)	20 (*R*)	21	**L19i**	100 (0.5)	6 (*R*)
11	**L19a**	100 (3)	3 (*S*)				

[a] All reactions were run at room temperature. 0.5 mol% $[PdCl(\eta^3\text{-}C_3H_5)]_2$. 1 mmol **S1**. 3 mmol BSA. 3 mmol dimethyl malonate. KOAc as base. CH_2Cl_2 as solvent. [b] Conversion determined by GC. Reaction time shown in parenthesis. [c] Enantiomeric excesses of **4** determined by GC. Absolute configuration drawn in parentheses. [d] Data from ref. 3f.

5.2.2.2. Allylic alkylation of cyclic substrates

As for the unhindered substrate **S3**, enantioselectivity in cyclic substrates is difficult to control, mainly because of the presence of less sterically *anti* substituents. These *anti* substituents are thought to play a crucial role in the enantioselection observed with cyclic substrates in the corresponding Pd-allyl intermediate. In this section we report the results obtained using the furanoside heterodonor P,S-ligand library **L6-L26a-i** in the Pd-catalyzed allylic substitution of cyclic substrates. In this case, three cyclic substrates were tested (equation 2): *rac*-3-acetoxycyclohexene **S4** (which is widely used as a model substrate), *rac*-3-acetoxycycloheptene **S5** and *rac*-3-acetoxycyclopentene **S6**.



S4 n = 1
S5 n = 2
S6 n = 0

5 n = 1
6 n = 2
7 n = 0

(2)

The most noteworthy results are shown in Table 5.2.6. In general, the results using ligands **L6-L26a-i** follow the same trends as for the allylic alkylation of **S3**. Although enantioselectivities were higher for cyclic substrates than for dimethylated linear substrate **S3**. The best enantioselectivities (up to 77%) were therefore obtained using pseudo-enantiomeric phosphite-thioether ligands **L6a**,**f** and **L13a**,**f** (i.e. Table 5.2.6, entries 1, 8, 17 and 20).

The furanoside heterodonor P,S-ligand library was also effective (ee's up to 82%) in the allylic alkylation of the seven-membered ring substrate **S5** (Table 5.2.6, entries 25-27). However, only moderate enantiocontrol (ee's up to 54%) was achieved for the more demanding five-membered ring substrate **S6** (Table 5.2.6, entry 28).

Table 5.2.6. Selected results for the Pd-catalyzed allylic alkylation of **S4-S6** using ligands **L6-L26a-i**.

Entry	Ligand	% Conv (t/h)[b]	% ee[c]	Entry	Ligand	% Conv (t/h)[b]	% ee[c]
1	**L6a**	98 (3)	76 (*S*)	15	**L6c**	100 (3)	65 (*S*)
2	**L7a**	100 (3)	68 (*S*)	16	**L6e**	100 (3)	9 (*S*)
3	**L8a**	100 (3)	55 (*S*)	17	**L6f**	100 (3)	77 (*R*)
4	**L9a**	98 (3)	44 (*S*)	18	**L6g**	100 (3)	35 (*S*)
5	**L10a**	100 (3)	75 (*S*)	19	**L6h**	100 (3)	2 (*S*)
6	**L11a**	100 (3)	71 (*S*)	20	**L13f**	100 (3)	72 (*R*)
7	**L12a**	96 (3)	25 (*S*)	21	**L6i**	98 (0.5)	4 (*R*)[d]
8	**L13a**	100 (3)	71 (*R*)	22	**L13i**	100 (0.5)	11 (*S*)
9	**L14a**	100 (3)	41 (*R*)	23	**L16i**	100 (0.5)	4 (*S*)
10	**L17a**	100 (3)	40 (*R*)	24	**L17i**	100 (0.5)	42 (*S*)
11	**L19a**	100 (3)	3 (*S*)	25[e]	**L6a**	100 (10)	82 (*S*)
12	**L21a**	73 (3)	21 (*S*)	26[e]	**L13a**	100 (10)	36 (*R*)
13	**L24a**	68 (3)	9 (*S*)	27[e]	**L17i**	100 (4)	48 (*S*)
14	**L6b**	100 (3)	68 (*S*)	28[f]	**L6a**	100 (3)	54 (*S*)

[a] All reactions were run at room temperature. 0.5 mol% $[PdCl(\eta^3\text{-}C_3H_5)]_2$. 1 mmol of substrate. 3 mmol BSA. 3 mmol dimethyl malonate. KOAc as base. CH_2Cl_2 as solvent. [b] Conversion determined by ^{1}H-NMR. Reaction times shown in parenthesis. [c] Enantiomeric excesses determined by GC or ^{1}H-NMR using $Eu(hfc)_3$. Absolute configuration drawn in parentheses. [d] Data from ref. 3e. [e] Using **S5** as substrate. [f] Using **S6** as substrate.

5.2.3. Conclusions

We have tested the previously described furanoside thioether-phosphite (**L6-L20a-h**), thioether-phosphinite (**L6-L20i**) and thioether-phosphoroamidite (**L21-L26a-f**) ligands for the Pd-catalyzed allylic substitution reactions of acyclic and cyclic allylic substrates. Our results indicated that selectivity depended strongly on the position of the thioether group at either C-5 or C-3, the configuration of C-3, the substituents/configuration in the thioether and biaryl phosphite moieties, the replacement of the phosphite moiety by a phosphinite or a phosphoroamidite group and the substrate structure. For sterically hindered substrates **S1** and **S2**, enantioselectivities (ee's up to 92%) were best with thioether-phosphinite ligands, whereas for unhindered

substrates **S3**-**S6**, the best enantioselectivities (ee's up to 82%) were obtained with thioether-phosphite ligands. Interestingly, both enantiomers of the substituents product can be obtained by changing either the configuration of C-3 in thioether-phosphite ligands or the position of thioether group (C-3 or C-5) in thioether-phosphinite ligands.

5.2.4. Experimental Section

5.2.4.1. General Considerations

All reactions were carried out using standard Schlenk techniques under an atmosphere of argon. Solvents were purified and dried by standard procedures. Ligands were prepared as previously described in Chapter 3. Racemic substrates **S1**-**S6** were prepared as previously reported.[10] ^{1}H, $^{13}C\{^{1}H\}$, and $^{31}P\{^{1}H\}$ NMR spectra were recorded using a 400 MHz spectrometer.

5.2.4.2. Typical procedure of allylic alkylation of substrates S1-S6

A degassed solution of $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (0.005 mmol for **S1** and **S3**-**S6**; 0.01 mmol for **S2**) and the corresponding ligand (0.011 mmol for **S1** and **S3**-**S6**; 0.022 mmol for **S2**) in dichloromethane (0.5 mL) was stirred for 30 min. Subsequently, a solution of the corresponding substrate (1 mmol) in dichloromethane (1.5 mL), dimethyl malonate (342 μL, 3.0 mmol), *N*,*O*-bis(trimethylsilyl)-acetamide (720 μL, 3.0 mmol) and a pinch of KOAc were added. The reaction mixture was stirred at room temperature. After the desired reaction time the reaction mixture was diluted with Et_2O (5 mL) and saturated NH_4Cl (aq) (25 mL) was added. The mixture was extracted with Et_2O (3 x 10 mL) and the extract dried over $MgSO_4$. For substrate **S1**, solvent was removed and conversion was measured by ^{1}H-NMR. To determine the enantioselectivity by HPLC (Chiralcel OD, 0.5% 2-propanol/hexane, flow 0.5 mL/min), a sample was filtered over basic alumina using dichloromethane as the eluent.[4] For substrates **S3**-**S5** conversion and enantiomeric excess was determined by GC.[4d,11] For substrates **S2** and **S6**, conversion and enantiomeric excess was determined by ^{1}H-NMR using $Eu(hfc)_3$ as resolving agent.

5.2.4.3. Typical procedure of allylic amination of rac-1,3-diphenyl-3-acetoxyprop-1-ene S1

A degassed solution of $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (1.8 mg, 0.005 mmol) and the corresponding ligand (0.011 mmol) in dichloromethane (0.5 mL) was stirred for 30 min. Subsequently, a solution of **S1** (126 mg, 0.5 mmol) in dichloromethane (1.5 mL) and benzylamine (131 μL, 1.5 mmol) were added. The reaction mixture was stirred at room temperature. After 12 hours the reaction mixture was diluted with Et_2O (5 mL) and saturated NH_4Cl (aq) (25 mL) was added. The mixture was extracted with Et_2O (3 x 10 mL) and the extract dried over $MgSO_4$. Solvent was removed and conversion was measured by ^{1}H-NMR. To determine the enantioselectivity by HPLC (Chiralcel OJ, 13% 2-propanol/hexane, flow 0.5 mL/min), a sample was filtered over silica using 10% Et_2O/hexane mixture as the eluent.[4]

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.[12]

5.2.6. References

[1] For reviews, see: a) Tsuji, J. Palladium Reagents and Catalysis, *Innovations in Organic Synthesis*; Wiley: New York, **1995**; b) Trost, B. M.; van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395; c) Johannsen, M.; Jorgensen, K. A. *Chem. Rev.* **1998**, *98*, 1689; d) Pfaltz, A.; Lautens, M. in *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds.; Springer-Verlag: Berlin, **1999**; Vol. 2, Chapter 24; e) Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000**, *33*, 336; f) Masdeu-Bultó, A. M.; Diéguez, M.; Martin, E.; Gómez, M. *Coord. Chem. Rev.* **2003**, *242*, 159; g) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921; h) Martin, E.; Diéguez, M. *C. R.*

Chemie **2007**, *10*, 188; i) Lu, Z.; Ma, S. *Angew. Chem. Int. Ed.* **2008**, *47*, 258; j) Diéguez, M.; Pàmies, O. *Acc. Chem. Res*. **2010**, *43*, 312.

[2] For selected publications, see: a) Albinati, A.; Pregosin, P. S.; Wick, K. *Organometallics* **1996**, *15*, 2419; b) Enders, D.; Peters, R.; Runsink, J.; Bats, J. W. *Org. Lett.* **1999**, *1*, 1863; c) Enders, D.; Peters, R.; Lochtman,R.; Raabe, G.; Runsink, J.; Bats, J. W. *Eur. J. Org. Chem*. **2000**, 3399; d) Tu, T.; Zhou, Y. G.; Hou, X. L.; Dai, L. X.; Dong, X. C.; Yu, Y. H.; Sun, J. *Organometallics* **2003**, *22*, 1255; e) Priego, J.; Garcia, O.; Cabrera, S.; Gomez, R.; Llamas, T.; Carretero, J. C. *Chem. Commun*. **2002**, 2512; f) García, O.; Priego, J.; Cabrera, S.; Gómez, R.; Llamas, T.; Carretero, J. C. *J. Org. Chem.* **2003**, *68*, 3679; g) Routaboul, L.; Vincendeau, S.; Daran, J. C.; Manoury, E. *Tetrahedron: Asymmetry* **2005**, *16*, 2685; h) Lam. F. L.; Au-Yeung, T. T.L.; Cheung, H. Y.; Kok, S. H. L.; Lam, W. S.; Wong, K. Y.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2006**, *17*, 497; i) Lam. F. L.; Au-Yeung, T. T. L.; Kwong, F. Y.; Zhou, Z.; Wong, K. Y.; Chan, A. S. C. *Angew. Chem. Int. Ed.* **2008**, *47*, 1280; j) Cheung, H. Y.; Yu, W. Y.; Lam, F. L.; Au-Yeung, T. T. L.; Zhou, Z.; Chan, T. H.; Chan, A. S. C. *Org. Lett.* **2007**, *9*, 4295; k) Hiroi, K.; Suzuki, Y.; Abe, I. *Tetrahedron: Asymmetry* **1999**, *10*, 1173; l) Yan, Y.-Y.; RajanBabu, T. V. *Org. Lett*. **2000**, *2*, 199; m) Nakano, H.; Okuyama, Y.; Yanagida, M.; Hongo, H. *J. Org. Chem*. **2001**, *66*, 620; n) Nakano, H.; Takahashi, K.; Suzuki, Y.; Fujita, R. *Tetrahedron: Asymmetry* **2005**, *16*, 609; o) Zhang, W.; Shi, M. *Tetrahedron: Asymmetry* **2004**, *15*, 3467; p) Molander, G. A.; Burke, J. P.; Carroll, P. J. *J. Org. Chem.* **2004**, *69*, 8062; q) Khiar, N.; Suárez, B.; Fernández, I. *Inorg. Chim. Acta* **2006**, *359*, 3048.

[3] See, for instance: a) Evans, D. A.; Campos, K. R.; Tedrow, J. R.; Michael, F. E.; Gagné, M. R. *J. Org. Chem.* **1999**, *64*, 2994; b) Evans, D. A.; Campos, K. R.; Tedrow, J. R.; Michael, F. E.; Gagné, M. R. *J. Am. Chem. Soc.* **2000**, *122*, 7905; c) Khiar, N.; Suárez, B.; Stiller, M.; Valdivia, V.; Fernández, I. *Phosphorus Sulfur Silicon Relat. Elem.* **2005**, *180*, 1253; d) Khiar, N.; Navas, R.; Suárez, B.; Álvarez, E.; Fernández, I. *Org. Lett*. **2008**, *10*, 3697; e) Guimet, E.; Diéguez, M.; Ruiz, A.; Claver, C. *Tetrahedron: Asymmetry* **2005**, *16*, 959; f) Diéguez, M.; Pàmies, O.; Claver, C. *J. Organomet. Chem*. **2006**, *691*, 2257; g) Caldentey, X.; Pericàs, M. A. *J. Org. Chem.* **2010**, *75*, 2628.

[4] Pàmies, O.; Van Strijdonck, G. P. F.; Diéguez, M.; Deerenberg, S.; Net, G.; Ruiz, A.; Claver, C.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *J. Org. Chem*. **2001**, *66*, 8867.

[5] See for instance: a) Prétôt, R.; Pfaltz, A. *Angew. Chem. Int. Ed.* **1998**, *37*, 323; b) Pàmies, O.; Diéguez, M.; Claver, C. *J. Am. Chem. Soc.* **2005**, *127*, 3646; c) Mata, Y.; Diéguez, M.; Pàmies, O.; Claver, C. *Adv. Synth. Catal.* **2005**, *347*, 1943; d) Diéguez, M.; Pàmies, O.; Claver, C. *Adv. Synth. Catal.* **2005**, *347*, 1257; e) Pàmies, O.; Diéguez, M. *Chem. Eur. J*. **2008**, *14*, 944; f) Diéguez, M.; Pàmies, O. *Chem. Eur. J.* **2008**, *14*, 3653; g) Mata, Y.; Pàmies, O.; Diéguez, M. *Adv. Synth. Catal*. **2009**, *351*, 3217; h) Raluy, E.; Pàmies, O.; Diéguez, M. *Adv. Synth. Catal.* **2009**, *351*, 1648.

[6] To our knowledge phosphoroamidite-thioether ligands have never been applied in Pd-catalyzed asymmetric allylic substitution reactions.

[7] For reviews on the use of carbohydrate-based ligands in asymmetric catalysis, see for instance: a) Diéguez, M.; Pàmies, O.; Claver, C. *Chem. Rev.* **2004**, *104*, 3189; b) Diéguez, M.; Pàmies, O.; Ruiz, A.; Díaz, Y.; Castillón, S.; Claver, C. *Coord. Chem. Rev.* **2004**, *248*, 2165; c) Diéguez, M.; Ruiz, A.; Claver, C. *Dalton Trans.* **2003**, 2957; d) Diéguez, M.; Claver, C.; Pàmies, O. *Eur. J. Org. Chem*. **2007**, 4621; e) Woodward, S.; Diéguez, M.; Pàmies, O. *Coord. Chem. Rev.* **2010**, *254*, 2007; f) Boysen, M. M. K. *Chem. Eur. J.* **2007**, *13*, 8648; g) Benessere, V.; Del Litto, R.; De Roma, A.; Ruffo, F. *Coord. Chem. Rev.* **2010**, *254*, 390.

[8] For reviews on the use of phosphite-based ligands in asymmetric catalysis, see for instance a) Diéguez, M.; Ruiz, A.; Claver, C. *Dalton Trans.* **2003**, 2957; b) Diéguez, M.; Pàmies, O.; Ruiz, A.; Claver, C. in *Methodologies in Asymmetric Catalysis* (Ed. Malhotra, S. V.); American Chemical Society, Washington DC, **2004**; c) Diéguez, M.; Pàmies, O.; Claver, C. *Tetrahedron: Asymmetry* **2004**, *15*, 2113; d) Claver, C.; Pàmies, O.; Diéguez, M, in *Phosphorous Ligands in Asymmetric Catalysis*, Vol. 2 (Ed. Börner, A.), Wiley-VCH, Weinheim, **2008**, Chapter 3; e) van Leeuwen, P. W. N. M.; Kamer, P. C. J.; Claver, C.; Pàmies, O.; Diéguez, M. *Chem. Rev.* **2011**, *111*, 2077.

[9] Porte, A. M.; Reinbenspies, J.; Burgess, K. *J. Am. Chem. Soc.* **1998**, *120*, 9180.

[10] a) Auburn, P. R.; Mackenzie, P. B.; Bosnich B. *J. Am. Chem. Soc.* **1985**, *107*, 2033; b) Jia, C.; Müller, P.; Mimoun, H. *J. Mol. Cat. A: Chem*. **1995**, *101*, 127; c) Lehman, J.; Lloyd-Jones, G. C. *Tetrahedron* **1995**, *51*, 8863.

[11] Pericàs, M. A.; Puigjaner, C.; Riera, A.; Vidal-Ferran, A.; Gómez, M.; Jiménez, F.; Muller, G.; Rocamora, M. *Chem. Eur. J.* **2002**, *8*, 4164.

CHAPTER 6

Conclusions

UNIVERSITAT ROVIRA I VIRGILI
SUGAR-BASED LIGAND LIBRARIES FOR ASYMMETRIC REDUCTIONS AND C-C BOND FORMING REACTIONS
M. Mercè Coll Serrahima
DL:T. 150-2012

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 esters and enamides) using a furanoside phosphite-phosphoroamidite and diphosphoroamidite ligand library, we observed important effects on the catalytic performance of the position of the phosphoroamidite group, the configuration at C-3 of the furanoside backbone, the introduction of second phosphoroamidite moiety and the substituents/configurations in the biaryl phosphite/phosphoroamidite moieties. By judicious choice of the ligand components, high enantioselectivities were obtained in the reduction of dimethyl itaconate (up to >99% ee), α-dehydroamino acid esters (up to 99% ee) and several enamides (up to 92% ee).

Kinetic studies indicate that the rate dependence is first order in rhodium and hydrogen pressure and zero order in substrate concentration. NMR studies on the intermediates formed under hydrogenation conditions indicate that: (a) the [Rh(P-P')(substrate)]BF_4 species is the resting state (P-P' = phosphite-phosphoroamidite ligands); (b) the olefin coordination mode is controlled by the electronic properties of ligand; and (c) the enantioselectivity is mainly dictated by steric factors which controls the substrate rotation that follows the oxidative addition of hydrogen.

- In the Ir-catalyzed asymmetric hydrogenation of minimally functionalized olefins, using a furanoside thioether-phosphite, thioether-phosphinite and thioether-phosphoroamidite ligand libraries, we found that its effectiveness at transferring the chiral information in the product can be tuned by correctly choosing the ligand components (the position of the thioether group at either C-5 or C-3 of the furanoside backbone, the configuration at C-3, the substituents/configurations in the thioether and in the biaryl phosphite moieties, and the effect of replacing the phosphite moiety by a phosphinite/phosphoroamidite group). Enantioselectivities were therefore excellent (ee's up to 99%) in a wide range of *E*- and *Z*-trisubstituted alkenes using the thioether-phosphite ligands. The good performance extends to the very challenging class of terminal disubstituted aryl/alkyl olefins. For this substrate class, our results indicated that enantioselectivity is dependent on the nature of the alkyl substrate substituent. Enantioselectivities were therefore best in the asymmetric reduction of aryl and

heteroaryl/*tert*-butyl substrates (ee's up to 99%). Interestingly, for 1,1-disubstitued substrates, both enantiomers of the hydrogenation product can be obtained in high enantioselectivity, simply by changing the configuration of the biaryl phosphite moiety. These results constitute the first example of non N-donor heterodonor ligands applied to this process.

2. Chapter 4. *Asymmetric transfer hydrogenation of ketones*. The conclusions of this chapter can be summarized as follows:

- In the asymmetric transfer hydrogenation reactions with catalysts precursors based on pseudo-dipeptides ligands containing a 1,2-amino alcohol sugar core, we have found that the enantioselectivity is exclusively controlled by the sugar moiety which enables the use of inexpensive achiral or racemic α-amino acid derivatives. Excellent enantioselectivities (ranging from 98% to >99%) were therefore obtained in the reduction of a broad range of ketones. Moreover, these carbohydrate-based pseudo-dipeptide ligands showed a higher degree of substrate versatility than previous successful pseudo-dipeptide analogues reported in the literature.
- In the asymmetric transfer hydrogenation reactions with catalysts precursors containing 1,3-amino alcohol sugar based pseudo-dipeptides and thioamide ligands we found that catalytic performance is highly affected by position of the amino acids/thioamide groups at either C-5 or C-3 of the furanoside backbone, the configuration at C-3 of the furanoside backbone, and substituents/configurations in the amino acid/thioamide moieties. By carefully selecting the ligand components, we have developed the first carbohydrate-based thioamide ligand library that provides high enantioselectivity in a broad range of aryl-alkyl ketones (ee's up to 99%). It should be noted that both enantiomers of alcohol products can be obtained with high enantioselectivities by simply changing the absolute configuration of the thioamide substituent. In contrast to previous successful thioamides, enantioselectivity is hardly affected by the presence of electron-withdrawing or electron-donating groups, therefore, a range of *para*- and *meta*-substituted aryl-alkyl ketones were efficiently reduced.

3. Chapter 5. *Asymmetric Pd-catalyzed allylic substitution*. The conclusions of this chapter can be summarized as follows:

- In the asymmetric Pd-catalyzed allylic substitution reactions using furanoside thioether-phosphite, thioether-phosphinite and thioether-phosphoroamidite

ligand libraries, we observed important effects of the position of the thioether, the configuration at C-3, the substituents/configurations in the thioether and biaryl phosphite moieties, and the effect of replacing the phosphite moiety by a phosphinite/phosphoroamidite group. However, the effect of these parameters depended on each substrate. For sterically hindered substrates, enantioselectivities (ee's up to 92%) were best with thioether-phosphinite ligands, whereas for unhindered substrates, the best enantioselectivities (ee's up to 82%) were obtained with thioether-phosphite ligands. Interestingly, we were able to identify pseudo-enantiomeric ligands.

UNIVERSITAT ROVIRA I VIRGILI
SUGAR-BASED LIGAND LIBRARIES FOR ASYMMETRIC REDUCTIONS AND C-C BOND FORMING REACTIONS
M. Mercè Coll Serrahima
DL:T. 150-2012

CHAPTER 7

Resum

UNIVERSITAT ROVIRA I VIRGILI
SUGAR-BASED LIGAND LIBRARIES FOR ASYMMETRIC REDUCTIONS AND C-C BOND FORMING REACTIONS
M. Mercè Coll Serrahima
DL:T. 150-2012

7. Resum

En els últims anys, la creixent demanda de compostos enantiomèricament purs (fàrmacs, productes agroquímics, additius…) ha impulsat el desenvolupament de la catàlisi asimètrica, sobretot emprant compostos organometàl·lics quirals com a catalitzadors. En aquest context, 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.

Aquesta tesi s'ha centrat en la síntesi de compostos derivats de sucre i l'aplicació com a lligands de catalitzadors homogenis quirals en tres reaccions asimètriques d'interès industrial: hidrogenació, transferència d'hidrogen i substitució al·lílica. Per assolir aquest objectiu s'ha plantejar la síntesi de varies famílies de compostos derivats de la D-(+)-xilosa i D-(+)-glucosa. Concretament, fosfit-fosforoamidit i difosforoamidit, tioèter-fosfit, tioèter-fosfinit i tioèter-fosforoamidit i finalment les famílies de lligands pseudo-dipèptids i tioamides.

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 l'aplicació de varies llibreries de lligands furanòsids. La primera part inclou el manuscrit, *Asymmetric Rh-catalyzed hydrogenation using a furanoside phosphite-phosphoroamidite and diphosphoroamidite ligand library*, on es descriu l'aplicació de lligands fosfit-fosforoamidit i difosforoamidit en la reacció d'hidrogenació asimètrica, catalitzada per Rh, de diverses olefines funcionalitzades. S'ha observat un important efecte de la posició del grup fosforoamidit, de la configuració del carboni-3 de l'esquelet furanòsid, la presència d'un segon grup fosforoamidit i dels substituents/configuracions dels grups biaril. Així, els millors resultants s'obtenen amb els sistemes Rh/fosfit-fosforoamidit que han proporcionat elevades activitats i excessos enantiomèrics de fins al 99%. En aquesta secció també s'estudia el mecanisme de la hidrogenació utilitzant aquest lligands. La segona part composada per l'article, *A modular furanoside thioether-phosphite/phosphinite ligand library for asymmetric Ir-catalyzed hydrogenation of minimally functionalized olefins*,

descriu l'ús dels compostos tioèter-fosfit i tioèter-fosfinit com a lligands en la hidrogenació asimètrica d'olefines no funcionalitzades catalitzada per iridi. Els resultats catalítics indiquen un important efecte de la posició del grup tioèter i de la configuració del carboni-3 de l'esquelet furanòsid, de les propietats electròniques i estèriques del substituent del grup tioèter, dels substituents/configuració dels grups biaril i del tipus de grup funcional. Els sistemes Ir/tioèter-fosfit han proporcionat excel·lents activitats i enantioselectivitats de fins al 99% en la hidrogenació d'un ampli rang d'olefines no funcionalitzades. Aquest resultats són el primer exemple de lligands heterodadors no N-dador aplicats amb èxit en aquest procés. La tercera part inclou l'article, *Asymmetric hydrogenation of alkenes lacking coordinating groups with a furanoside thioether-phosphoroamidite ligand library,* on es descriu l'ús dels compostos tioèter-fosforoamidit com a lligands en la hidrogenació asimètrica d'olefines no funcionalitzades catalitzada per iridi. Els resultats mostren que la introducció del grup fosforoamidit té un efecte negatiu en l'enantioselectivitat. Els millors excessos enantiomèrics (fins al 87%) s'obtenen en la hidrogenació de substrats terminals.

En el **capítol 4** s'estudia la transferència d'hidrogen asimètrica de cetones. Aquest capítol es divideix en dues parts on es tracta la síntesi i aplicació de varies llibreries de nous lligands pseudo-dipèptids i tioamides basats en carbohidrats. La primera part esta formada per l'article, *Carbohydrate-based pseudo-dipeptides: New ligands for the highly enantioselective Ru-catalyzed transfer hydrogenation reaction*, on es descriu la síntesi i aplicació d'una nova família de lligands pseudo-dipèptids, basats en carbohidrats, en la transferència asimètrica d'hidrogen, catalitzada per Ru, de diverses cetones. Els resultats indiquen que l'enantioselectivitat està controlada exclusivament per l'esquelet carbohidrat el que fa posible l'ús de derivats d'amino àcids aquirals o racèmics de baix cost. S'han obtingut excellent enantioselectivitats (>99%) en la reducció d'un ampli rang de cetones. A més a més, aquest lligands pseudo-dipèptids derivats de carbohidrat mostren una versatilitat de substrat major que els seus anàlegs prèviament aplicats amb èxit en aquesta reacció. La segona part esta formada per l'article, *Modular furanoside pseudo-dipeptides and thioamides, readily available ligand libraries for metal-catalyzed transfer hydrogenation reactions. Scope and limitations*, on s'estudia la síntesi i aplicació de dos llibreries de lligands pseudo-dipèptids i tioamides, basats en carbohidrats modificats en les posicions 3 i 5 de l'anell furanòsid, en la transferència d'hidrogen de cetones catalitzada per Rh i Ru. La

modificació sistemàtica dels paràmetres dels lligands ens han permès descobrir la primera família de lligands tioamida derivats de sucre que han proporcionat excel·lents enantioselectivitats (fins al 99%) en la reducció d'un ampli rang de cetones.

Per últim, el **capítol 5** inclou el manuscrit, *Novel P,S Ligands for Pd-catalyzed Asymmetric Allylic Substitution Reactions* i descriu l'ús dels compostos furanòsid tioèter-fosfit, tioèter-fosfinit i tioèter-fosforoamidit com a lligands en reaccions de substitució al·lílica asimétrica (alquilació i aminació) catalitzades per pal·ladi. Concretament s'ha estudiat la reacció d'alquilació al·lílica de substrats amb propietats estèriques diferents. Els sistemes Pd/tioèter-fosfit i Pd/tioèter-fosfinit han proporcionat excessos enantiomèrics de fins al 92%. S'ha observat un important efecte de la posició del grup tioèter i de la configuració del carboni-3 de l'esquelet furanòsid, de les propietats electròniques i estèriques del substituent del grup tioèter, dels substituents/configuració dels grups biaril, del tipus de grup funcional i del substrat. Així, per substrats impedits estèricament les millors enantioselectivitats (92%) s'obtenen amb el lligands tioèter-fosfinit, mentre que pels substrats menys impedits s'obtenen amb els sistemes Pd/tioèter-fosfit.

UNIVERSITAT ROVIRA I VIRGILI
SUGAR-BASED LIGAND LIBRARIES FOR ASYMMETRIC REDUCTIONS AND C-C BOND FORMING REACTIONS
M. Mercè Coll Serrahima
DL:T. 150-2012

CHAPTER 8

Appendix

UNIVERSITAT ROVIRA I VIRGILI
SUGAR-BASED LIGAND LIBRARIES FOR ASYMMETRIC REDUCTIONS AND C-C BOND FORMING REACTIONS
M. Mercè Coll Serrahima
DL:T. 150-2012

8. List of papers and meeting contributions

8.1. List of papers

1. Coll, M.; Pàmies, O.; Diéguez, M. "*Thioether-phosphite: new ligands for the highly enantioselective Ir-catalyzed hydrogenation of minimally functionalized olefins*" *Chem. Commun*. **2011**, *47*, 9215. (Chapter 3).

2. Coll, M.; Pàmies, O.; Diéguez, M. "*Asymmetric Rh-catalyzed hydrogenation using a furanoside phosphite-phosphoroamidite and diphosphoroamidite ligand library*" submitted for publication to *Dalton Trans.* (Chapter 3).

3. Coll, M.; Pàmies, O.; Diéguez, M. "*A modular furanoside thioether-phosphite/phosphinite ligand library for asymmetric Ir-catalyzed hydrogenation of minimally functionalized olefins*" in preparation (Chapter 3).

4. Coll, M.; Pàmies, O.; Diéguez, M. "*Asymmetric hydrogenation of alkenes lacking coordinating groups with a furanoside thioether-phosphoroamidite ligand library*" in preparation (Chapter 3).

5. Coll, M.; Pàmies, O.; Adolfsson, H.; Diéguez, M. "*Carbohydrate-based pseudo-dipeptides: New ligands for the highly enantioselective Ru-catalyzed transfer hydrogenation reaction*" *Chem. Commun*. **2011**, *47*, 12188. (Chapter 4).

6. Coll, M.; Ahlford, K.; Pàmies, O.; Adolfsson, H.; Diéguez, M. "*Modular furanoside pseudo-dipeptides and thioamides, readily available ligand libraries for metal-catalyzed transfer hydrogenation reactions. Scope and limitations*" submitted for publication to *Adv. Synth. Catal*. (Chapter 4).

7. Coll, M.; Pàmies, O.; Diéguez, M. "*1,2-Amino alcohol sugar based pseudo-dipeptides and thioamide ligands for enantioselective Ru- and Rh-catalyzed transfer hydrogenation reaction*" in preparation (Chapter 4).

8. Coll, M.; Pàmies, O.; Diéguez, M. "*Novel P,S Ligands for Pd-catalyzed Asymmetric Allylic Substitution Reactions*" in preparation (Chapter 5).

Publications not included in this thesis (Reprints are included at the end of this chapter):

9. Mazuela, J.; Coll, M.; Pàmies, O.; Diéguez, M. "*Rh-Catalyzed Asymmetric Hydroformylation of Heterocyclic Olefins Using Chiral Diphosphite Ligands. Scope and Limitations*" *J. Org. Chem*. **2009**, *74*, 5440.

10. Mazuela, J.; Verendel, J. J.; Coll, M.; Schäffner, B.; Börner, A.; Andersson, P. G.; Pàmies, O.; Diéguez, M. "*Iridium Phosphite-Oxazoline Catalysts for the Highly Enantioselective Hydrogenation of Terminal Alkenes*" *J. Am. Chem. Soc*. **2009**, *131*, 12344.

Reprints were made with permission from the Publisher.

8.2. Meeting contributions

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

2. Coll, M. M.; Mazuela, J.; Pàmies, O.; Diéguez, M. "*Diphosphite Ligands for the Rh-Catalyzed Asymmetric Hydroformylation of Heterocyclic Olefins*". COSTD40 Innovation IV Meeting Ankara. Turkey. 2010. Poster communication.

3. Coll, M. M.; Mazuela, J.; Pàmies, O.; Diéguez, M. "*Rh-Catalyzed Asymmetric Hydroformylation of Heterocyclic Olefin Using Chiral Diphosphite Ligands. Scope and Limitations*". XVII International Symposium on Homogeneous Catalysis-ISHC. Poznàn. Polish. 2010. Poster communication.

JOC Article
pubs.acs.org/joc

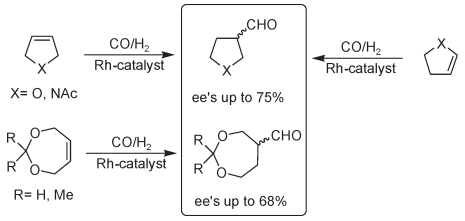
Rh-Catalyzed Asymmetric Hydroformylation of Heterocyclic Olefins Using Chiral Diphosphite Ligands. Scope and Limitations

Javier Mazuela, Mercedes Coll, Oscar Pàmies,* and Montserrat Diéguez*

Departament de Química Física i Inorgànica, Universitat Rovira i Virgili, Campus Sescelades, C/ Marcel·lí Domingo, s/n 43007 Tarragona, Spain

oscar.pamies@urv.cat; montserrat.dieguez@urv.cat

Received May 8, 2009



We used a series of diphosphite ligands to study the effect of the ligand backbone, the length of the bridge, and the substituents of the biphenyl moieties and determine the scope of this type of ligand in the Rh-catalyzed asymmetric hydroformylation of several hetereocylic olefins. By carefully selecting the ligand components, we achieved high chemo-, regio-, and enantioselectivities in different substrate types. Unprecedentedly high enantioselectivities for five-membered heterocyclic olefins were therefore obtained. Note that both enantiomers of the hydroformylation products can be synthesized using the same ligand by a simple substrate change. For the seven-membered heterocyclic dioxepines, our results are among the best obtained. Also, both enantiomers of the hydroformylation products can be obtained by using pseudoenantiomer ligands or by carefully tuning the ligand parameters.

1. Introduction

Asymmetric hydroformylation has attracted much attention as a potential tool for preparing enantiomerically pure aldehydes.[1] Despite its importance, asymmetric hydroformylation is underdeveloped compared to other processes such as hydrogenation. Traditionally, vinylarenes have been the most studied substrates. Although Rh−diphosphites and Rh−Binaphos-type phosphine−phosphites have proved to be the most efficient catalytic systems,[2] recently diphospholane,[3] bis(diazaphospholodine),[4] and phosphine−phosphoroamidite[5] have emerged as suitable alternatives. The use of these latter ligands has allowed the successful Rh-catalyzed hydroformylation of other type of substrates, like allyl cyanide, vinyl acetate, and some byciclic olefins.[3−5] However, more research is still needed to expand the range of substrates to be studied. In this respect, few studies have been made on the asymmetric hydroformylation of heterocyclic

(1) See, for example: (a) Claver, C.; Diéguez, M.; Pàmies, O.; Castillón, S. In *Topics in Organometallic Chemistry*; Beller, M., Ed.; Springer: Berlin, 2006; Chapter 2, p 35. (b) Claver, C.; Godard, C., Ruiz, A.; Pàmies, O.; Diéguez, M. In *Modern Carbonylation Methods*; Kollár, L., Ed.; Wiley-VCH: Weinheim, 2008; Chapter 3. (c) Nozaki, K. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Chapter 11, p 382.

(2) See, for example: (a) Diéguez, M.; Pàmies, O.; Claver, C. *Tetrahedron: Asymmetry* **2004**, *15*, 2113. (b) Breit, B. *Top. Curr. Chem.* **2007**, *279*, 139. (c) Klosin, J.; Landis, C. R. *Acc. Chem. Res.* **2007**, *40*, 1251. (d) *Rhodium Catalysed Hydroformylation*; van Leeuwen, P. W. N. M., Claver, C., Eds.; Kluwer Academic Press: Dordrecht, 2000. (e) Claver, C.; Pàmies, O.; Diéguez, M. In *Phosphorous Ligands in Asymmetric Catalysis*; Börner, A., Ed.; Wiley-VCH: Weinheim, 2008; Chapter 3, Vol. 2.

(3) See, for example: (a) Axtell, A. T.; Cobley, C. J.; Klosin, J.; Whiteker, G. T.; Zanotti-Gerosa, A.; Abboud, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 5834. (b) Huang, J.; Bunel, E.; Allgeier, A.; Tedrow, J.; Storz, T.; Preston, J.; Correll, T.; Manley, D.; Soukup, T.; Jensen, R.; Syed, R.; Moniz, G.; Larsen, R.; Martinelli, M.; Reider, P. J. *Tetrahedon Lett.* **2005**, *46*, 7831.

(4) See, for instance: (a) Clark, T. P.; Landis, C. R.; Freed, S. L.; Klosin, J.; Abboud, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 5040. (b) Thomas, P. J.; Axtell, A. T.; Klosin, J.; Peng, W.; Rand, C. L.; Clark, T. P.; Landis, C. R.; Abboud, K. A. *Org. Lett.* **2007**, *9*, 2665. (c) Breeden, S.; Cole-Hamilton, D. J.; Foster, D. F.; Schwarz, G. J.; Wills, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 4106. (d) Peng, X.; Wang, Z.; Xia, C.; Ding, K. *Tetrahedron Lett.* **2008**, *49*, 4862.

(5) Yan, Y.; Zhang, X. *J. Am. Chem. Soc.* **2006**, *128*, 7198.

Published on Web 07/02/2009 DOI: 10.1021/jo900958k

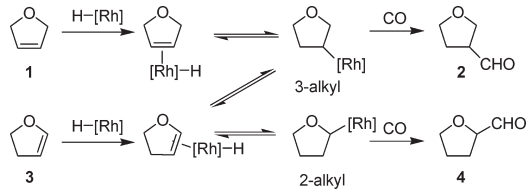
olefins, which provide access to important building blocks for synthesizing natural products and pharmaceuticals.[6] This is mainly because, for this kind of substrate, as well as having to control the enantioselectivity of the process, chemo- and regioselectivity are often a problem.[6,7] For example, in the hydroformylation of 2,5-dihydrofuran **1** the expected product is tetrahydrofuran-3-carbaldehyde **2** (Scheme 1). However, considerable amounts of 2,3-dihydrofuran **3** and tetrahydrofuran-2-carbaldehyde **4** can also be formed due to an isomerization process that takes place simultaneously with the hydroformylation reaction. When the 2,5-dihydrofuran **1** reacts with the rhodium hydride complex, the 3-alkyl intermediate is formed. This can evolve to 2,3-dihydrofuran **3** via the β-hydride elimination reaction. Similarly, this new substrate can evolve to produce the 2-alkyl and 3-alkyl intermediates. Although the formation of the 3-alkyl intermediate is thermodynamically favored, the acylation occurs faster in the 2-alkyl intermediate.[6b] Regioselectivity is therefore dominated by the rate at which the acyl complex is formed.

For a considerable time, only the phosphine−phosphite binaphos ligand provided good regio- and enantiocontrol in the Rh-catalyzed asymmetric hydroformylation of heterocyclic compounds.[8] Several diphosphines,[6c] including some diphospholanes and the bis-(diazaphospholodine) ESPHOS ligand,[9] have been applied but with little success (ee's up to 32%). When diphosphites were used as ligands for the Rh-catalyzed hydroformylation of vinylarenes, activities and enantioselectivities were comparable to the best in the literature, obtained using the binaphos ligand.[2] However, they have been used very little in the hydroformylation of heterocyclic substrates. This is mainly because extensive isomerization had been observed when phosphite ligands are used.[7]

In 2005, we reported the first successful application of a diphosphite ligand in the Rh-catalyzed asymmetric hydroformylation of 2,5- and 2,3-dihydrofurans.[10] Despite this success, other diphosphite ligands have not yet been reported, and the possibilities offered by diphosphites as new ligands for this process still need to be studied. To fully investigate these possibilities, in this paper we extend our previous study (2005) to other diphosphite ligands (Figure 1) and other types of heterocyclic olefins.

To do so, we have synthesized and screened a library of 64 potential diphosphite ligands.[11] The ligands we have chosen are representative of the most successfully applied families of diphosphite ligands in hydroformylation (chiraphite **L3**, sugar derivatives **L4** and **L7**, and kelliphite **L17**). We have also evaluated systematic modifications of several ligand parameters in these prominent ligands, which are known to have an important effect on catalytic performance. Therefore, with this library, we have investigated how the ligand backbone, the length of the bridge, and the substituents of the biphenyl moieties affected activities and selectivities (chemo-, regio-, and enantioselectivity). By carefully selecting these elements, we have achieved high regio- and enantioselectivities and activities in different substrates.

SCHEME 1. Proposed Mechanism for the Isomerization Process



2. Results and Discussion

2.1. Asymmetric Hydroformylation of Five-Membered Heterocyclic Olefins. Diphosphite ligands **L1**−**L17a**−**e** were first used in the Rh-catalyzed asymmetric hydroformylation of 2,5-dihydrofuran **1**. The catalysts were prepared in situ by adding the corresponding diphosphite ligand to [Rh(acac)-$(CO)_2$] as a catalyst precursor.

Initially, we determined the optimal reaction conditions by conducting a series of experiments with ligand **L10c** in which the ligand-to-rhodium ratio, CO/H_2 pressure ratio, temperature, reaction time, and substrate-to-rhodium ratio were varied (Table 1).

Varying the ligand-to-rhodium ratio showed that the combination of chemo-, regio-, and enantioselectivities was best when 2 equiv of ligand was used (Table 1, entries 1−3). A lower ligand-to-rhodium ratio decreased the regio- and enantioselectivities in aldehyde **2** (Table 1, entry 1), while a higher ligand-to-rhodium ratio negatively affected chemoselectivity and increased the formation of isomerized product **3** (Table 1, entry 3).

It is generally accepted that isomerization occurs as a result of competition between the β-hydride elimination process and CO insertion (Scheme 1). Since a high CO pressure is needed to suppress isomerization, we conducted experiments with increased CO partial pressure. This did not affect the rate of hydroformylation vs isomerization (Table 1, entries 2 vs 5), though decreasing the CO/H_2 pressure ratio negatively affected chemoselectivity, which increased the formation of isomerized product **3** (Table 1, entries 2 vs 6).

A prolonged reaction time increased conversion into aldehydes (Table 1, entry 4) but decreased regio- and enantioselectivity in the desired product **2** (Table 1, entry 2 vs 4). To study whether the hydroformylation of the formed isomer 2,3-dihydrofuran **3** accounts for this lost of selectivity, we performed the hydroformylation of **3** under the same reaction conditions. After 48 h, the hydroformylation of **3** afforded a 78:22 mixture of (*R*)-**2** (48% ee) and **4** in 88% conversion (Table 3, entry 11). By comparing these results, we concluded that the loss of regioselectivity with the

(6) (a) Vietti, D. E. U.S. Patent 4376208, 1983.(b) Hoiuchi, T.; Ota, T.; Shirakawa, E.; Nozaki, K.; Takaya, H. *J. Org. Chem.* **1997**, *62*, 4285. (c) del Rio, I.; van Leeuwen, P. W. N. M.; Claver, C. *Can. J. Chem.* **2001**, *79*, 560.

(7) (a) Polo, A.; Real, J.; Claver, C.; Castillón and, S.; Bayón, J. C. *J. Chem. Soc., Chem. Commun.* **1990**, 600. (b) Polo, A.; Claver, C.; Castillón, S.; Ruiz, A.; Bayón, J. C.; Real, J.; Mealli and, C.; Masi, D. *Organometallics* **1992**, *11*, 3525.

(8) Several modifications of the Binaphos-type ligand have been studied. See ref 6b.

(9) Unpublished results. For instance: (*R,R*)-Ph-BPE (22% ee), (*R,R*)-^{i}Pr-BPE (18% ee), and ESPHOS (32% ee).

(10) Diéguez, M.; Pàmies, O.; Claver, C. *Chem. Commun.* **2005**, 1221.

(11) These ligands have the advantages of phosphite ligands: they are obtainable at a low price from readily available alcohols, are highly resistant to oxidation, and have facile modular constructions. See, for instance: (a) Reference 2e. (b) Diéguez, M.; Pàmies, O.; Ruiz, A.; Claver, C. In *Methodologies in Asymmetric Catalysis*; American Chemical Society: Washington, DC, 2004; Chapter 11.

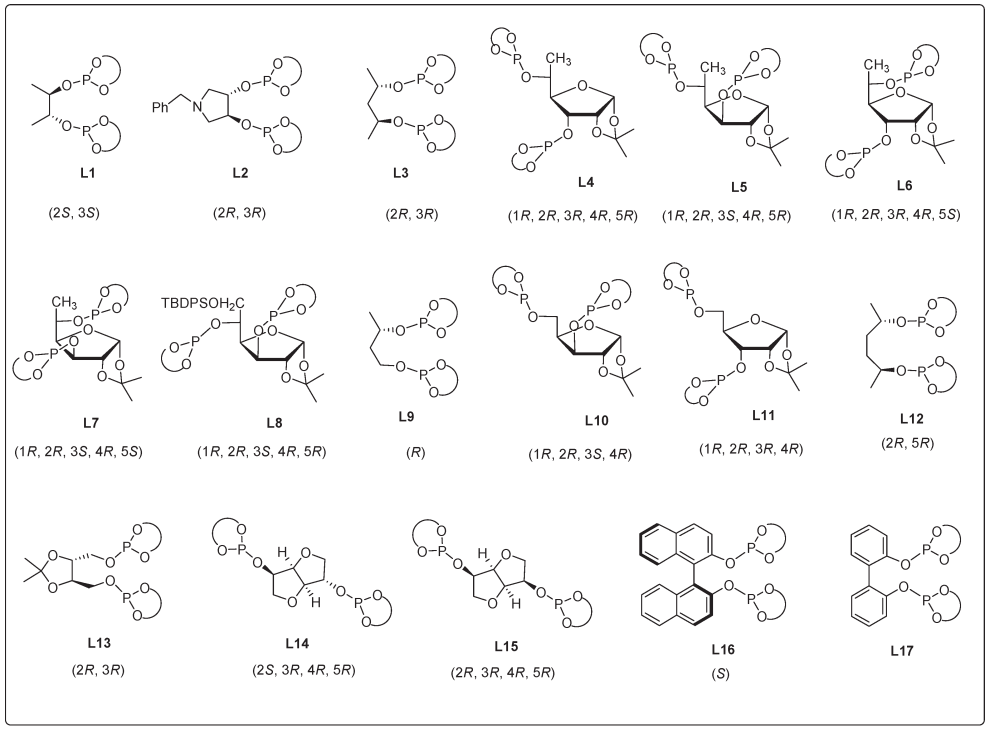


FIGURE 1. Disphosphite ligands **L1**−**L17a**−**e** used in the Rh-catalyzed asymmetric hydroformylation of heterocyclic olefins.

prolonged reaction time was due to the hydroformylation of the 2,3-dihydrofuran **3** formed under reaction conditions. This also caused a loss of enantioselectivity because the absolute configuration of the predominant enantiomer of **2** obtained from **3** is *R*, which is opposite to that which is obtained from **1**. These results show that the absence of isomerization of the substrate is important for achieving high enantioselectivity from the reaction of **1**. Indeed, the ee of **2** dropped when the hydroformylation of **3** (which is formed from the isomerization of **1**) took place at a low ligand-to-rhodium ratio (Table 1, entry 1). Accordingly, a decrease in the substrate-to-rhodium ratio had a negative effect on regio- and enantioselectivity because of the hydroformylation of the isomerization product **3** (Table 1, entry 7).

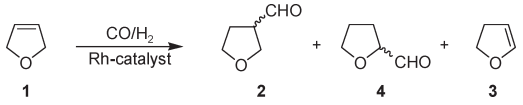
Varying the temperature strongly affects chemo- and regioselectivity (Table 1, entries 2, 8, and 9). Increasing the temperature negatively affected regioselectivity, whereas lowering the temperature to 25 °C negatively affected activity and chemoselectivity. This is because at high temperature hydroformylation of the isomerized 2,3-dihydrofuran **3** takes place. The best trade-off between chemo- and regioselectivities was therefore achieved at 45 °C.

For the purpose of comparison, the other ligands were tested under optimized conditions (i.e., ligand-to-rhodium ratio of 2, $P_{CO/H2} = 1$, 24 h reaction time at 45 °C). Our results indicate that selectivity is affected by the length of the bridge, the backbone of the ligand, and the substituents of the biphenyl moieties (see Table 2). In no cases were hydrogenated or polymerized products of 2,5-dihydrofuran observed.

The influence of the bridge length indicates that the use of 1,3-diphosphites provided a better catalytic performance than 1,2- and 1,4-diphosphites. Ligands **L3**−**L11**, which have three carbon atoms in the bridge (Table 2, entries 3−18), therefore provided higher regio- and enantioselectivities than ligands **L1**−**L2** (Table 2, entries 1 and 2), which have two carbon atoms in the bridge, and ligands **L12**−**L17** (Table 2, entries 19−24), which have four carbon atoms in the bridge.

The influence of the ligand backbone indicates that increasing the rigidity of the ligand is beneficial. Our results with ligands **L3c** and **L9c** are therefore worse than those with the corresponding ligands **L4c** and **L11c**, which have the same configuration of carbons adjacent to the phosphite

TABLE 1. Rh-Catalyzed Asymmetric Hydroformylation of 1 Using Ligand L10c. Optimization of the Reaction Conditions[a]



1 2 4 3

entry	ligand	L/Rh	CO/H_2	% conv[b]	% aldehyde (2:4)[c]	% 3[d]	% ee of 2[e]
1	**L10c**	1.1	1	100	82 (89:11)	18	31 (*S*)
2	**L10c**	2	1	100	88 (100:0)	12	53 (*S*)
3	**L10c**	4	1	100	75 (100:0)	25	53 (*S*)
4[f]	**L10c**	2	1	100	98 (95:5)	2	37 (*S*)
5	**L10c**	2	2	100	87 (100:0)	13	53 (*S*)
6	**L10c**	2	0.5	91	59 (100:0)	32	52 (*S*)
7[f,g]	**L10c**	2	1	100	100 (92:8)	0	34 (*S*)
8[h]	**L10c**	2	1	26	13 (100:0)	13	54 (*S*)
9[i]	**L10c**	2	1	100	94 (98:2)	6	51 (*S*)

[a] P = 18 bar, [Rh(acac)$(CO)_2$] (0.012 mmol), **1**/Rh = 400, toluene (5 mL). T = 45 °C, t = 24 h. [b] Total conversion measured by ^{1}H NMR. [c] Conversion into aldehydes determined by ^{1}H NMR. [d] Isomerization measured by ^{1}H NMR. [e] Enantioselectivity of **2** measured by ^{1}H NMR using Eu(hfc)$_3$ on the corresponding methyl ester. [f] t = 48 h. [g] **1**/Rh= 200. [h] T = 25 °C. [i] T = 65 °C.

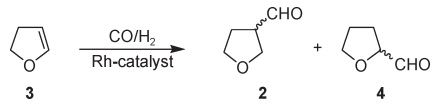
TABLE 2. Rh-Catalyzed Asymmetric Hydroformylation of 1 Using Ligands L1−L16a−d[a]

entry	ligand	% conv[b]	% aldehyde (2:4)[c]	% 3[d]	% ee of 2[e]
1	**L1c**	100	100 (72:28)	0	> 5
2	**L2c**	100	70 (97:3)	30	6 (*S*)
3	**L3c**	100	99 (95:5)	1	23 (*R*)
4	**L4c**	100	92 (98:2)	8	47 (*R*)
5	**L5a**	76	64 (99:1)	8	> 5
6	**L5b**	98	86 (98:2)	12	43 (*S*)
7	**L5c**	100	99 (99:1)	1	74 (*S*)
8	**L5d**	100	98 (99:1)	2	63 (*S*)
9	**L6c**	90	75 (96:4)	15	27 (*R*)
10	**L7c**	100	94 (98:2)	6	25 (*R*)
11	**L8c**	100	92 (97:3)	8	61 (*S*)
12	**L9c**	100	100 (85:15)	0	14 (*R*)
13	**L10a**	61	55 (99:1)	6	> 5
14	**L10b**	73	66 (98:2)	7	15 (*S*)
15	**L10c**	100	88 (100:0)	12	53 (*S*)
16	**L10d**	100	89 (99:1)	11	34 (*S*)
17	**L11b**	100	100 (77:23)	0	5 (*S*)
18	**L11c**	100	91 (95:5)	9	24 (*R*)
19	**L12c**	100	100 (64:36)	0	> 5
20	**L13c**	100	100 (99:1)	0	> 5
21	**L14c**	100	100 (78:22)	0	7 (*S*)
22	**L15c**	100	100 (82:18)	0	> 5
23	**L16c**	100	100 (96:4)	0	15 (*R*)
24	**L17e**	100	100 (100:0)	0	24 (*R*)
25[f]	**binaphos**	100	100 (100:0)	0	64 (*R*)

[a] P = 18 bar, [Rh(acac)$(CO)_2$] (0.012 mmol), **1**/Rh = 400, toluene (5 mL), T = 45 °C, t = 24 h. [b] Total conversion measured by ^{1}H NMR. [c] Conversion into aldehydes determined by ^{1}H NMR. [d] Isomerization measured by ^{1}H NMR. [e] Enantioselectivity of **2** measured by ^{1}H NMR using Eu(hfc)$_3$ on the corresponding methyl ester. [f] P = 20 bar, [Rh(acac)-$(CO)_2$] (0.012 mmol), **1**/Rh = 400, benzene (1.5 mL), ligand/Rh = 4, T = 40 °C, t = 24 h (see ref 6b).

groups but also a more rigid furanoside backbone (Table 2, entries 3 and 12 vs 4 and 18, respectively). We also found that both carbon atoms adjacent to the phosphite moieties must be substituted if regio-, chemo-, and enantioselectivity need to be high. Accordingly, ligands **L3**−**L5**, substituted at both carbon atoms adjacent to the phosphite, provided higher selectivities than ligands **L9**−**L11**, which are substituted only

TABLE 3. Selected Results for the Rh-Catalyzed Asymmetric Hydroformylation of 3[a]



3 2 4

entry	ligand	% conv[b]	% aldehyde (2:4)[c]	% ee of 2[d]
1	**L1c**	100	100 (54:46)	< 5
2	**L3c**	100	100 (68:32)	43 (*S*)
3	**L4c**	100	100 (73:27)	48 (*S*)
4	**L5a**	80	80 (75:25)	< 5
5	**L5b**	100	100 (74:26)	49 (*R*)
6	**L5c**	100	100 (76:24)	75 (*R*)
7	**L5d**	100	100 (73:27)	61 (*R*)
8	**L6c**	100	97 (70:30)	29 (*S*)
9	**L7c**	100	92 (69:31)	21 (*S*)
10	**L8c**	100	100 (72:28)	58 (*R*)
11	**L10c**	88	88 (78:22)	48 (*R*)
12	**L12c**	100	100 (55:45)	< 5
13	**L13c**	100	100 (50:50)	< 5
14[e]	**binaphos**	100	100 (50:50)	38 (*S*)

[a] P = 18 bar, [Rh(acac)$(CO)_2$] (0.012 mmol), **3**/Rh = 400, toluene (5 mL), T = 45 °C, t = 48 h. [b] Total conversion measured by ^{1}H NMR. [c] Conversion into aldehydes determined by ^{1}H NMR. [d] Enantioselectivity of **2** measured by ^{1}H NMR using Eu(hfc)$_3$ on the corresponding methyl ester. [e] P = 100 bar, [Rh(acac)$(CO)_2$] (0.012 mmol), **3**/Rh = 400, benzene (1.5 mL), ligand/Rh = 4, T = 40 °C, t = 24 h (see ref 6b).

at one carbon atom (Table 2, entries 3, 4, and 7 vs 12, 15, and 18). For disubstituted ligands, we also found that the presence of a methyl substituent is more effective at transferring the chiral information than the presence of a *tert*-butyldimethylsilyl group (Table 2, entries 7 vs 11). Finally, our results with ligands **L4**−**L7** indicate that there is a cooperative effect between stereocenters C-3 and C-5 of the furanoside backbone that resulted in a matched combination for ligand **L5** (Table 2, entries 7 vs 4, 9 and 10).

We investigated the effect of the biphenyl substituents with ligands **L5**, **L10**, and **L11** (Table 2, entries 5−8, 13−18) and found that these moieties affect catalytic performance. Bulky substituents in the *ortho* and *para* positions of the biphenyl moieties are needed for high enantioselectivity. Therefore, ligand **L5c** provided the highest enantioselectivity (Table 2, entry 7).

In summary, if chemo-, regio-, and enantioselectivities are to be high, the length of the bridge and the rigidity of the ligand backbone need to be correctly combined and bulky *tert*-butyl groups in both the *ortho* and *para* positions of the biphenyl phosphite moieties need to be present. Accordingly, ligand **L5c** showed practically no isomerization with excellent regioselectivity (99%) and unprecedently high enantioselectivity (ee's of 74%). Ligand **L5c** therefore competes favorably with the binaphos ligand, which so far has provided the best enantioselectivities for this substrate (Table 2, entry 7 vs 25).

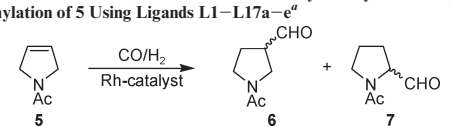
Next we applied diphosphite ligands **L1**−**L17a**−**e** in the Rh-catalyzed asymmetric hydroformylation of 2,3-dihydrofuran **3**. Our results are summarized in Table 3. In no cases were isomerized (product **1**), hydrogenated, or polymerized products of 2,3-dihydrofuran observed.

Our results followed the same trend as for the hydroformylation of **1**. The selectivities of the process were affected by the length of the bridge, the backbone of the ligand, and the

substituents of the biphenyl moieties. Accordingly, 1,3-diphosphites (Table 3, entries 2−11) were superior in terms of regio- and enantioselectivities to the 1,2- and 1,4-diphosphites (Table 3, entries 1 and 12−13, respectively). Again, ligand **L5c**, with a methyl substituent at the C-5 position, provided unprecedented enantioselectivities in favor of the tetrahydrofuran-3-carbaldehyde **2** (Table 3, entry 6). Note, however, that the sense of the enantioselectivity was opposite to that in the hydroformylation of 2,5-dihydrofuran **1** (Table 2, entry 7 vs Table 3, entry 6). Using the same ligand **L5c**, therefore, both enantiomers of tetrahydrofuran-3-carbaldehyde **2** can be accessed in high enantioselectivity by simple substrate change. Again, these results compete favorably with the best of those reported using the binaphos ligand (Table 3, entry 6 vs 14).

Encouraged by our excellent results in the Rh-catalyzed asymmetric hydroformylation of substrates **1** and **3**, we examined the hydroformylation of *N*-acetyl-3-pyrroline (**5**). These results, which are summarized in Table 4, follow the same trend as in the hydroformylation of **1** and **3**. As expected, activities were lower than in the hydroformylation of **1**.[6b] Again, using ligand **L5c** is highly advantageous as it provides the highest enantioselectivities obtained so far (Table 4, entry 3 vs 6).

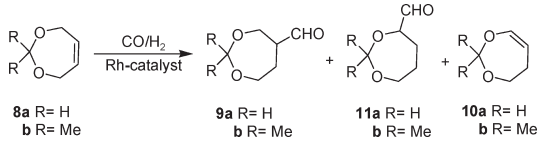
TABLE 4. Selected Results for the Rh-Catalyzed Asymmetric Hydroformylation of 5 Using Ligands L1−L17a−e[a]



entry	ligand	% conv[b]	% aldehyde (**6**:**7**)[c]	% ee of **6**[d]
1	**L1c**	100	100 (98:2)	< 5
2	**L3c**	100	100 (100:0)	19 (−)
3	**L5c**	100	100 (100:0)	71 (+)
4	**L10c**	100	100 (99:1)	49 (+)
5	**L12c**	100	100 (98:2)	< 5
6[e]	**binaphos**	92	92 (100:0)	66 (−)

[a] P = 18 bar, [Rh(acac)(CO)$_2$] (0.012 mmol), **5**/Rh = 400, toluene (5 mL), T = 45 °C, t = 72 h. [b] Total conversion measured by ^{1}H NMR. [c] Conversion into aldehydes determined by ^{1}H NMR. [d] Enantioselectivity of **6**. [e] P = 100 bar, [Rh(acac)(CO)$_2$] (0.012 mmol), 1/Rh = 400, benzene (1.5 mL), ligand/Rh = 4, T = 40 °C, t = 24 h (see ref 6b).

TABLE 5. Selected Results for the Rh-Catalyzed Asymmetric Hydroformylation of 8a,b Using Ligands L1−L17a−e[a]



entry	ligand	substrate	% conv[b]	% aldehyde (**9**:**11**)[c]	% **10**[d]	% ee of **9**[e]
1	**L1c**	**8a**	100	100 (100:0)	0	8 (−)
2[f]	**L1c**	**8a**	89	89 (100:0)	0	8 (−)
3[g]	**L1c**	**8a**	88	88 (100:0)	0	7 (−)
4	**L2c**	**8a**	88	88 (100:0)	0	9 (+)
5	**L3c**	**8a**	100	100 (100:0)	0	13 (−)
6	**L4c**	**8a**	79	79 (100:0)	0	37 (−)
7	**L5a**	**8a**	54	54 (100:0)	0	< 5
8	**L5b**	**8a**	75	75 (100:0)	0	18 (+)
9	**L5c**	**8a**	85	85 (100:0)	0	23 (+)
10	**L5d**	**8a**	83	83 (100:0)	0	22 (+)
11	**L6c**	**8a**	78	51 (100:0)	27	30 (+)
12	**L7c**	**8a**	90	90 (100:0)	0	35 (+)
13	**L8c**	**8a**	93	93 (100:0)	0	47 (+)
14	**L9c**	**8a**	91	91 (100:0)	0	8 (+)
15	**L10c**	**8a**	59	59 (100:0)	0	40 (+)
16	**L11c**	**8a**	74	48 (100:0)	26	30 (+)
17	**L13c**	**8a**	100	100 (100:0)	0	5 (−)
18	**L14c**	**8a**	96	96 (100:0)	0	15 (+)
19	**L15c**	**8a**	100	100 (100:0)	0	14 (+)
20	**L16c**	**8a**	56	56 (100:0)	0	56 (−)
21	**L17e**	**8a**	98	98 (99:1)	0	37 (+)
22[h]	**L16c**	**8a**	7	7 (100:0)	0	60 (−)
23[h]	**L10c**	**8a**	12	12 (100:0)	0	60 (+)
24[h]	**L8c**	**8a**	18	18 (100:0)	0	68 (+)
25[i]	**binaphos**	**8a**	> 99	> 99 (100:0)	0	76 (−)
26[j]	**L8c**	**8b**	94	94 (100:0)	0	55 (*S*)
27[j]	**L10c**	**8b**	86	86 (100:0)	0	51 (*S*)
28[j]	**L16c**	**8b**	73	73 (100:0)	0	59 (*R*)
29[i]	**binaphos**	**8b**	98	98 (100:0)	0	69 (*R*)

[a] P = 18 bar, CO/H$_2$ = 1/2, [Rh(acac)(CO)$_2$] (0.012 mmol), L/Rh = 2, **8**/Rh = 400, toluene (5 mL), T = 45 °C, t = 4 h. [b] Total conversion measured by ^{1}H NMR. [c] Conversion into aldehydes determined by ^{1}H NMR. [d] Isomerization measured by ^{1}H NMR. [e] Enantioselectivity of **9**. [f] CO/H$_2$ = 1. [g] CO/H$_2$ = 2. [h] T = 25 °C. t = 24 h. [i] See ref 6b. [j] t = 24 h.

2.2. Asymmetric Hydroformylation of Seven-Membered Heterocyclic Olefins. To further study the potential of these diphosphite ligands, we then tested them in the hydroformylation of *cis*-4,7-dihydro-1,3-dioxepin (**8a**) and *cis*-2,2-dimethyl-4,7-dihydro-1,3-dioxepin (**8b**).

Our most important results are shown in Table 5. Again, the selectivities of the process were affected by the length of the bridge, the backbone of the ligand, and the substituents of the biphenyl moieties. However, the effect of these parameters was different from their effect on the hydroformylation of the previous substrates (**1**, **3**, and **5**). In contrast to **1**, **3**, and **5**, therefore, both 1,3- and 1,4-diphosphites can provide good regio- and enantioselectivities if the appropriate rigidity of the ligand's backbone is chosen. Accordingly, not only 1,3-diphosphite ligands **L8c** and **L10c** were shown to be effective, but the 1,4-diphosphite ligand **L16c** also provided good results. Also, and in contrast to the previous substrates, for disubstituted furanoside 1,3-diphosphites the presence of a *tert*-butyldimethylsilyl group is more effective than the presence of a methyl substituent (Table 5; entries 13 vs 9). Interestingly, both enantiomers of the hydroformylation products **9** can be obtained by using pseudoenantiomer ligands (i.e., ligands **L4** and **L7**; Table 5, entries 6 and 12) or by carefully tuning the ligand parameters (i.e., ligands **L8c** and **L10c** vs **L16c**; Table 5; entries 23 and 24 vs 22 for substrate **9a**, and entries 26 and 27 vs 28 for substrate **9b**).

We also observed an important effect of the temperature, and this was more pronounced for the furanoside-based ligands **L8c** and **L10c**; therefore, lowering the temperature to 25 °C substantially increased enantioselectivity (up to 68%) and provided an excellent regioselectivity.

3. Conclusions

We have screened a library of modular diphosphite ligands **L1**−**L17a**−**e** in the Rh-catalyzed asymmetric hydroformylation of several hetereocylic olefins. Using this library we studied how the backbone of the ligand, the length of the bridge and the substituents of the biphenyl moieties affected the catalytic performance and determined the scope of diphosphite ligands. By carefully selecting the ligand components, we achieved high chemo-, regio- and enantioselectivities in different substrate types. Unprecedentedly high enantioselectivities for five-membered heterocyclic olefins were obtained using the furanoside diphosphite ligand **L5c**. Note that both enantiomers of the hydroformylation products can be synthesized using the same ligand by simple substrate change.[6b] For the seven-membered heterocyclic dioxepines, our results are among the best obtained. Also, both enantiomers of the hydroformylation products can be obtained by using pseudoenantiomer ligands or by carefully tuning the ligand parameters. These results open up the hydroformylation of heterocyclic compounds to the potentially effective use of readily available and highly modular diphosphite ligands.

4. Experimental Section

4.1. General Considerations. All experiments were carried out under argon atmosphere. All solvents were dried using standard methods and distilled prior to use. Ligands **L1**,[12] **L2**,[13] **L3**,[12] **L4**−**L7**,[14] **L8**,[15] **L9**,[12] **L10**,[16] **L11**,[17] **L12**,[12] **L13**,[13] **L14**,[18] and **L15**−**L16**[13] were prepared by previously described methods. Kelliphite (**L17e**) and commercial substrates **1**, **3**, and **8a** and were used without further purification. *N*-Acetyl-2-pyrroline (**5**)[6b] and *cis*-2,2-dimethyl-4,7-dihydro-1,3-dioxepine (**8b**)[19] were prepared according to the methods in the literature. The formation of **10a** was confirmed on the basis of the NMR assignments.[20] ^{1}H and ^{19}F NMR spectra were recorded on a 400 MHz spectrometer. Hydroformylation reactions were carried out in a Parr series 4593 stainless steel autoclave.

4.2. Typical Hydroformylation Procedure. The autoclave was purged three times with carbon monoxide. The solution of [Rh(acac)(CO)$_2$] (3.1 mg, 0.012 mmol), diphosphite (0.024 mmol), and substrate (4.8 mmol) in toluene (5 mL) was transferred to the stainless-steel autoclave. After pressurizing to 18 bar of syngas and heating the autoclave to 45 °C, the reaction was stirred for 24 h. Conversions and selectivities of the reaction were determined immediately by ^{1}H NMR analysis of the crude reaction without evaporation of the solvent. The determination of the enantiomeric excesses and absolute configurations was carried out using the procedures described in ref 6b.

Acknowledgment. We are indebted to Prof. C. Claver for her comments and suggestions. We thank the Spanish Government (Consolider Ingenio CSD2006-0003, CTQ2007-62288/BQU, 2008PGIR/07 to O.P. and 2008PGIR/08 to M.D.) and the Catalan Government (2005SGR007777 and Distinction to M.D.) for financial support.

(12) Buisman, G. J. H.; Vos, E. J.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *J. Chem. Soc., Dalton Trans*. **1995**, 409.
(13) Diéguez, M.; Pàmies, O.; Claver, C. *J. Org. Chem*. **2005**, *70*, 3363.
(14) (a) Diéguez, M.; Pàmies, O.; Castillón, S.; Ruiz and, A.; Claver, C. *Chem.—Eur. J*. **2001**, *7*, 3086. (b) Diéguez, M.; Pàmies, O.; Ruiz, A.; Claver, C. *New J. Chem*. **2002**, *26*, 827.
(15) Diéguez, M.; Pàmies, O.; Claver, C. *Adv. Synth. Catal*. **2005**, *347*, 1257.
(16) Buisman, G. J. H.; Martin, M. E.; Vos, E. J.; Klootwijk, A.; Kamer and, P. C. J.; van Leeuwen, P. W. N. M. *Tetrahedron: Asymmetry* **1995**, *8*, 719.
(17) Pàmies, O.; Net, G.; Ruiz and, A.; Claver, C. *Tetrahedron: Asymmetry* **1999**, *11*, 1097.
(18) Reetz, M. T.; Neugebauer, T. *Angew. Chem., Int. Ed*. **1999**, *38*, 179.
(19) Elliott, W. J.; Fried, J. *J. Org. Chem*. **1976**, *41*, 2469.
(20) Taskinen, E.; Ihlainen, P. *Struct. Chem*. **1999**, *10*, 295.

J|A|C|S ARTICLES

Published on Web 08/06/2009

Iridium Phosphite−Oxazoline Catalysts for the Highly Enantioselective Hydrogenation of Terminal Alkenes

Javier Mazuela,[†] J. Johan Verendel,[‡] Mercedes Coll,[†] Benjamín Schäffner,[§] Armin Börner,*[,§] Pher G. Andersson,*[,‡] Oscar Pàmies,[†] and Montserrat Diéguez*[,†]

Departament de Química Física i Inorgànica, Universitat Rovira i Virgili, Campus Sescelades, C/ Marcel·lí Domingo, s/n, 43007 Tarragona, Spain, Department of Biochemistry and Organic Chemistry, Uppsala University, Box 576, 751 23 Uppsala, Sweden, and Leibniz-Institut für Katalyse e.V.Universität Rostock, Albert-Einstein-Strasse 29a, 18059 Rostock, Germany

Received May 25, 2009; E-mail: montserrat.dieguez@urv.cat; pher.andersson@kemi.uu.se; Armin.Boerner@catalysis.de

Abstract: A modular library of readily available phosphite−oxazoline ligands (**L1**−**L16a**−**f**) has been successfully applied for the first time in the Ir-catalyzed asymmetric hydrogenation of a broad range of highly unfunctionalized 1,1,-disubstituted terminal alkenes. Enantioselectivities up to >99% and full conversions were obtained in several 1,1-disubstituted alkenes, including substrate classes that have never been asymmetrically hydrogenated before (i.e., 1,1-heteroaryl-alkyl, 1,1-diaryl, trifluoromethyl, etc.). The results indicated that these catalytic systems have high tolerance to the steric and electronic requirements of the substrate and also to the presence of a neighboring polar group. The asymmetric hydrogenations were also performed using propylene carbonate as solvent, which allowed the Ir catalyst to be reused and maintained the excellent enantioselectivities.

1. Introduction

The challenging conversion of largely unfunctionalized 1,1-disubstituted terminal alkenes into chiral hydrocarbons remains a frontier in the realm of asymmetric catalysis. Asymmetric hydrogenation is potentially a synthetic tool for preparing these compounds (Scheme 1).

Asymmetric hydrogenation is of interest because of its atom economy and operational simplicity.[1] Even so, few studies have been made of the asymmetric hydrogenation of 1,1-disubstituted terminal alkenes. This is mainly due to two reasons. The first one is that the two substituents R^1 and R^2 easily can exchange positions in the chiral environment formed by the catalysts, thus reversing the face selectivity (Scheme 2(a)). The second reason is that the terminal double bond can isomerize to form the more stable internal alkene, which usually leads to the predominant formation of the other enantiomer of the hydrogenated product (Scheme 2(b)). Few catalytic systems, then, provide high enantioselectivities and those that do are limited in substrate scope.[2]

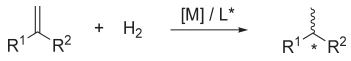
One of these systems uses samarium complexes and provides enantioselectivities up to 96% ee in the asymmetric hydrogenation of 2-phenylbut-1-ene (**S1**) but at −78 °C (or 64% ee at 25 °C).[3] Another system uses $RuCl_2$[(*R*,*R*)-Me-Duphos](dmf)$_n$ in the asymmetric hydrogenation of a limited range of 2-phenylbut-1-enes under basic conditions and provides ee's up to 89%.[4] Recently, M-chiral (iminophosphoranyl)ferrocene catalyst precursors (M = Rh and Ir) have been successfully used in the hydrogenation of 6-methoxy-1-methylene-1,2,3,4-tetrahydronaphthalene (ee's up to 94%; using M = Rh) and 2-(4-methoxyphenyl)-1-butene **S2** (ee's up to 97% using M = Rh).[5] In recent years, iridium complexes with chiral P,N ligands have become established as efficient catalysts for the hydrogenation of unfunctionalized olefins, with complementary scope to Rh− and Ru−diphosphine complexes.[2,6] In this context the groups of Pfaltz and Andersson found that some 2-phenylbut-1-enes can be hydrogenated with high enantioselectivity (88−97% ee) using Ir complexes modified with phosphinite−oxazoline ligands.[7,8] Furthermore, Pfaltz also found that in hydrogenation of terminal alkenes, the selectivity is highly pressure dependent. Hydrogenation at atmospheric pressure of H_2 gave significantly higher ee's than at higher pressures.[7] In 2008, we reported the

[†] Universitat Rovira i Virgili.
[‡] Uppsala University.
[§] Leibniz-Institut für Katalyse e.V.Universität Rostock.

(1) See for instance: (a) *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: Weinheim, 2000. (b) *Applied Homogeneous Catalysis with Organometallic Compounds*, 2nd ed.; Cornils, B., Herrmann, W. A., Eds.; Wiley-VCH: Weinheim, 2002. (c) *Asymmetric Catalysis on Industrial Scale: Challenges, Approaches and Solutions*, Blaser, H. U., Schmidt, E., Eds.; Wiley-VCH: Weinheim, 2004.
(2) Cui, X.; Burgess, K. *Chem. Rev.* **2005**, *105*, 3272.
(3) (a) Conticello, V. P.; Brard, L.; Giardello, M. A.; Tsuji, Y.; Sabat, M.; Stern, C. L.; Marks, T. J. *J. Am. Chem. Soc.* **1992**, *114*, 2761. (b) Giardello, M. A.; Conticello, V. P.; Brard, L.; Gagne, M. R.; Marks, T. J. *J. Am. Chem. Soc.* **1994**, *116*, 10241.
(4) Forman, G. S.; Ohkuma, T.; Hems, W. P.; Noyori, R. *Tetrahedron Lett.* **2000**, *41*, 9471.
(5) Co, T. T.; Kim, T. J. *Chem. Commun.* **2006**, 3537.
(6) For recent reviews, see also: (a) Källström, K.; Munslow, I.; Andersson, P. G. *Chem.—Eur. J.* **2006**, *12*, 3194. (b) Roseblade, S. J.; Pfaltz, A. *Acc. Chem. Res.* **2007**, *40*, 1402. (c) Church, T. L.; Andersson, P. G. *Coord. Chem. Rev.* **2008**, *252*, 513.
(7) (a) Blankenstein, J.; Pfaltz, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4445. (b) McIntyre, S.; Hörmann, E.; Menges, F.; Smidt, S. P.; Pfaltz, A. *Adv. Synth. Catal.* **2005**, *347*, 282.
(8) Källström, K.; Hedberg, C.; Brandt, P.; Bayer, P.; Andersson, P. G. *J. Am. Chem. Soc.* **2004**, *126*, 14308.

10.1021/ja904152r CCC: $40.75

Scheme 1. Asymmetric Hydrogenation of Largely Unfunctionalized 1,1-Disubstituted Terminal Alkenes



application of a new type of ligand for the Ir-catalyzed asymmetric hydrogenation of unfunctionalized alkenes: phosphite−oxazoline.[9] We also found that the introduction of a biaryl phosphite moiety into the ligand design is highly adventitious in terms of catalytic activity and substrate versatility.[10] These Ir/phosphite−oxazoline catalytic systems, then, were able to hydrogenate 2-phenylbut-1-enes with higher enantioselectivities (ee's up to 99%) than previous Ir/phosphinite−oxazoline systems. Despite these successes, Ir-catalyzed hydrogenation has not been extended to other 1,1-disubstituted terminal alkenes and the potential of Ir/P,N catalytic systems in this process still needs to be systematically studied. To fully investigate this potential, in this contribution we extend our previous study of 2008 to other amino alcohol-based phosphite−oxazoline ligands (Figure 1) and to other types of 1,1-disubsituted terminal alkenes.

We synthesized and screened a library of 96 potential phosphite−oxazoline ligands (Figure 1),[11] which have the advantages of phosphite ligands: they are obtainable from readily available alcohols and are highly resistant to oxidation.[12] 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 (Figure 1), we investigated the effect of systematically varying the substituents in the oxazoline (R) moiety and in the alkyl backbone chain (H, **L1**−**L4**; Me, **L5**−**L11** and Ph, **L15**−**L16**). We also studied the configuration of the alkyl backbone chain (ligands **L5** and **L12**), the presence of a second stereogenic center in the heterocycle ring and its configuration (ligands **L13** and **L14**) and the substituents and configurations in the biaryl phosphite moiety (**a**−**f**). By carefully selecting these elements, we achieved high enantioselectivities and activities in a wide range of 1,1-disubstituted terminal alkenes.

2. Results and Discussions

2.1. Synthesis of the Ir Catalyst Precursors. The catalyst precursors were made by refluxing a dichloromethane solution of the appropriate ligand (**L1**−**L16a**−**f**) in the presence of 0.5 equiv of $[Ir(cod)Cl]_2$ for 2 h followed by counterion exchange with sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (NaBArF) (1 equiv), in the presence of water (Scheme 3). All complexes were isolated as air-stable orange solids and were used without further purification.

The complexes were characterized by elemental analysis and ^{1}H, ^{13}C, and ^{31}P NMR spectroscopy. The spectral assignments (see Experimental Section) were based on information from ^{1}H−^{1}H and ^{13}C−^{1}H correlation measurements and were as expected for these C_1 iridium complexes. The VT-NMR spectra indicate that only one isomer is present in solution. One singlet in the ^{31}P−{^{1}H} NMR spectra was obtained in all cases. We were able to obtain [Ir(cod)(**L6a**)]BArF crystals that were suitable for X-ray analysis (Figure 2).[13] The crystal structure confirmed the expected boat conformation of the chelate ring. It also showed that the biphenyl phosphite moiety adopts an R-configuration when coordinated to the iridium center.[14]

2.2. Asymmetric Hydrogenation of 1,1-Aryl-Alkyl Terminal Olefins. 2.2.1. Asymmetric Hydrogenation of 1,1-Phenyl-Alkyl Terminal Olefins. In the first set of experiments, we used the Ir-catalyzed hydrogenation of 2-phenylbut-1-ene **S1** to scope the potential of ligands **L1**−**L16a**−**f**. The results are summarized in Table 1. The reaction proceeded smoothly at room temperature under 1 bar of H_2 at low catalyst loading (0.2 mol %). The results indicate that enantioselectivity is affected by the substituents at the oxazoline and in the alkyl backbone chain, the presence of a second sterogenic center in the oxazoline ring and the substituents/configuration in the biaryl phosphite moiety.

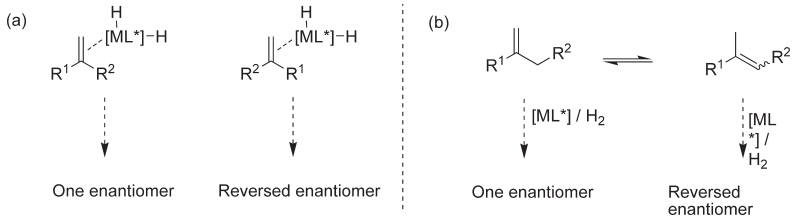
The effect of the substituents and the configuration at the alkyl backbone chain was studied with ligands **L1a**, **L5a**, **L12a**, and **L15a** (Table 1, entries 1, 5, 17 and 20). Our results showed that introducing bulky substituents into the alkyl backbone chain has a positive effect on enantioselectivity (i.e., Ph > Me > H) and that the sense of enantioselectivity is governed by the absolute configuration of the alkyl backbone chain (Table 1, entry 5 vs 17). Both enantiomers of the hydrogenation product can therefore be accessed with high enantioselectivity by changing the absolute configuration of the alkyl backbone chain.

We studied the effect of the oxazoline substituent using ligands **L5**−**L11a** (Table 1, entries 5, 11−16). Our results showed that enantioselectivity is dependent on both the electronic and steric properties of the substituents in the oxazoline moiety. Therefore, either bulky or electron-withdrawing substituents in this position decreased enantioselectivities. Enantioselectivities were best with ligand **L5a**, which contains a phenyl-oxazoline group (Table 1, entry 5).

To study how a second stereogenic center in the oxazoline and its configuration affect the catalytic performance, we also tested ligands **L13a** and **L14a** (Table 1, entries 18 and 19). The results show a cooperative effect between the configuration of this second stereocenter and the configuration of the alkyl backbone chain on enantioselectivity that results in a matched combination for ligand **L13a**, which contains an *R*-configuration at the second stereocenter and an *S*-configuration at the alkyl backbone chain (Table 1, entry 18 vs 19).

Finally, the effects of the biaryl phosphite moiety were studied using ligands **L5a-f** (Table 1, entries 5−10). The results indicated that enantioselectivity is mainly affected by the configuration of the biaryl phosphite moiety (Table 1, entries 9 and 10), while the substituents at both ortho and para positions of

Scheme 2



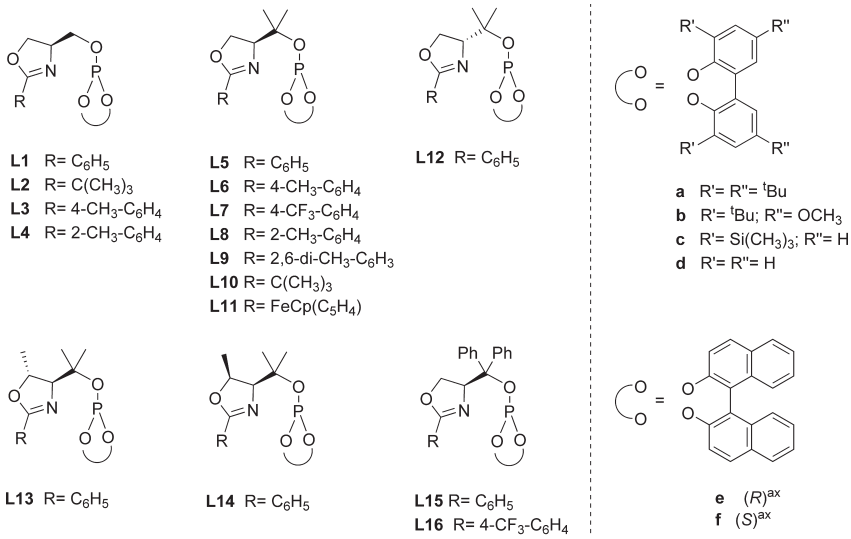
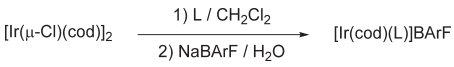


Figure 1. Phosphite−oxazoline ligand library **L1**−**L16a**−**f**.

Scheme 3. Synthesis of Iridium Catalyst Precursors [Ir(cod)(L)]BArF (L = **L1**−**L16a**−**f**)



the biphenyl phosphite moiety has little effect on enantioselectivity (Table 1, entries 5−8). The best enantioselectivities were therefore obtained when an enantiopure *S*-binaphthyl phosphite moiety was present in the ligand (Table 1, entry 10). Moreover, comparing the results of using atropoisomerically flexible biphenyl phosphite based ligands (**a**−**d**) with enantiopure binaphthyl phosphite ligands (**e** and **f**), we can conclude that the biphenyl phosphite moiety in ligands **L5a**−**d** and **L6a** adopts an *R*-configuration upon complexation to the iridium.[14] This is in agreement with the configuration of the biphenyl phosphite moiety observed in the X-ray structure of the [Ir(cod)(**L6a**)]-BArF (vide supra).

In summary, phenyl substituents need to be present in the oxazoline and in the alkyl backbone chain, and there must also be an enantiopure (*S*)-binaphthyl phosphite moiety if enantioselectivities are to be excellent. The best result (100% conversion; 99% ee) was therefore obtained with ligand **L15f** (Table 1, entry 22), which contains the optimal combination of the ligand parameters. Using ligand **L15f**, then, we were able to obtain the highest level of enantioselectivity (99% ee; Table 1, entry 22), which was an improvement on the enantioselectivity previously communicated using ligand **L5f**.[10] Moreover, both enantiomers of the hydrogenation product can be accessed in high enantioselectivity simply by changing the absolute configuration of the alkyl backbone chain. These results clearly show the efficiency of using highly modular scaffolds in the ligand design.

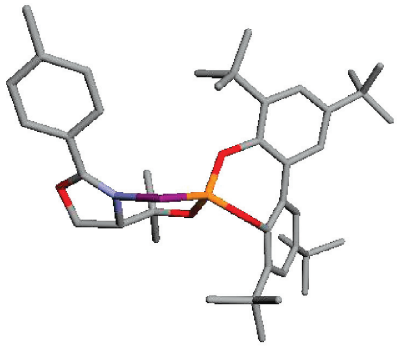
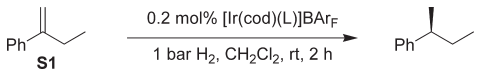


Figure 2. Structure of the [Ir(cod)(**L6a**)]BArF in the crystal (H atoms, BArF ion and cod ligand have been omitted for clarity).

Table 1. Selected Results for the Ir-Catalyzed Hydrogenation of **S1** Using the Ligand Library **L1**−**L16a**−**f**[a]

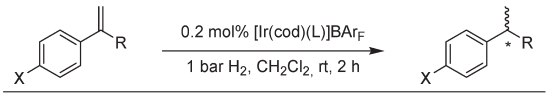


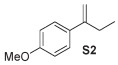
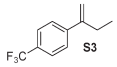
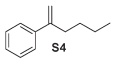
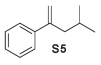
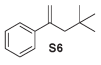
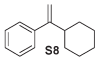
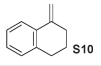
entry	ligand	% conv[b]	% ee[c]	entry	ligand	% conv[b]	% ee[c]
1	**L1a**	100	67 (*S*)	13	**L8a**	100	53 (*S*)
2	**L2a**	100	14 (*S*)	14	**L9a**	100	35 (*S*)
3	**L3a**	100	65 (*S*)	15	**L10a**	100	46 (*S*)
4	**L4a**	100	24 (*S*)	16	**L11a**	100	50 (*S*)
5	**L5a**	100	88 (*S*)	17	**L12a**	100	87 (*R*)
6	**L5b**	100	85 (*S*)	18	**L13a**	100	85 (*S*)
7	**L5c**	100	87 (*S*)	19	**L14a**	100	62 (*S*)
8	**L5d**	100	89 (*S*)	20	**L15a**	100	92 (*S*)
9	**L5e**	100	88 (*S*)	21	**L15c**	100	91 (*S*)
10	**L5f**	100	95 (*S*)	22	**L15f**	100	99 (*S*)
11	**L6a**	100	85 (*S*)	23	**L16a**	100	78 (*S*)
12	**L7a**	100	60 (*S*)				

[a] Reactions carried out using 1 mmol of **S1** and 0.2 mol % of Ir catalyst precursor at 1 bar of H_2. [b] Conversion measured by ^1H NMR after 2 h. [c] Enantiomeric excesses determined by chiral GC.

We then studied the asymmetric hydrogenation of other 1,1-disubstituted aryl-alkyl substrates (**S2**-**S10**) using the phosphite−oxazoline ligand library **L1**−**L16a**-**f**. The most noteworthy results are shown in Table 2. In general, they follow the same trends as for the hydrogenation of **S1**. Again, the catalyst precursor containing the phosphite−oxazoline ligand **L15f** provided the best enantioselectivities (ee's up to >99%).

Table 2. Selected Results for the Ir-Catalyzed Hydrogenation of Aryl-Alkyl Terminal Olefins Using the Ligand Library **L1**−**L16a**−**f**[a]



Entry	Substrate	Ligand	% Conv[b]	% ee[c]
1		**L15f**	100	99 (*S*)
2		**L5f**	100	97 (*S*)
3		**L15f**	100	>99 (*S*)
4		**L15f**	100	96 (*S*)
5		**L15f**	100	94 (*S*)
6		**L5f**	100	93 (*S*)
7		**L15f**	100	93 (*S*)
8		**L15f**	100	90 (*S*)
9		**L5f**	100	88 (*S*)
10		**L15f**	100	97 (*S*)
11		**L15f**	100	97 (*S*)
12		**L15f**	100	>99 (*S*)
13		**L15f**	100	25 (*R*)
14[d]		**L15f**	99[e]	87 (*R*)

[a] Reactions carried out using 1 mmol of substrate and 0.2 mol % of Ir catalyst precursor at 1 bar of H_2. [b] Conversion measured by ^{1}H NMR or GC. [c] Enantiomeric excesses determined by chiral GC. [d] Reaction carried out at 100 bar of H_2 and 1 mol % of catalyst precursor using PC as solvent at 40 °C for 10 h. [e] 8% of non-hydrogenated isomerized trisubstituted olefin observed by ^{1}HNMR.

Our results using several para-substituted 2-phenylbut-2-enes (**S1**−**S3**) indicated that enantioselectivity is relatively insensitive to the electronic effects in the aryl ring (Table 2, entries 1−4). However, the enantioselectivity (up to >99%) was highest with electron-rich alkene **S2** (Table 2, entry 3), and lowest (up to 96%) with the electron-deficient alkene **S3** (Table 2, entry 4). A similar trend was obtained using the previously published Ir/phosphinite−oxazoline (ee's up to 94% for **S2**)[7] and Ru/Me-Duphos (ee's up to 86% for **S1**)[4] catalysts.

Several α-alkylstyrenes bearing increasingly sterically demanding alkyl substituents (**S4**−**S9**) were equally reactive and were hydrogenated with similar results using the Ir−**L15f** catalytic system (full conversion, 90−99% ee; Table 2, entries 5−12). This represents the first catalysts able to hydrogenate **S4**−**S9** with high enantioselectivities.

Under standard conditions, our catalyst systems were unable to hydrogenate 1-methylene-1,2,3,4-tetrahydronaphthalene **S10** with high enantioselectivities (Table 2, entry 13). This has been attributed to the fact that this olefin easily isomerizes to the trisubstituted internal olefin under reaction conditions. The hydrogenation of the trisubstituted olefin produces the opposite configuration of the hydrogenated product than when **S10** is hydrogenated, which results in low enantioselectivities.[15] Recently, Börner and co-workers discovered that the use of propylene carbonate (PC) as solvent reduces the isomerization considerably so **S10** can be hydrogenated in high enantioselectivities (up to 85% ee).[15] Using this strategy we also managed to hydrogenate **S10** in high enantioselectivities (ee's up to 87%, Table 2, entry 14).

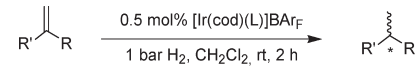
In conclusion, our Ir/phosphite−oxazoline catalytic system is highly tolerant to the steric and electronic properties of the α-alkylstyrene derivatives so enantioselectivities can be high in the asymmetric hydrogenation of this type of aryl-alkyl 1,1-disubsituted alkenes.

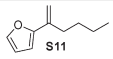
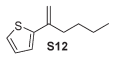
2.2.2. Asymmetric Hydrogenation of 1,1-Heteroaromatic-Alkyl Terminal Olefins. We then applied this ligand library in the asymmetric hydrogenation of 1,1-heteroaromatic alkenes. This is interesting because heterocycles are used in industry and because the heterocyclic part can be modified posthydrogenation. Despite this, no previous studied have been made. The results are summarized in Table 3. Again enantioselectivities were excellent under mild reaction conditions (ee's up to >99%). Even though it has been reported that the catalytic activity using Ir complexes with P,N ligands can be diminished in the presence of coordinating groups (or solvents),[2,16] the heteroaromatic alkenes **S11**-**S14** were hydrogenated in 100% conversion using 1 bar of H_2. Hydrogenation of alkenes with thiophene **S12** and pyridyl **S13**-**S14** substituents followed the same trends as those observed for the previous substrates **S1**-**S9**. Therefore, enantioselectivities were best when ligand **L15f** was used (Table 3, entries 2−4). However, for furan-substituted substrate **S11** the enantioselectivity was best with ligand **L5a** (Table 3, entry 1). Once again, these results clearly show the efficiency of using highly modular scaffolds in the ligand design.

2.3. Asymmetric Hydrogenation of 1,1-Diaryl Terminal Olefins. To further study the potential of this ligand library, we also screened **L1**−**L16a**−**f** in the Ir-catalyzed hydrogenation of 1,1-diaryl terminal olefins (**S15**−**S17**). Enantiopure diaryla-

(9) Diéguez, M.; Mazuela, J.; Pàmies, O.; Verendel, J. J.; Andersson, P. G. *J. Am. Chem. Soc.* **2008**, *130*, 7208.
(10) Diéguez, M.; Mazuela, J.; Pàmies, O.; Verendel, J. J.; Andersson, P. G. *Chem. Commun.* **2008**, 3888.
(11) Part of this ligand library has also been successfully applied in the Pd-catalyzed allylic substitution reaction. See: Diéguez, M.; Pàmies, O. *Chem.*−*Eur. J.* **2008**, *14*, 3653.
(12) (a) Diéguez, M., Pàmies, O.; Ruiz, A.; Claver, C. In *Methodologies in Asymmetric Catalysis*; Malhotra, S. V., Ed.; American Chemical Society: Washington, DC, 2004. (b) Diéguez, M. ; Pàmies, O.; Claver, C. In *Trivalent Phosphorus Compounds in Asymmetric Catalysis, Synthesis and Applications*; Börner, A. Ed.; Wiley: Weinheim, 2008; p 506.
(13) Crystals of [Ir(cod)(**L6a**)]BArF could be obtained by slow evaporation of a solution of the compound in ethanol.
(14) The rapid ring inversions (atropoisomerization) in the biaryl phosphite moiety is usually stopped upon coordination to the metal center. See for example: (a) Buisman, G. J. H.; van der Veen, L. A.; Klootwijk, A.; de Lange, W. G. J.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Vogt, D. *Organometallics* **1997**, *16*, 2929. (b) Diéguez, M.; Pàmies, O.; Ruiz, A.; Claver, C.; Castillón, S. *Chem.*−*Eur. J.* **2001**, *7*, 3086. (c) Pàmies, O.; Diéguez, M.; Net, G.; Ruiz, A.; Claver, C. *J. Org. Chem.* **2001**, *66*, 8364. (d) Diéguez, M.; Pàmies, O.; Ruiz, A.; Claver, C. *New J. Chem.* **2002**, *26*, 827. (e) Pàmies, O.; Diéguez, M. *Chem.*−*Eur. J.* **2008**, *14*, 944.
(15) Similar behavior has been observed using related Ir-phosphinite−oxazoline ligands. See: Bayardon, J.; Holz, J.; Schäffner, B.; Andrushko, V.; Verevkin, S.; Preetz, A.; Börner, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 5971.
(16) Pfaltz and coworkers have successfully hydrogenated trisubstituted aryl alkenes with one aromatic heterocyclic substituent. See: Pfaltz, A.; Blankenstein, J.; Hilgraf, R.; Hormann, E.; McIntyre, S.; Menges, F.; Schonleber, M.; Smidt, S. P.; Wustenberg, B.; Zimmermann, N. *Adv. Synth. Catal.* **2003**, *345*, 33.

Table 3. Selected Results for the Ir-Catalyzed Hydrogenation of Heteroaryl-Alkyl Terminal Olefins Using the Ligand Library **L1**−**L16a**−**f**[a]



Entry	Substrate	Ligand	% Conv[b]	% ee[c]
1	 S11	**L5a**	100	99 (-)
2	 S12	**L15f**	100	96 (-)
3	 S13	**L15f**	100	99 (+)
4	 S14	**L15f**	100	>99 (+)

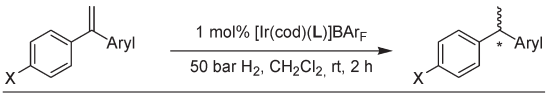
[a] Reactions carried out using 1 mmol of substrate and 0.5 mol % of Ir catalyst precursor at 1 bar of H_2. [b] Conversion measured by ^{1}H NMR. [c] Enantiomeric excesses determined by chiral HPLC.

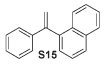
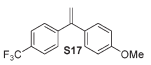
lkanes are important intermediates for the preparation of drugs and research materials.[17] To date optically active diarylalkanes can be prepared through some rather laborious approaches.[17,18] The asymmetric hydrogenation can provide a more efficient approach to prepare these compound. However, to our knowledge there is no enantioselective hydrogenation of this kind of substrates.

In a first set of experiments we examined the Ir-catalyzed asymmetric hydrogenation of diaryl alkenes **S15** and **S16**. In contrast to the previous aryl-alkyl substrates **S1**−**S14**, enantioselectivities are slightly better at higher pressures (i.e., using Ir/**L5a**; 26% ee at 1 bar and 30% ee at 50 bar). The enantioselectivity is also mainly affected by the substituents at the oxazoline and at the biaryl phosphite moieties, while the substituents in the alkyl backbone chain have little effect. Although high enantioselectivities (ee's up to 90%) can be obtained by replacing the bulky tetra *tert*-butyl substituted biphenyl phosphite moieties by less sterically demanding *S*-binaphthyl phosphite moieties (Table 4, entries 2, 4, 5, and 8 vs 3, 7, and 9), the enantiocontrol is highest (>99% ee) with bulky substituents on the oxazoline ring (ligand **L9a**, Table 4, entries 6 and 10).

We also tested the Ir/phosphite−oxazoline catalytic systems in the asymmetric hydrogenation of **S17**. We anticipated that for this substrate enantiodiscrimination would be more difficult to control because it would be mainly due to the electronic differentiation of both phenyl substituents.[19] While the effect of the pressure dependence on enantioselectivity is similar to that observed for **S15** and **S16**, the effect of the ligand parameters on enantioselectivity is different. Therefore, the presence of bulky oxazoline substituents and/or the replacement

Table 4. Selected Results for the Ir-Catalyzed Hydrogenation of 1,1-Diaryl Terminal Alkenes **S15**−**S17** Using the Ligand Library **L1**−**L16a**−**f**[a]



Entry	Substrate	Ligand	% Conv[b]	% ee[c]
1	 S15	**L1a**	100	26 (+)
2		**L5a**	100	30 (+)
3		**L5f**	100	90 (+)
4		**L6a**	100	31 (+)
5		**L7a**	100	30 (+)
6		**L9a**	100	>99 (+)
7		**L15f**	100	90 (+)
8	 S16	**L5a**	100	23 (+)
9		**L5f**	100	64 (+)
10		**L9a**	99	99 (+)
11	 S17	**L1a**	100	43 (+)
12		**L5a**	100	61 (+)
13		**L5f**	100	38 (+)
14		**L6a**	100	60 (+)
15		**L7a**	100	65 (+)
16		**L9a**	100	39 (+)
17		**L15a**	100	63 (+)

[a] Reactions carried out using 1 mmol of substrate and 1 mol % of Ir catalyst precursor at 50 bar of H_2. [b] Conversion measured by ^{1}H NMR. [c] Enantiomeric excesses determined by chiral HPLC.

of a bulky tetra *tert*-butyl-phenyl phosphite moiety by an *S*-binaphthyl moiety has a negative effect on enantioselectivity (Table 4, entry 11 vs entries 13 and 16). Enantioselectivity is highest (ee's up to 65%) using ligand **L7a** (Table 4, entry 15).

2.4. Asymmetric Hydrogenation of 1,1-Disubstituted Terminal Olefins Containing a Neighboring Polar Group. Encouraged by the excellent results obtained up to this point, we examined the asymmetric hydrogenation of 1,1-disubstituted terminal olefins containing a polar neighboring group (**S18**−**S21**). The results are summarized in Table 5.

We initially tested the ligand library in the hydrogenation of the allylic alcohol **S18**. Derivatives of the hydrogenation product 2-phenylpropanol are frequently used as components of fragrance mixtures (i.e., commercial odorants, Muguesia and Pamplefleur) and also as intermediates for the synthesis of natural products and drugs (i.e., modulators of dopamine D3 receptors).[20] Complex Ir−**L15f** proved to be the most selective

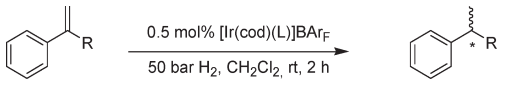
(17) (a) Fessard, T. C.; Andrews, S. P.; Motoyohsi, H.; Carreira, E. *Angew. Chem., Int. Ed.* **2007**, *46*, 9331. (b) Prat, L.; Dupas, G.; Duflos, J.; Quéguiner, G.; Bourguignon, J.; Levacher, V. *Tetrahedron Lett.* **2001**, *42*, 4515. (c) Wilkinson, J. A.; Rossington, S. B.; Ducki, S.; Leonard, J.; Hussain, N. *Tetrahedron* **2006**, *62*, 1833.

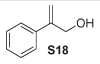
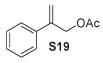
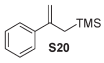
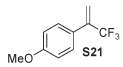
(18) (a) Okamoto, K.; Nishibayashi, Y.; Uemura, S.; Toshimitsu, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 3588. (b) Hatanaka, Y.; Hiyama, T. *J. Am. Chem. Soc.* **1990**, *112*, 7793.

(19) In this context, Noyori and coworkers have found moderate enantioselectivities in the Ru-catalyzed asymmetric transfer hydrogenation of differently para-substituted benzophenone derivatives. See: Fujii, A.; Hashiguchi, S.; Uematsu, N.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 2521.

(20) See for instance: (a) Abate, A.; Brenna, E.; Fuganti, C.; Gatti, G. G.; Givenzana, T.; Malpezzi, L.; Serra, S. *J. Org. Chem.* **2005**, *70*, 1281. (b) Drescher, K.; Haupt, A.; Unger, L.; Rutner, S. C.; Braje, W.; Grandel, R.; Henry, C.; Backfisch, G.; Beyerbach, A.; Bisch, W. WO Patent 2006/040182 A1, 2006.

Table 5. Selected Results for the Ir-Catalyzed Hydrogenation of 1,1-Disubstituted Terminal Olefins Containing a Neighboring Polar Group Using the Ligand Library **L1**−**L16a**−**f**[a]



Entry	Substrate	Ligand	% Conv[b]	% ee[c]
1	 **S18**	**L15f**	100	95 (*R*)
2	 **S19**	**L15f**	100	91 (*R*)
3	 **S20**	**L15f**	100	96 (*S*)
4	 **S21**	**L15f**	100	75 (-)

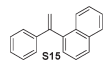
[a] Reactions carried out using 1 mmol of substrate and 0.5 mol % of Ir catalyst precursor at 50 bar of H_2. [b] Conversion measured by ^{1}H NMR. [c] Enantiomeric excesses determined by chiral GC.

catalyst, giving 95% ee at room temperature (Table 5, entry 1). This result competes favorably with the results obtained using related phosphinite−oxazoline ligands.[7b] In addition, the enantioselectivities and activities obtained are higher than those reported in the asymmetric Zr-catalyzed methylalumination of α-olefins[21] and the lipase-mediated kinetic resolution of racemic 2-phenyl propanol.[20a] Similarly, the hydrogenation of the allylic acetate **S19** also proceeds with high activity and enantioselectivity with the catalyst system Ir−**L15f** (Table 5, entry 2).

We next screened ligands **L1**−**L16a**−**f** in the asymmetric hydrogenation of the allylic silane **S20** and the trifluoromethyl olefin **S21**. The hydrogenation of these compounds gave rise to important organic intermediates and a number of innovative new organosilicon[22] and organofluorine[23] drugs are being developed. The enantioselectivities (96% ee for **S20** and 75% ee for **S21**) were best with ligand **L15f** (Table 5, entries 3 and 4). To the best of our knowledge this is the first successful asymmetric hydrogenation of allylic silanes and terminal trifluoromethyl olefins.

2.5. Recycling Experiments. Encouraged by the excellent results obtained, we decided to go one step further and to 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. Recently, propylene carbonate (PC) has emerged as an environmentally friendly alternative to standard organic solvents that allow catalyst to be repeatedly recycled by a simple two-phase extraction with an apolar solvent.[15] For this purpose, substrates **S9**, **S14**, and **S15** were hydrogenated in PC with the catalyst precursor [Ir(cod)(**L15f**)]BArF (substrates **S9** and **S14**) and [Ir(cod)(**L9a**)]BArF (substrate **S15**), and the products were removed by extraction with hexane (Table 6). Catalysts can be used up to five 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[15] and/or the formation of inactive triiridium hydride clusters.[24]

Table 6. Recycling Experiments with the Catalyst [Ir(cod)(**L**)]BArF and **S9**, **S14**, and **S15** as Substrates in PC[a]

Cycle	Substrate	Ligand	% Conv (h)[b]	% ee[c]
1	 **S9**	**L15f**	98 (4)	99 (S)
2			98 (4)	99 (S)
3			94 (6)	98 (S)
4			95 (10)	97 (S)
5			82 (12)	97 (S)
1[d]	 **S14**	**L15f**	98 (12)	99 (+)
2[d]			94 (12)	99 (+)
3[d]			84 (18)	97 (+)
1[d]	 **S15**	**L9a**	100 (12)	99 (+)
2[d]			95 (15)	99 (+)
3[d]			93 (24)	99 (+)

[a] Reactions carried out using 1 mmol of substrate and 1 mol % of Ir catalyst precursor at 50 bar of H_2. [b] Conversion measured by ^{1}H NMR. [c] Enantiomeric excesses determined by chiral GC. [d] Reaction carried out at 100 bar and 40 °C.

3. Conclusions

A library of readily available phosphite−oxazoline ligands (**L1**−**L16a**−**f**) has been applied in the Ir-catalyzed asymmetric hydrogenation of several 1,1,-disubstituted terminal largely unfunctionalized alkenes. We found that their effectiveness at transferring the chiral information in the product can be tuned by correctly choosing the ligand components. Enantioselectivities were therefore excellent (ee's up to >99%) in a wide range of 1,1-disubstituted terminal alkenes. These Ir/phosphite−oxazoline catalytic systems, then, compete favorably in terms of enantioselectivity and, more important, in terms of substrate versatility with a few other ligand series that also have provided high ee's for a limited range of 1,1-aryl-alkyl disubstituted alkenes. Of particular note are the unprecedented excellent enantioselectivities (ee's up to >99%) obtained with 1,1-heteroaryl-alkyl and 1,1-diaryl substrates, for which no asymmetric hydrogenation was reported. It should be noted that these catalytic systems also have high tolerance to the presence of a neighboring polar group and therefore 1,1-disubstituted allylic alcohols, acetates, and silanes can be hydrogenated in high enantioselectivities (ee's up to 96%). The asymmetric hydrogenations were also performed using propylene carbonate as solvent, which allowed the Ir catalyst to be reused and maintained the excellent enantioselectivities. These results open up a new class of Ir catalysts for the highly enantioselective

(21) Wipf, P.; Ribe, S. *Org. Lett.* **2000**, *2*, 1713.
(22) See for instance: (a) Fleming, I.; Barbero, A.; Walter, D. *Chem. Rev* **1997**, *97*, 2063. (b) Jones, G. R.; Landais, Y. *Tetrahedron* **1996**, *52*, 7599. (c) Bains, W.; Tacke, R. *Curr. Opin. Drug Discovery Dev.* **2003**, *6*, 526.
(23) See for instance: Schlosser, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 1496. (b) Smart, B. E. *J. Fluorine Chem.* **2001**, *109*, 3. (c) *Asymmetric Fluoroorganic Chemistry: Synthesis, Application and Future Directions*; Ramachandran, P. V., Ed.; American Chemical Society: Washington, DC, 2000. (d) A special issue has been devoted to "Fluorine in the Life Sciences", *ChemBioChem* **2004**, *5*, 559.
(24) (a) Crabtree, R. H. *Acc. Chem. Res.* **1979**, *12*, 331. (b) Smidt, S. P.; Pfaltz, A.; Martinez-Viviente, E.; Pregosin, P. S.; Albinati, A. *Organometallics* **2003**, *22*, 1000.

Ir-catalyzed hydrogenation of largely unfunctionalized 1,1-disubstituted terminal alkenes, which is of great practical interest.

4. Experimental Section

4.1. General Considerations. All reactions were carried out using standard Schlenk techniques under an atmosphere of argon. Solvents were purified and dried by standard procedures. Phosphite−oxazoline ligands **L1**−**L7a**−**f** and **L11**−**L16a** were prepared as previously described.[11] [Ir(cod)(L)]BArF (L= **L3a**, **L5a**−**c**, **L5e**−**f**, **L6a**, **L7a**, **L13a**, and **L16a**) were prepared previously.[10] Substrates **S1**,[25] **S2**−**S3**,[7b] **S4**,[26] **S5**,[27] **S6**,[28] **S7**,[29] **S8**,[30] **S9**,[29] **S10**,[31] **S15**,[32] **S16**,[33] **S17**,[34] **S18**,[35] and **S20**[36] were prepared as previously described. ^{1}H, ^{13}C−{^{1}H}, and ^{31}P−{^{1}H} NMR spectra were recorded using a 400 MHz spectrometer. Chemical shifts are relative to that of $SiMe_4$ (^{1}H and ^{13}C) as internal standard or H_3PO_4 (^{31}P) as external standard. ^{1}H and ^{13}C assignments were made on the basis of ^{1}H−^{1}H gCOSY and ^{1}H−^{13}C gHSQC experiments.

4.2. General Procedure for the Preparation of the Phosphite−Oxazoline Ligands. The corresponding phosphorochloridite (3.0 mmol) produced *in situ* was dissolved in toluene (12.5 mL), and pyridine (1.14 mL, 14 mmol) was added. The corresponding hydroxyl-oxazoline compound (2.8 mmol) was azeotropically dried with toluene (3 × 2 mL) and then dissolved in toluene (12.5 mL) to which pyridine (1.14 mL, 14 mmol) was added. The oxazoline solution was transferred slowly at 0 °C to the solution of phosphorochloridite. The reaction mixture was stirred overnight at 80 °C, and the pyridine salts were removed by filtration. Evaporation of the solvent gave a white foam, which was purified by flash chromatography in alumina to produce the corresponding ligand as a white solid.

L8a. Yield: 1.4 g (76%). ^{31}P NMR ($CDCl_3$) δ = 148.4 (s). ^{1}H NMR ($CDCl_3$) δ = 1.26 (s, 9H, CH_3, *t*Bu), 1.28 (s, 9H, CH_3, *t*Bu), 1.35 (s, 3H, CH_3), 1.58 (s, 9H, CH_3, *t*Bu), 1.59 (s, 9H, CH_3, *t*Bu), 1.85 (s, 3H, CH_3), 2.65 (s, 3H, CH_3−Ph), 3.87 (m, 1H, CH_2), 4.22 (m, 1H, CH_2), 4.50 (m, 1H, CH), 7.1−8.0 (m, 8H, CH═). ^{13}C NMR ($CDCl_3$) δ = 22.9 (CH_3−Ph), 23.8 (d, CH_3, J_{C-P} = 6.8 Hz), 28.7 (d, CH_3, J_{C-P} = 11 Hz), 31.8 (CH_3, *t*Bu), 31.9 (CH_3, *t*Bu), 34.9 (C, *t*Bu), 35.9 (C, *t*Bu), 68.3 (CH_2), 76.9 (CH), 82.3 (d, CMe_2, J_{C-P} = 4.5 Hz), 124.5 (CH═), 126.0 (CH═), 127.5 (CH═), 127.7 (C), 128.9 (CH═), 129.6 (CH═), 130.8 (CH═), 131.1 (CH═), 131.9 (CH═), 134.3 (C), 138.2 (C), 140.0 (C), 140.9 (C), 146.8 (C), 165.6 (C═N). Anal. Calcd (%) for $C_{41}H_{56}NO_4P$: C 74.85, H 8.58, N 2.13; found: C 74.99, H 8.67, N 2.22.

L9a. Yield: 1.3 g (69%). ^{31}P NMR ($CDCl_3$) δ = 148.9 (s). ^{1}H NMR ($CDCl_3$) δ = 1.23 (s, 9H, CH_3, *t*Bu), 1.24 (s, 9H, CH_3, *t*Bu), 1.46 (s, 3H, CH_3), 1.55 (s, 9H, CH_3, *t*Bu), 1.56 (s, 9H, CH_3, *t*Bu), 1.83 (s, 3H, CH_3), 2.22 (s, 6H, CH_3−Ph), 3.97 (m, 1H, CH_2), 4.19 (m, 1H, CH_2), 4.53 (m, 1H, CH), 6.8−7.5 (m, 7H, CH═). ^{13}C NMR ($CDCl_3$) δ = 20.6 (CH_3−Ph), 24.7 (d, CH_3, J_{C-P} = 6.2 Hz), 28.7 (d, CH_3, J_{C-P} = 12.4 Hz), 31.7 (CH_3, *t*Bu), 31.8 (CH_3, *t*Bu), 31.9 (CH_3, *t*Bu), 35.5 (C, *t*Bu), 35.9 (C, *t*Bu), 36.0 (C, *t*Bu), 68.8 (CH_2), 77.0 (CH), 82.2 (d, CMe_2, J_{C-P} = 4.6 Hz), 124.5 (CH═), 124.6 (CH═), 127.5 (CH═), 127.6 (CH═), 128.0 (C), 129.8 (CH═), 130.3 (CH═), 134.3 (b, CH═), 140.9 (C), 141.0 (C), 146.9 (C), 165.7 (C═N). Anal. Calcd (%) for $C_{42}H_{58}NO_4P$: C 75.08, H 8.70, N 2.08; found: C 75.13, H 8.73, N 2.13.

L10a. Yield: 1.3 g (74%). ^{31}P NMR ($CDCl_3$) δ = 148.9 (s). ^{1}H NMR ($CDCl_3$) δ = 1.14 (s, 9H, CH_3, *t*Bu), 1.22 (s, 9H, CH_3, *t*Bu), 1.23 (s, 9H, CH_3, *t*Bu), 1.30 (s, 3H, CH_3), 1.53 (s, 9H, CH_3, *t*Bu), 1.56 (s, 9H, CH_3, *t*Bu), 1.76 (s, 3H, CH_3), 3.78 (m, 1H, CH_2), 4.12 (m, 1H, CH_2), 4.26 (m, 1H, CH), 7.3−7.6 (m, 4H, CH═). ^{13}C NMR ($CDCl_3$) δ = 23.7 (d, CH_3, J_{C-P} = 6.0 Hz), 28.3 (CH_3, *t*Bu), 28.5 (d, CH_3, J_{C-P} = 12.1 Hz), 31.7 (CH_3, *t*Bu), 31.8 (CH_3, *t*Bu), 31.9 (CH_3, *t*Bu), 33.7 (C, *t*Bu), 34.9 (C, *t*Bu), 36.0 (C, *t*Bu), 69.2 (CH_2), 75.7 (CH), 82.3 (d, CMe_2, J_{C-P} = 4.5 Hz), 124.5 (CH═), 124.6 (CH═), 127.5 (CH═), 127.6 (CH═), 128.0 (C), 129.6 (CH═), 134.3 (b, CH═), 140.8 (C), 140.9 (C), 146.9 (C), 147.1 (C), 175.2 (C═N). Anal. Calcd (%) for $C_{38}H_{58}NO_4P$: C 73.16, H 9.37, N 2.25; found: C 73.22, H 9.41, N 2.29.

L15f. Yield: 1.1 g (64%). ^{31}P NMR ($CDCl_3$) δ = 151.8 (s). ^{1}H NMR ($CDCl_3$) δ = 3.91 (m, 1H, CH_2), 4.48 (m, 1H, CH_2), 5.36 (m, 1H, CH), 6.7−8.3 (m, 27H, CH═). ^{13}C NMR ($CDCl_3$) δ = 69.7 (CH_2), 73.6 (CH), 86.4 (d, CPh_2, J_{C-P} = 6.5 Hz), 122−149 (aromatic carbons), 172.9 (C═N). Anal. Calcd (%) for $C_{42}H_{30}NO_4P$: C 78.37, H 4.70, N 2.18; found: C 78.42, H 4.69, N 2.20.

4.3. Typical procedure for the preparation of [Ir(cod)(L)]-BArF. The corresponding ligand (0.074 mmol) was dissolved in CH_2Cl_2 (2 mL) and $[Ir(COD)Cl]_2$ (25 mg, 0.037 mmol) was added. The reaction was refluxed at 50 °C for 1 h. After 5 min at room temperature, NaBArF (77.1 mg, 0.082 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 filtered through a Celite plug, dried with $MgSO_4$ and the solvent was evaporated to give the product as an orange solid.

[Ir(cod)(L1a)]BArF. Yield: 125 mg (95%). ^{31}P NMR ($CDCl_3$) δ = 103.6 (s). ^{1}H NMR ($CDCl_3$) δ = 1.36 (s, 9H, CH_3, *t*Bu), 1.38 (s, 9H, CH_3, *t*Bu), 1.57 (b, 18H, CH_3, *t*Bu), 1.71 (b, 4H, CH_2, cod), 2.33 (m, 3H, CH_2, cod), 2.54 (b, 1H, CH_2, cod), 3.74 (m, 1H, CH═, cod), 4.12 (m, 2H, CH_2−OP), 4.21 (m, 2H, CH_2), 4.24 (b, 1H, CH═, cod), 4.66 (m, 1H, CH), 4.84 (b, 1H, CH═, cod), 5.45 (b, 1H, CH═ cod), 7.1 − 8.5 (m, 21H, aromatics). ^{13}C NMR ($CDCl_3$) δ = 24.8 (b, CH_2 cod), 28.8 (b, CH_2, cod), 31.3 (CH_3, *t*Bu), 31.4 (CH_3, *t*Bu), 31.6 (b, CH_3, *t*Bu), 33.7 (b, CH_2, cod), 34.9 (C, *t*Bu), 35.1 (C, *t*Bu), 35.5 (C, *t*Bu), 36.0 (C, *t*Bu), 37.3 (b, CH_2, cod), 67.1 (CH═, cod), 68.7 (CH), 69.8 (b, CH_2−O and CH_2−OP), 70.2 (CH═, cod), 94.6 (d, CH═, cod, J_{C-P} = 22.2 Hz), 106.1 (d, CH═, cod, J_{C-P} = 12.2 Hz), 117.7 (b, CH═, BAr_F), 119−134 (aromatic carbons), 135.0 (b, CH═, BAr_F), 136−149 (aromatic carbons), 161.9 (q, C−B, BAr_F, $^{1}J_{C-B}$ = 49.6 Hz), 171.5 (C═N). Anal. Calc (%) for $C_{78}H_{74}BF_{24}IrNO_4P$: C 52.65, H 4.19, N 0.79; found: C 52.62, H 4.22, N 0.83.

[Ir(cod)(L2a)]BArF. Yield: 118 mg (91%). ^{31}P NMR ($CDCl_3$) δ = 106.1 (s). ^{1}H NMR ($CDCl_3$) δ = 1.35 (s, 9H, CH_3, *t*Bu), 1.37 (s, 9H, CH_3, *t*Bu), 1.53 (s, 9H, CH_3, *t*Bu), 1.55 (b, 18H, CH_3, *t*Bu), 1.65 (b, 2H, CH_2, cod), 1.76 (b, 2H, CH_2, cod), 2.07 (m, 1H, CH_2, cod), 2.22 (m, 1H, CH_2, cod), 2.38 (m, 1H, CH_2, cod), 2.51 (m, 1H, CH_2, cod), 3.87 (m, 1H, CH═, cod), 4.08 (m, 3H, CH_2−OP and CH_2−O), 4.32 (b, 1H, CH), 4.48 (b, 1H, CH═, cod), 4.73 (b, 2H, CH═, cod and CH_2−O), 5.47 (b, 1H, CH═, cod), 7.1 − 8.5 (m, 16H, aromatics). ^{13}C NMR ($CDCl_3$) δ = 24.4 (b, CH_2 cod), 28.4 (b, CH_2, cod), 29.2 (CH_3, *t*Bu), 31.2 (CH_3, *t*Bu), 31.4 (CH_3, *t*Bu), 31.5 (CH_3, *t*Bu), 31.6 (CH_3, *t*Bu), 34.5 (C, *t*Bu), 34.8 (b, CH_2, cod), 34.9 (C, *t*Bu), 35.0 (C, *t*Bu), 35.4 (C, *t*Bu), 36.0 (C, *t*Bu), 37.4 (b, CH_2, cod), 67.7 (b, CH═, cod), 69.2 (CH), 69.9 (CH_2−O), 70.0 (CH_2−OP), 70.6 (CH═, cod), 90.5 (d, CH═, cod, J_{C-P} = 26.2 Hz), 103.2 (d, CH═, cod, J_{C-P} = 10.5 Hz), 117.7 (b, CH═, BAr_F), 119−134 (aromatic carbons), 135.0 (b, CH═, BAr_F), 136−149 (aromatic carbons), 161.9 (q, C−B, BAr_F, $^{1}J_{C-B}$ = 49.5 Hz), 182.8 (C═N). Anal. Calc (%) for $C_{76}H_{78}BF_{24}IrNO_4P$: C 51.88, H 4.47, N 0.80; found: C 51.93, H 4.52, N 0.77.

(25) Reitz, D. B.; Beak, P.; Farney, R. F.; Helmick, L. S. *J. Am. Chem. Soc.* **1978**, *100*, 5428.
(26) Nakamura, E.; Mori, S.; Nakamura, M.; Morokuma, K. *J. Am. Chem. Soc.* **1997**, *119*, 4887.
(27) Limmert, M. E.; Roy, A. H.; Hartwig, J. F. *J. Org. Chem.* **2005**, *70*, 9364.
(28) Barlunega, J.; Fañanás, F. J.; Sanz, R.; Marcos, C.; Ignacio, J. M. *Chem. Commun.* **2005**, 933.
(29) Baciocchi, E.; Ruzziconi, R. *J. Org. Chem.* **1991**, *56*, 4772.
(30) Hansen, A. L.; Ebran, J. P.; Ggsig, T. M.; Skrydstrup, T. *J. Org. Chem.* **2007**, *72*, 6464.
(31) Cesati, R. R.; de Armas, J.; Hoveyda, A. H. *Org. Lett.* **2002**, *4*, 395.
(32) Bajracharya, G. B.; Nakamura, I.; Yamamoto, Y. *J. Org. Chem.* **2005**, *70*, 892.
(33) Xing, D.; Guan, B.; Cai, G.; Fang, Z.; Yang, L.; Shi, Z. *Org. Lett.* **2006**, *8*, 693.

[Ir(cod)(L4a)]BArF. Yield: 122 mg (92%). ^{31}P NMR ($CDCl_3$) δ = 102.0 (s). ^{1}H NMR ($CDCl_3$) δ = 1.37 (s, 9H, CH_3, *t*Bu), 1.38 (s, 9H, CH_3, *t*Bu), 1.55 (s, 9H, CH_3, *t*Bu), 1,61 (b, 4H, CH_2, cod) 1.72 (s, 9H, CH_3, *t*Bu), 2.17 (m, 3H, CH_2, cod), 2.33 (b, 1H, CH_2, cod), 2.36 (s, 3H, CH_3−Ph), 3.47 (m, 1H, CH═, cod), 4.26 (b, 5H, CH-N, CH_2−O, CH_2−OP and CH═, cod), 4.83 (b, 2H, CH_2−O and CH═, cod), 5.27 (b, 1H, CH═, cod), 7.1 − 8.3 (m, 20H, aromatics). ^{13}C NMR ($CDCl_3$) δ = 25.6 (b, CH_2, cod), 29.3 (b, CH_2, cod), 31.3 (CH_3, *t*Bu), 31.5 (CH_3, *t*Bu), 31.6 (b, CH_3, *t*Bu), 32.4 (b, CH_2, cod), 34.9 (C, *t*Bu), 35.0 (C, *t*Bu), 35.5 (b, CH_2, cod), 36.0 (C, *t*Bu), 36.1 (CH_3−Ph), 36.2 (C, *t*Bu), 65.1 (CH), 66.0 (CH═, cod), 69.0 (CH_2−O), 72.2 (CH═, cod), 70.7 (CH_2−OP), 99.0 (d, CH═, cod, J_{C-P} = 20.2 Hz), 106.8 (d, CH═, cod, J_{C-P} = 13.7 Hz), 117.7 (b, CH═, BAr_F), 119−134 (aromatic carbons), 135.0 (b, CH═, BAr_F), 136−149 (aromatic carbons), 161.9 (q, C−B, BAr_F, $^1J_{C-B}$ = 49.5 Hz), 174.4 (C═N). Anal. Calc (%) for $C_{79}H_{76}BF_{24}IrNO_4P$: C 52.91, H 4.27, N 0.78; found: C 52.33, H 4.20, N 0.75.

[Ir(cod)(L5d)]BArF. Yield: 109 mg (93%). ^{31}P NMR ($CDCl_3$) δ = 102.4 (s). ^{1}H NMR ($CDCl_3$) δ = 1.29 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 1.67 (m, 3H, CH_2, cod), 2.22 (m, 2H, CH_2, cod), 2.40 (m, 3H, CH_2, cod), 3.58 (m, 1H, CH═, cod), 3.94 (b, 1H, CH═, cod), 4.58 (dd, 1H, CH_2, $^2J_{H-H}$ = 10.2 Hz, $^3J_{H-H}$ = 3 Hz), 4.73 (t, 1H, CH_2, $^2J_{H-H}$ = 9 Hz), 4.90 (dd, 1H, CH, $^3J_{H-H}$ = 8.7 Hz, $^3J_{H-H}$ = 2.4 Hz), 5.00 (b, 1H, CH═, cod), 5.42 (b, 1H, CH═, cod), 7.1 − 7.8 (m, 25H, aromatics). ^{13}C NMR ($CDCl_3$) δ = 20.9 (CH_3), 25.4 (b, CH_2, cod), 27.0 (CH_3), 29.3 (b, CH_2, cod), 32.1 (b, CH_2, cod), 36.9 (b, CH_2, cod), 66.1 (CH═, cod), 68.0 (CH═, cod), 70.6 (CH_2), 73.6 (CH), 86.0 (d, CMe_2, J_{C-P} = 6.5 Hz), 100.4 (d, CH═, cod, J_{C-P} = 18.7 Hz), 108.8 (d, CH═, cod, J_{C-P} = 14.0 Hz), 117.7 (b, CH═, BAr_F), 119−132 (aromatic carbons), 135.0 (b, CH═, BAr_F), 136−150 (aromatic carbons), 161.9 (q, C−B, BAr_F, $^1J_{C-B}$ = 49.5 Hz), 172.6 (C═N). Anal. Calc (%) for $C_{64}H_{46}BF_{24}IrNO_4P$: C 48.56, H 2.93, N 0.88; found: C 48.63, H 2.98, N 0.90.

[Ir(cod)(L8a)]BArF. Yield: 129 mg (96%). ^{31}P NMR ($CDCl_3$) δ = 96.2 (s). ^{1}H NMR ($CDCl_3$) δ = 1.08 (s, 3H, CH_3), 1.27 (s, 3H, CH_3), 1.36 (s, 9H, CH_3, *t*Bu), 1.38 (s, 9H, CH_3, *t*Bu), 1.54 (s, 9H, CH_3, *t*Bu), 1.72 (s, 9H, CH_3, *t*Bu), 1.62 (b, 4H, CH_2, cod), 2.11 (m, 2H, CH_2, cod), 2.24 (b, 2H, CH_2, cod), 2.36 (s, 3H, CH_3−Ph), 3.42 (m, 1H, CH═, cod), 4.19 (b, 1H, CH═, cod), 4.33 (b, 1H, CH═, cod), 4.48 (dd, 1H, CH_2, $^2J_{H-H}$ = 9.3 Hz, $^3J_{H-H}$ = 2.7 Hz), 4.70 (m, 2H, CH and CH_2), 5.19 (b, 1H, CH═, cod), 7.1 − 8.4 (m, 20H, aromatics). ^{13}C NMR ($CDCl_3$) δ = 20.6 (CH_3), 21.6 (b, CH_2, cod), 25.4 (CH_3), 26.9 (b, CH_2, cod), 29.2 (b, CH_2, cod), 31.2 (CH_3−Ph), 31.3 (CH_3, *t*Bu), 31.4 (CH_3, *t*Bu), 31.6 (b, CH_3, *t*Bu), 34.9 (C, *t*Bu), 35.0 (C, *t*Bu), 35.4 (b, CH_2, cod), 35.8 (C, *t*Bu), 36.0 (C, *t*Bu), 65.0 (CH═, cod), 69.5 (CH═, cod), 70.6 (CH_2), 72.7 (CH), 84.6 (b, C, CMe_2), 98.5 (d, CH═, cod, J_{C-P} = 19.9 Hz), 106.8 (b, CH═, cod), 117.7 (b, CH═, BAr_F), 119−134 (aromatic carbons), 135.0 (b, CH═, BAr_F), 136−149 (aromatic carbons), 161.9 (q, C−B, BAr_F, $^1J_{C-B}$ = 49.5 Hz), 175.1 (C═N). Anal. Calc (%) for $C_{81}H_{80}BF_{24}IrNO_4P$: C 53.41, H 4.43, N 0.77; found: C 53.48, H 4.39, N 0.83.

[Ir(cod)(L9a)]BArF. Yield: 124 mg (91%). ^{31}P NMR ($CDCl_3$) δ = 94.1 (s). ^{1}H NMR ($CDCl_3$) δ = 1.12 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 1.35 (s, 9H, CH_3, *t*Bu), 1.37 (s, 9H, CH_3, *t*Bu), 1.58 (s, 9H, CH_3, *t*Bu), 1.59 (s, 9H, CH_3, *t*Bu), 1.72 (b, 4H, CH_2, cod), 2.02 (m, 2H, CH_2, cod), 2.15 (b, 2H, CH_2, cod), 2.26 (s, 3H, CH_3−Ph), 2.80 (s, 3H, CH_3−Ph), 3.70 (m, 1H, CH═, cod), 4.01 (b, 2H, CH═, cod), 4.42 (dd, 1H, CH_2, $^2J_{H-H}$ = 10.2 Hz, $^3J_{H-H}$ = 5.1 Hz), 4.27 (t, 1H, CH_2, $^2J_{H-H}$ = 10.5 Hz), 4.51 (dd, 1H, CH, $^2J_{H-H}$ = 10.8 Hz, $^3J_{H-H}$ = 5.1 Hz), 5.19 (b, 1H, CH═, cod), 7.1 − 7.9 (m, 19H, aromatics). ^{13}C NMR ($CDCl_3$) δ = 20.5 (CH_3), 22.6 (b, CH_2, cod), 23.3 (CH_3), 27.7 (b, CH_2, cod), 29.7 (b, CH_2, cod), 31.2 (CH_3−Ph), 31.4 (CH_3, *t*Bu), 31.6 (b, CH_3, *t*Bu), 34.9 (C, *t*Bu), 35.0 (b, CH_2, cod), 35.2 (C, *t*Bu), 35.4 (b, C, *t*Bu), 35.8 (CH_3−Ph), 63.9 (CH═, cod), 66.0 (CH═, cod), 69.3 (CH_2), 74.0 (CH), 83.5 (b, C, CMe_2), 103.4 (d, CH═, cod, J_{C-P} = 18.0 Hz), 106.0 (d, CH═, cod, J_{C-P} = 10.5 Hz), 117.7 (b, CH═, BAr_F), 119−134 (aromatic carbons), 135.0 (b, CH═, BAr_F), 136−149 (aromatic carbons), 161.9 (q, C−B, BAr_F, $^1J_{C-B}$ = 49.8 Hz), 176.6 (C═N). Anal. Calc (%) for $C_{82}H_{82}BF_{24}IrNO_4P$: C 53.66, H 4.50, N 0.76; found: C 53.69, H 4.47, N 0.73.

[Ir(cod)(L10a)]BArF. Yield: 119 mg (90%). ^{31}P NMR ($CDCl_3$) δ = 102.5 (s). ^{1}H NMR ($CDCl_3$) δ = 1.16 (s, 3H, CH_3), 1.27 (s, 3H, CH_3), 1.34 (s, 9H, CH_3, *t*Bu), 1.37 (s, 9H, CH_3, *t*Bu), 1.54 (s, 9H, CH_3, *t*Bu), 1.55 (s, 18H, CH_3, *t*Bu and *t*Bu-C═N), 1.71 (m, 4H, CH_2, cod), 2.07 (m, 1H, CH_2, cod), 2.20 (m, 1H, CH_2, cod), 2.37 (m, 1H, CH_2, cod), 2.55 (m, 1H, CH_2, cod), 4.09 (m, 1H, CH═, cod), 4.16 (dd, 1H, CH_2, $^2J_{H-H}$ = 10.5 Hz, $^3J_{H-H}$ = 3 Hz), 4.25 (t, 1H, CH_2, $^2J_{H-H}$ = 10.5), 4.51 (b, 2H, CH and CH═, cod), 4.76 (b, 1H, CH═, cod), 5.36 (b, 1H, CH═, cod), 7.1 − 7.8 (m. 16H, aromatics). ^{13}C NMR ($CDCl_3$) δ = 21.1 (CH_3), 24.5 (b, CH_2, cod), 26.4 (CH_3), 28.3 (b, CH_2, cod), 29.4 (CH_3, *t*Bu), 31.2 (CH_3, *t*Bu), 31.3 (CH_3, *t*Bu), 31.5 (CH_3, *t*Bu), 31.6 (CH_3, *t*Bu), 34.5 (C, *t*Bu), 34.7 (b, CH_2, cod), 34.9 (C, *t*Bu), 35.3 (C, *t*Bu), 35.8 (C, *t*Bu), 37.6 (b, CH_2, cod), 69.1 (CH═, cod), 69.5 (CH═, cod), 69.6 (CH_2), 74.8 (CH), 83.8 (d, CMe_2, J_{C-P} = 5.7 Hz), 89.6 (d, CH═, cod, J_{C-P} = 26.2 Hz), 103.1 (d, CH═, cod, J_{C-P} = 10.5 Hz), 117.7 (b, CH═, BAr_F), 119−131 (aromatic carbons), 135.0 (b, CH═, BAr_F), 136−150 (aromatic carbons), 161.9 (q, C−B, BAr_F, $^1J_{C-B}$ = 49.8 Hz), 183.9 (C═N). Anal. Calc (%) for $C_{78}H_{82}BF_{24}IrNO_4P$: C 52.41, H 4.62, N 0.78; found: C 52.38, H 4.60, N 0.75.

[Ir(cod)(L11a)]BArF. Yield:125 mg (88%). ^{31}P NMR ($CDCl_3$) δ = 98.3 (s). ^{1}H NMR ($CDCl_3$) δ = 1.16 (b, 3H, CH_3), 1.28 (b, 3H, CH_3), 1.39 (b, 18H, CH_3, *t*Bu), 1.55 (b, 18H, CH_3, *t*Bu), 1.69 (b, 3H, CH_2, cod), 2.27 (b, 3H, CH_2, cod), 2.46 (b, 2H, CH_2, cod), 4.01 (b, 1H, CH═, cod), 4.30 (b, 9H, CH═, Cp), 4.50 (b, 2H, CH═, cod), 4.70 (b, 2H, CH_2), 4.90 (b, 1H, CH), 5.23 (b, 1H, CH═, cod), 5.42 (b, 1H, CH═, cod), 7.1 − 7.8 (m, 16H, aromatics). ^{13}C NMR ($CDCl_3$) δ = 22.0 (b, CH_2, cod), 28.8 (b, CH_2, cod), 31.5 (CH_3, *t*Bu), 31.6 (CH_3, *t*Bu), 31.9 (CH_3, *t*Bu), 32.1 (CH_3, *t*Bu), 33.7 (b, CH_2, cod), 34.9 (C, *t*Bu), 35.0 (C, *t*Bu), 35.4 (C, *t*Bu), 35.9 (C, *t*Bu), 37.0 (b, CH_2, cod), 67.5 (CH═, cod), 70.4 (CH═, cod), 71.0 (b, CH═, Cp), 71.9 (CH_2), 73.8 (CH), 84.9 (b, CMe_2), 95.0 (CH═, cod), 100.9 (CH═, cod), 117.7 (b, CH═, BAr_F), 119−131 (aromatic carbons), 135.0 (b, CH═, BAr_F), 136−150 (aromatic carbons), 161.9 (q, C−B, BAr_F, $^1J_{C-B}$ = 49.8 Hz), 176.9 (C═N). Anal. Calc (%) for $C_{84}H_{82}BF_{24}FeIrNO_4P$: C 52.67, H 4.32, N 0.73; found: C 52.78, H 4.34, N 0.74.

[Ir(cod)(L12a)]BArF. Yield 123 mg (92%). ^{31}P NMR ($CDCl_3$) δ = 97.8 (s). 1H NMR ($CDCl_3$) δ = 1.06 (s, 3H, CH_3), 1.29 (s, 3H, CH_3), 1.35 (s, 9H, CH_3, *t*Bu), 1.38 (s, 9H, CH_3, *t*Bu), 1.54 (s, 9H, CH_3, *t*Bu), 1.61 (s, 9H, CH_3, *t*Bu), 1.70 (m, 4H, CH_2, cod), 2.32 (m, 3H, CH_2, cod), 2.51 (m, 1H, CH_2, cod), 3.60 (b, 1H, CH═, cod), 4.41 (m, 2H, CH═, cod and CH_2), 4.58 (b, 2H, CH═, cod and CH_2), 4.67 (dd, 1H, CH, $^3J_{H-H}$ = 10. 0 Hz, $^3J_{H-H}$ = 3.2 Hz), 5.32 (b, 1H, CH═, cod), 7.1−8.5 (m, 21H, CH═, aromatics). ^{13}C NMR ($CDCl_3$) δ = 21.3 (CH_3), 24.8 (b, CH_2, cod), 26.5 (m, CH_3), 28.09 (b, CH_2, cod), 31.2 (CH_3, *t*Bu), 31.4 (CH_3, *t*Bu), 31.6 (CH_3, *t*Bu), 33.2 (b, CH_2, cod), 34.8 (C, tBu), 34.9 (C, tBu), 35.2 (C, tBu), 37.3 (b, CH_2, cod), 66.3 (CH═, cod), 69.8 (CH═, cod), 70.0 (CH_2), 71.2 (CH), 84.9 (d, CMe_2, J_{C-P} = 5.2 Hz), 93.5 (d, CH═, cod, J_{C-P} = 21.1 Hz), 106.3 (d, CH═, cod, J_{C-P} = 6.2 Hz), 117.7 (b, CH═, BArF), 119−132 (aromatic carbons), 135.0 (b, CH═, BArF), 135.5−150 (aromatic carbons), 161.9 (q, C−B, BArF, $^1J_{C-B}$ = 48.6 Hz), 173.7 (C═N). Anal. Calc (%) for $C_{80}H_{78}BF_{24}IrNO_4P$: C 53.16, H 4.35, N 0.77; found: C 53.22, H 4.40, N 0.76.

[Ir(cod)(L14a)]BArF. Yield: 124 mg (92%). ^{31}P NMR ($CDCl_3$) δ = 99.1 (s). ^{1}H NMR ($CDCl_3$) δ = 1.12 (s, 3H, CH_3), 1.31 (s, 3H, CH_3), 1.37 (b, 18H, CH_3, *t*Bu), 1.57 (s, 9H, CH_3, *t*Bu), 1.63 (s, 9H, CH_3,*t*Bu), 1.70 (b, 4H, CH_2, cod), 2.15 (s, 3H, CH_3), 2.33 (b, 3H, CH_2, cod), 2.55 (b, 1H, CH_2, cod), 3.65 (b, 1H, CH═, cod), 3.65 (b, 1H, CH═, cod), 4.22 (b, 1H, CH-N), 4.41 (b, 1H, CH═, cod), 4.41 (b, 1H, CH═, cod), 4.61 (b, 1H, CH═, cod), 4.74 (b, 1H, CH−O), 5.25 (b, 1H, CH═, cod), 7.1 − 8.4 (m, 21H, aromatics). ^{13}C NMR ($CDCl_3$) δ = 21.0 (CH_3), 21.8 (CH_3), 24.9 (b, CH_2, cod), 26.2 (b, CH_2, cod), 28.9 (b, CH_2, cod), 31.3 (CH_3,

*t*Bu), 31.4 (CH_3, *t*Bu), 31.6 (b, CH_3, *t*Bu), 33.6 (CH_3), 35.0 (C, *t*Bu), 35.1 (C, *t*Bu), 35.4 (b, C, *t*Bu), 35.8 (C, *t*Bu), 37.2 (b, CH_2, cod), 68.4 (CH═, cod), 70.2 (CH═, cod), 79.1 (CH−O), 80.3 (CH-N), 84.5 (d, C, CMe_2, J_{C-P} = 5.4 Hz), 94.7 (d, CH═, cod, J_{C-P} = 22.2 Hz), 105.7 (d, CH═, cod, J_{C-P} = 12.5 Hz), 117.7 (b, CH═, BAr_F), 119−134 (aromatic carbons), 135.0 (b, CH═, BAr_F), 136−149 (aromatic carbons), 161.9 (q, C−B, BAr_F, $^1J_{C-B}$ = 49.5 Hz), 171.5 (C═N). Anal. Calc (%) for $C_{81}H_{80}BF_{24}IrNO_4P$: C 53.41, H 4.42, N 0.77; found: C 53.49, H 4.40, N 0.78.

[Ir(cod)(L15a)]BArF. Yield: 133 mg (93%). ^{31}P NMR ($CDCl_3$) δ = 92.7 (s). ^{1}H NMR ($CDCl_3$) δ = 1.37 (s, 9H, CH_3, *t*Bu), 1.39 (s, 9H, CH_3, *t*Bu), 1.57 (s, 9H, CH_3, *t*Bu), 1.58 (s, 9H, CH_3, *t*Bu), 1.67 (m, 2H, CH_2, cod), 1.80 (m, 2H, CH_2, cod), 2.30 (m, 1H, CH_2, cod), 2.39 (m, 2H, CH_2, cod), 3.68 (m, 1H, CH═, cod), 4.40 (b, 2H, CH═, cod and CH_2−O), 4.59 (b, 2H, CH═, cod and CH_2−O), 4.69 (dd, 1H, CH, $^2J_{H-H}$ = 12.8 Hz, $^3J_{H-H}$ = 3.2 Hz), 5.35 (b, 1H, CH═ cod), 7.1 − 7.8 (m. 31H, aromatics). ^{13}C NMR ($CDCl_3$) δ = 22.9 (b, CH_2, cod), 28.9 (b, CH_2, cod), 31.4 (CH_3, *t*Bu), 31.5 (CH_3, *t*Bu), 31.6 (CH_3, *t*Bu), 31.7 (CH_3, *t*Bu), 33.4 (b, CH_2, cod), 35.0 (C, *t*Bu), 35.1 (C, *t*Bu), 35.4 (C, *t*Bu), 35.8 (C, *t*Bu), 37.1 (b, CH_2, cod), 68.1 (CH_2), 69.9 (CH), 70.2 (CH═, cod), 73.9 (CH═, cod), 84.8 (b, CPh_2), 95.1 (d, CH═, cod, J_{C-P} = 22 Hz), 106.4 (b, CH═, cod), 117.7 (b, CH═, BAr_F), 119−131 (aromatic carbons), 135.0 (b, CH═, BAr_F), 136−150 (aromatic carbons), 161.9 (q, C−B, BAr_F, $^1J_{C-B}$ = 49.3 Hz), 172.1 (C═N). Anal. Calc (%) for $C_{90}H_{82}BF_{24}IrNO_4P$: C 55.96, H 4.28, N 0.73; found: C 55.93, H 4.26, N 0.70.

[Ir(cod)(L15f)]BArF. Yield: 123 mg (92%). ^{31}P NMR ($CDCl_3$) δ = 113.2 (s). ^{1}H NMR ($CDCl_3$) δ = 1.48 (m, 1H, CH_2, cod), 1.70 (m, 2H, CH_2, cod), 1.78 (m, 3H, CH_2, cod), 2.00 (m, 1H, CH_2, cod), 2.10 (m, 1H, CH_2, cod), 3.41 (m, 1H, CH═, cod), 3.94 (m, 1H, CH═, cod), 4.35 (m, 1H, CH_2), 4.47 (b, 2H, CH and CH═, cod), 5.28 (b, 1H, CH═, cod), 6.00 (m, 1H, CH_2), 6.9−8.5 (m. 39H, aromatics). ^{13}C NMR ($CDCl_3$) δ = 22.7 (b, CH_2, cod), 27.0 (b, CH_2, cod), 33.5 (b, CH_2, cod), 38.1 (b, CH_2, cod), 61.2 (CH), 64.6 (CH_2), 70.4 (CH═, cod), 71.8 (CH═, cod), 87.8 (b, CPh_2), 102.1 (d, CH═, cod, J_{C-P} = 17 Hz), 103.0 (b, CH═, cod, J_{C-P} = 17 Hz), 117.7 (b, CH═, BAr_F), 119−131 (aromatic carbons), 135.0 (b, CH═, BAr_F), 136−150 (aromatic carbons), 161.9 (q, C−B, BAr_F, $^1J_{C-B}$ = 49.3 Hz), 173.5 (C═N). Anal. Calc (%) for $C_{90}H_{82}BF_{24}IrNO_4P$: C 54.50, H 3.01, N 0.78; found: C 54.43, H 3.09, N 0.79.

4.4. General Procedure for the Preparation of Terminal Alkenes S11−S14. To a suspension of methyltriphenylphosphonium bromide (5.7 g, 15.9 mmol, 1.5 equiv) in THF (400 mL) at 0 °C under Ar was added *n*-butyllithium (2.5 M, 5.9 mL, 14.8 mmol, 1.4 equiv) dropwise. The resulting orange solution was stirred at 0 °C for 30 min. A solution of the corresponding ketone (10.6 mmol, 1.00 equiv) in THF (10 mL) was added dropwise, and the resulting yellow solution was left overnight at room temperature. The reaction was quenched with water (10 mL), extracted with Et_2O, and dried over $MgSO_4$. The precipitate was removed by filtration through a silica plug. The collected solids were washed with pentane (3 × 10 mL), and the filtrate was concentrated *in vacuo*.

S11. The crude product was purified on silica eluting with pentane. Colorless liquid (1.07 g, 7.10 mmol, 67% Yield).^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.94 (t, 3H, CH_3, ^3J = 7.2 Hz), 1.38 (m, 2H, CH_2), 1.55 (m, 2H, CH_2), 2.36 (t, 2H, CH_2, ^3J = 7.6 Hz), 4.96 (s, 1H, CH_2═), 5.51 (s, 1H, CH_2═), 6.31 (m, 1H, CH═), 6.40 (m, 1H, CH═), 7.36 (m, 1H, CH═). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 14.8 (CH_3), 22.7 (CH_2), 31.1 (CH_2), 33.1 (CH_2), 106.1 (CH_2═), 109.2 (CH═), 111.2 (CH═), 129.9 (C), 137.9 (CH═), 141.9 (C).

S12. The crude product was purified on silica eluting with pentane. Colorless liquid (1.30 g, 7.80 mmol, 73% Yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.94 (t, 3H, CH_3, ^3J = 7.7 Hz), 1.41 (m, 2H, CH_2), 1.57 (m, 2H, CH_2), 2.48 (t, 2H, CH_2, ^3J = 7.2 Hz), 4.96 (s, 1H, CH_2═), 5.40 (s, 1H, CH_2═), 6.97 (m, 1H, CH═), 7.05 (m, 1H, CH═), 7.18 (m, 1H, CH═) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 14.1 (CH_3), 22.7 (CH_2), 30.8 (CH_2), 35.4 (CH_2), 110.8 (CH_2═), 123.4 (CH═), 124.2 (CH═), 127.5 (CH═), 142.1 (C), 145.7 (C).

S13. The crude product was purified on silica eluting with pentane/ethyl acetate (99:1). Pale-yellow liquid (0.9 g, 6.8 mmol, 65% Yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.17 (t, 3H, CH_3, ^3J = 7.6 Hz), 2.66 (q, 2H, CH_2, ^3J = 7.4 Hz) 5.29 (s, 1H, CH_2═), 5.77 (s, 1H, CH_2═), 7.17 (m, 1H, CH═), 7.47 (m, 1H, CH═), 7.66 (m, 1H, CH═), 8.61 (m, 1H, CH═) ppm.

S14. The crude product was purified on silica eluting with pentane/ethyl acetate (99:1). Pale-yellow liquid (1 g, 6.2 mmol, 59% Yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.21 (s, 9H, CH_3 *t*Bu), 5.00 (s, 1H, CH_2 ═), 5.31 (s, 1H, CH_2═), 7.17 (m, 2H, Ar), 7.62 (m, 1H, Ar), 8.58 (m, 1H, Ar) ppm.^{13}C NMR (100 MHz, $CDCl_3$) δ = 30.1 (CH_3), 36.4 (C), 113.5 (CH_2═), 121.6 (CH═), 123.9 (CH═), 136.0 (CH═), 148.4 (CH═), 159.1 (C), 162.5 (C) ppm.

4.5. Preparation of S21. To a suspension of methyltriphenylphosphonium bromide (1.33 g, 3.72 mmol, 1.5 equiv) in Et_2O (20 mL) under Ar was added potassium *tert*-butoxide (0.39 g, 3.47 mmol, 1.4 equiv) dropwise. The resulting orange solution was stirred at 0 °C for 30 min. A solution of 2,2,2-trifluoro-1-(4-methoxyphenyl)ethanone (0.51 g, 2.48 mmol, 1.00 equiv) in Et_2O (10 mL) was added dropwise, and the resulting yellow solution was left for 72 h at room temperature. The reaction was quenched with water (10 mL), extracted with Et_2O, and dried over $MgSO_4$. The crude product was purified on silica eluting with petroleum ether/ethylacetate (99:1) to obtain a colorless liquid (350 mg, 1.74 mmol, 70% yield). The characterization data are in agreement with the previously published data.[37]

4.6. Typical Procedure for the Hydrogenation of Olefins. The alkene (1 mmol) and Ir complex (0.2 mol %) were dissolved in CH_2Cl_2 (2 mL) in a high-pressure autoclave. The autoclave was purged four times with hydrogen. Then, it was pressurized at the desired pressure. After the desired reaction time, the autoclave was depressurized and the solvent evaporated off. The residue was dissolved in Et_2O (1.5 mL) and filtered through a short Celite plug. The enantiomeric excess was determined by chiral GC or chiral HPLC, and conversions were determined by ^{1}H NMR. The enantiomeric excesses of hydrogenated products from **S1**,[38] **S2**−**S3**,[7b] **S4**−**S5**,[39] **S7**,[38] **S8**,[39] **S9**,[38] **S10**,[8] **S18**,[40] **S20**[41] were determined using the conditions previously described.

(4-Methylpentan-2-yl)benzene. For characterization details see ref 42. R_t (GC, Chiraldex β-DM, isotherm 75 °C, 100 Kpa H_2) = 17.3 min (*S*), 18.1 min (*R*).

2-(Hexan-2-yl)furan. ^{1}H NMR: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.92 (t, 3H, CH_3, ^3J = 7.7 Hz), 1.32 (m, 7H, 2× CH_2 and CH_3), 1.63 (m, 2H, CH_2), 3.45 (m, 1H, CH), 6.98 (m, 1H, CH═), 7.15 (m, 1H, CH═), 7.28 (m, 1H, CH═). R_t (GC, Chiraldex β-DM, 50 °C for 30 min, 2 °C/min until 175 °C, 100 Kpa H_2) = 36.3 min (+), 37.2 min (−).

2-(Hexan-2-yl)thiophene. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.89 (t, 3H, CH_3, ^3J = 7.7 Hz), 1.31 (m, 7H, 2x CH_2 and CH_3), 1.62 (m, 2H, CH_2), 3.03 (m, 1H, CH), 6.83 (m, 1H, CH═), 6.94 (m, 1H, CH═), 7.14 (m, 1H, CH═). R_t (GC, Chiraldex β-DM, 50 °C for 30 min, 2 °C/min until 175 °C, 100 Kpa H_2) = 53.7 min (+), 54.2 min (−).

(34) Hixson, S. S.; Franke, L. A. *J. Org. Chem.* **1988**, *53*, 2706.
(35) Hatch, L. F.; Patton, T. L. *J. Am. Chem. Soc.* **1954**, *76*, 2705.
(36) Narayanan, B. A.; Bunelle, W. H. *Tetrahedron Lett.* **1987**, *28*, 6261.
(37) Koshy, K. M.; Roy, D.; Tidwell, T. T. *J. Am. Chem. Soc.* **1979**, *101*, 357.
(38) Ohta, T.; Ikegami, H.; Miyake, T.; Takaya, H. *J. Organomet. Chem.* **1995**, *502*, 169.
(39) Inagaki, K.; Ohta, T.; Nozaki, K.; Takaya, H. *J. Organomet. Chem.* **1997**, *531*, 159.
(40) Deerenberg, S.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Organometallics* **2000**, *19*, 2065.
(41) Källström, K.; Munslow, I. J.; Hedberg, C.; Andersson, P. G. *Adv. Synth. Catal.* **2006**, *348*, 2575.
(42) Fraenkel, G.; Geckle, J. M. *J. Am. Chem. Soc.* **1980**, *102*, 2869.

2-(Butan-2-yl)pyridine. For characterization details see ref 45. R_t (GC, Chiral β-Dex, 50 °C for 60 min, 3 °C/min until 150 °C, 120 Kpa H_2) = 75.1 min (−), 75.4 min (+).

2-(3,3-Dimethylbutan-2-yl)pyridine. For characterization details see ref 44. R_t (GC, Chiral β-Dex, 60 °C for 60 min, 3 °C/min until 150 °C, 120 Kpa H_2) = 63.5 min (−), 65.4 min (+).

1-(1-Phenylethyl)naphthalene. For characterization details see ref 45. R_t (HPLC, Chiracel OD-H, hexane/2-propanol = 98/2, 0.5 mL/min, 254 nm) = 11.0 min (+), 12.2 min (−).

1-Methyl-2-(1-phenylethyl)benzene. For characterization details see ref 46. R_t (HPLC, Chiracel IB, hexane/2-propanol = 99.8/0.2, 0.5 mL/min, 220 nm) = 8.9 min (+), 9.3 min (−).

1-Methoxy-4-{1-[4-(trifluoromethyl)phenyl]ethyl}benzene. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.62 (d, 3H, CH_3, ^3J = 7.2 Hz), 3.77 (s, 3H, CH_3−O), 4.28 (q, 1H, CH, ^3J = 7.2 Hz), 6.81 (m, 2H, CH═), 7.15 (m, 2H, CH═), 7.32 (m, 2H, CH═), 7.56 (m, 2H, CH). R_t (GC, Chiraldex β-DM, 50 °C for 30 min, 2 °C/min until 175 °C, 100 Kpa H_2) = 90.1 min (+), 90.4 min (−).

(43) Guanti, G.; Narisano, E.; Riva, R. *Tetrahedron: Asymmetry* **1997**, *8*, 2175.
(44) Salvadori, P.; Rosini, C.; Bertucci, C.; Pini, D.; Marchetti, M. *J. Chem. Soc., Perkin Trans. 2* **1983**, *3*, 399.
(45) Díaz Gómez, E.; Albert, D.; Mattiza, J.; Duddeck, H.; Chojnowsky, J.; Cypryk, M. *Tetrahedron: Asymmetry* **2006**, *17*, 1743.
(46) Miyai, T.; Onishi, Y.; Baba, A. *Tetrahedron* **1999**, *55*, 1017.

2-Phenylpropyl acetate. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.34 (d, 3H, CH_3, ^3J = 6.4 Hz), 2.00 (s, 3H, CH_3, OAc), 3.09 (m, 1H, CH), 4.17 (m, 2H, CH_2), 7.21 (m, 3H, CH═), 7.32 (m, 2H, CH═) ppm. For ee determination, the sample was hydrolyzed to the corresponding alcohol by adding 1 mL of methanol and 50 mg of LiOH.

1-Methoxy-4-(1,1,1-trifluoropropan-2-yl)benzene. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.42 (d, 3H, CH_3, ^3J = 7.2 Hz), 3.41 (q, 1H, CH, ^3J = 7.2 Hz), 3.74 (s, 3H, O−CH_3), 6.81 (m, 2H, CH═), 7.18 (m, 2H, CH═). R_t (GC, Chiraldex β-DM, 50 °C for 30 min, 2 °C/min until 175 °C, 100 Kpa H_2) = 9.2 min (−), 9.6 min (+).

Acknowledgment. We thank the Spanish (Consolider Ingenio CSD2006-0003, CTQ2007-62288/BQU, 2008PGIR/07 to O.P. and 2008PGIR/08 to M.D.) and Catalan (2005SGR007777) Governments, COST D40, Vetenskapsrådet (V.R.), and Astra Zeneca for support. A.B. and B.S. acknowledge financial supported by the Graduate School 1213 of Deutsche Forschungsgemeinschaft. We thank Dr. Jordi Benet and Eduardo Escudero (ICIQ) for the analysis of the single-crystal X-ray structure.

Supporting Information Available: X-ray crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

JA904152R