Synthesis of chiral furanoside diphosphinite and thioether-phosphinite compounds derived from D-(+)-xylose. Application as ligands in asymmetric catalytic processes

TESI DOCTORAL

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Tarragona, 2005

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1. Introduction

The growing demand for enantiomerically pure compounds for the development of pharmaceuticals, agrochemicals and flavors has captured the interest of the chemist in the last few decades. Of the various methods for producing enantiopure compounds, enantioselective homogeneous metal catalysis is an attractive one, as is reflected by the many publications in this field and the award of the Nobel Prize in 2001 to W.S. Knowles, R. Noyori and K. B. Sharpless.[i] 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.

To reach the highest levels of reactivity and selectivity in catalytic enantioselective reactions, several reaction 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 to obtain chiral ligands is to transform or derivatize natural chiral compounds, thus making tedious optical-resolution procedures unnecessary. In the last few years, impressive results have been obtained using carbohydrate derivative ligands in a wide range of catalytic asymmetric reactions.[1] Carbohydrates have many advantages: they are readily available, are highly functionalized and have several stereogenic centers. This enables series of chiral ligands to be synthesized and screened in the search for high activities and selectivities for each particular reaction. This tuning of the ligand structure allows for a rational design of ligands, which provides valuable information about the origin of the selectivity.

In this context, this thesis focuses on the development of new chiral ligands derived from carbohydrate, the synthesis of new catalyst precursors and their application in asymmetric catalysis

Asymmetric 1,4-addition.

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

Michael additions of organolithium, Grignard, diorganozinc and triorganoaluminium reagents to α,β-unsaturated compounds can be catalyzed by nickel, cobalt and copper-complexes.[2] The best results have been achieved with Cu(I)-catalysts, especially those in which copper is bound to a *soft* center (sulphur or phosphorus).[2] Initially, Grignard reagents were the first species to be applied in this process. However, in 1993 Alexakis and coworkers introduced the use of dialkylzinc reagents for this enantioselective reaction and found them to be more appropriate than the classical use of Grignard reagents. Trialkylaluminum reagents have been tested in only a few cases but these represented an interesting alternative. Nowadays, the copper-catalyzed asymmetric 1,4-addition of organozinc reagents has been adopted as standard procedure for testing new ligands.[2]

In the copper-catalyzed asymmetric 1,4-addition, the copper salt is also important for high catalytic activity and enantioselectivity. Copper (I) and copper (II) salts have been used. The true catalytic species is Cu(I), so the reduction of Cu(II) is the first step in the process. The copper (II) triflate is usually the salt of choice, though many other copper salts have demonstrated their power in this reaction.[2]

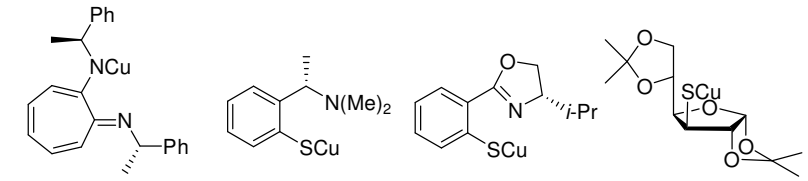
Cyclic and acyclic enones have been used as substrates in enantioselective copper-catalyzed conjugate addition. Traditionally, 2-cyclohexenone has been the substrate of choice for testing a new ligand. This cyclic enone avoids the *s-cis*/*s-trans* interconversion of acyclic substrates.[3] For acyclic enones, the most widely

studied substrate is benzylideneacetone. To achieve a high catalytic performance with this acyclic substrate, the class of ligands usually has to be different from those with cyclic substrates. Nitro-olefins are another class of excellent Michael acceptors for this reaction.[2] Again, the efficient ligands are different from the previous ones.

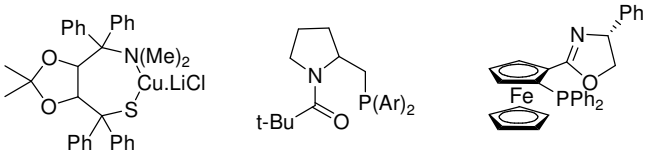
Comentario: Falta aqu substantiu.

Ligands

The first enantioselective copper catalysts were reported by Lippard *et al*. in 1988.[4] The reaction of 2-cyclohexenone with Grignard reagents in the presence of the chiral aminotroponeimine copper complex as catalyst (Figure 33) gave the 1,4-adducts with low enantioselectivity (up to 14%).**¡Error! Marcador no definido.** Selectivity increased to 74% ee with the addition of hexamethylphophoric triamide (HMPA) and silyl halides. Later, various copper thiolates gave moderate-to-good results on cyclic and acyclic enones. However, the best results were obtained with external ligands by Tomioka and Sammakia.**¡Error! Marcador no definido.**[e,f] Since the late 1990s all authors have focused on the dialkylzinc procedure. The selection of chiral ligands for the highly enantioselective conjugate addition of organozinc reagents to α,β-unsaturated compounds has mainly focused on P-donor and mixed P,N-donor.[5] Most phosphorus ligands are of the phosphite and phosphoramidite type. Non-phosphorus ligands have scarcely been used with dialkylzinc reagents.[6]

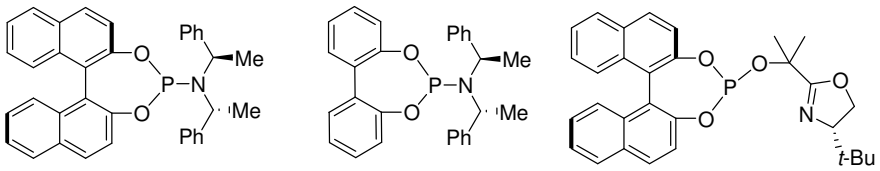


Lippard, 74 % ee van Koten, 76 % ee Pfaltz, 72 % ee Spescha, 60 % ee

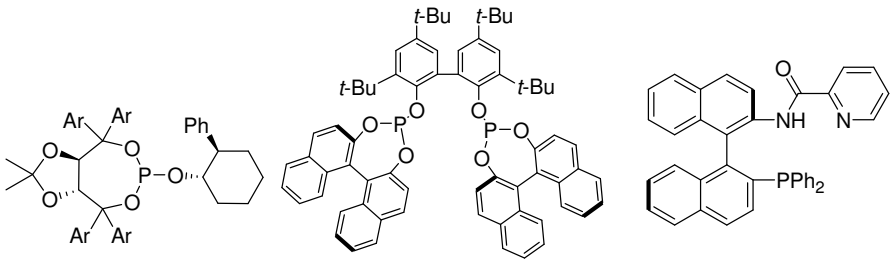


Seebach, 84 % ee Tomioka, 90 % ee Sammakia, 98 % ee

Figure 33. Heterocuprate-based ligand and chiral ligands using Grignard reagents.



Feringa, 98 % ee Alexakis, 98 % ee Pfaltz, 95 % ee



Alexakis, 98 % ee Chan, 99 % ee Zhang, 98 % ee

Figure 34. Representative phosphorus chiral ligands for 1,4-addition of organozinc reagents to α,β-unsaturated compounds.

Although carbohydrate ligands have been successfully used in other enantioselective reactions,[¡Error! Marcador no definido.a,b] there have been few reports on the highly enantioselective 1,4-addition using these systems. Notable examples,

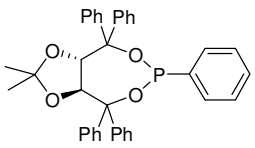
however, include monophosphonite,[ii] monophosphite,**¡Error! Marcador no definido.**[-iii] and mixed amino-thiolate.**¡Error! Marcador no definido.**[d,iv] ligands derived from TADDOL, and furanoside diphosphite ligands.[v] Other carbohydrate ligands, such as phosphoroamidite[**¡Error! Marcador no definido.**d,ii,iii,vi] and mixed S-O,[vii] N-P,[viii] S-P[ix] and P-P[nix] heterodonor ligands, have also been tested with low-to-moderate enantioselectivities.

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

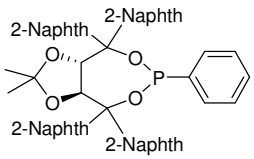
1.3.2.1. P-ligands

Phosphonite ligands

Alexakis used phosphonite ligands **69** and **70** (Figure 35), derived from (+)-TADDOL, in the asymmetric conjugate addition of diethylzinc to nitro-olefins[ii] and alkylidene malonates[x] with moderate-to-good enantioselectivities. Ligand **69** appears to be the optimal choice for the diethylzinc addition to aryl nitro-olefins (ee's up to 86%).



69



70

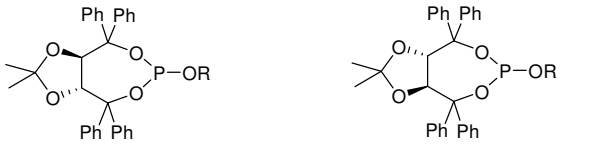
Figure 35. Phosphonite ligands **69** and **70** derived from (+)-TADDOL.

Phosphite ligands

Phosphite furanoside ligands **24-29** (Figure 11) were also applied in the Cu-catalyzed 1,4-addition of diethylzinc to cyclohexenone.[v] Results show that enantioselectivity depends strongly on the absolute configuration of the C-3 stereogenic center and on the biaryl substituents, while the sense of

enantiodiscrimination is predominantly controlled by the configuration of the biaryl groups of the phosphite moieties. The best enantioselectivites were obtained with ligands **24h** and **26g** with ee's of 81% (*R*) and 84% (*S*), respectively. Interestingly, both enantiomers of the product can be obtained. Introducing a stereogenic center in C-5 had a positive effect on activitybut did not affect enantioselectivity.

Alexakis and coworkers have developed a series of phosphite ligands **71** and **72**, derived from (-)-TADDOL and (+)-TADDOL (Figure 36). These ligands were applied in the Cu-catalyzed 1,4-addition of diethylzinc to 2-cyclohexenone (ee's up to 96%),[iii] benzalacetone (ee's up to 35%),**¡Error! Marcador no definido.**[d,iii] chalcone (ee's up to 50%),**¡Error! Marcador no definido.**[d,iii] nitro-olefins (ee's up to 96%)[ii] and alkylidene malonates (ee's up to 73%)[x] (Figure 36).



71 **72**

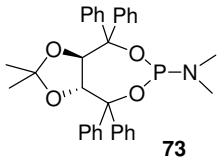
R = alkyl, cyclohexanyl, substituted cyclohexanyl, aryl

R= substituted cyclohexanyl

Figure 36. Basic structure of phosphite ligands **71** and **72**.

Phosphoroamidite ligands

In the last few years several mono- and diphosphoroamidite ligands, derived from TADDOL, have been developed for the Cu-catalyzed 1,4-addition of diethylzinc to several substrates with poor-to-moderate enantioselectivity.**¡Error! Marcador no definido.**[d,ii,iii] However, Feringa and coworkers observed an unexpected improvement in enantioselectivity in the Cu-**73** (Figure 37) catalyzed addition of diethyl zinc to cyclohexenone when they used powdered molecular sieves (ee's up to 71%).[vib]



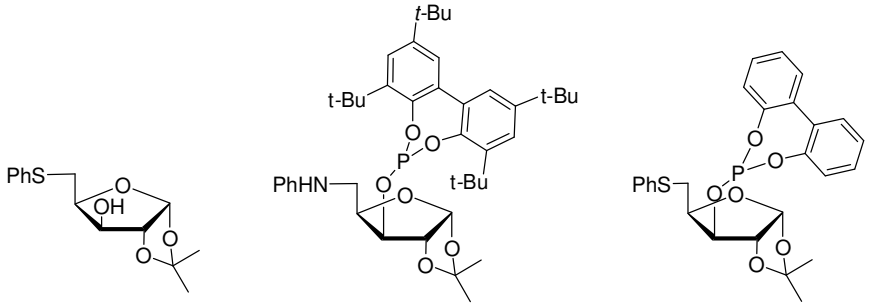
73

Figure 37. Phosphoroamidite ligand **73** derived from TADDOL.

1.3.2.2. Heterodonor ligands

The groups of Seebach and Alexakis have developed a series of heterodonor O-S, N-S and N-P ligands derived from TADDOL for the Cu-catalyzed 1,4-addition of organometallic reagents to cyclic and lineal enones.**¡Error! Marcador no definido.**[d,**¡Error! Marcador no definido.**,d,iii,iv] The best enantioselectivities were obtained with the previously mentioned N-S ligand (Figure 33) developed by Seebach and coworkers in the Cu-catalyzed addition of butylmagnesium cloride to cycloheptanone (ee's up to 84%).**¡Error! Marcador no definido.**[d,iv]

A series of heterodonor ligands (S-O, P-N, P-S and P-P') derived from D-(+)-xylose were recently applied in the Cu-catalyzed conjugate addition of diethyl zinc to α,β-unsaturated enones with low-to-moderate enantioselectivities (Figure 38, Figure 15 ligand **36b** with ee's up to 11% and Figure 16 ligand **37b** with ee's up to 30%)[vii-ix].

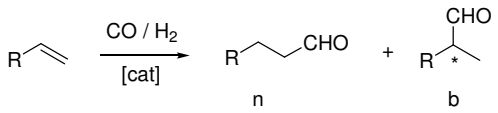


74 (62% ee) **75** (63% ee) **76** (41% ee)

Figure 38. Heterodonor ligands derived from D-(+)-xylose.

1.4. Asymmetric hydroformylation

Hydroformylation is an important and extensively studied process for the functionalization of carbon-carbon bonds. In this process, alkenes are converted into aldehydes by reaction with CO/H_2 via the addition of a formyl group to the double carbon-carbon bond (Scheme 5).[xi]

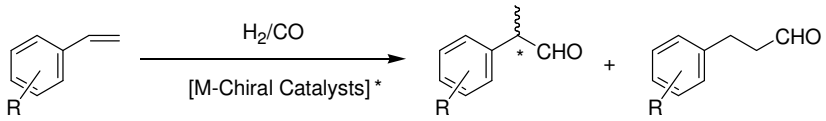


Scheme 5. Metal-catalyzed hydroformylation.

The regioselectivity is given by the ratio between the branched (b) and linear (n) aldehydes. The linear aldehydes (n) are preferred in industry because aldehydes are mostly made to react to the corresponding alcohols, which are used as solvents, detergents or plasticizer components. In the last few years, extensive research aimed at producing only linear aldehydes has provided impressive results. The application of phosphines with a wide bite angle in the rhodium-catalyzed hydroformylation of terminal alkenes enables regioselecitivity to be practically totally controlled .[xie]

The branched aldehydes (b) are the product of interest in the asymmetric hydroformylation version. Chiral aldehydes are an important pool for the preparation of fine chemicals (high-value-added compounds) such as flavors, fragances, pharmaceuticals and agrochemicals.[xib,xii] However, despite these advantages the hydroformylation reaction has been little used in the synthesis of fine chemicals. This may be due to the difficulty in simultaneously controlling chemo-, regio- and enantioselecitivity. To date, much effort in this field has concentrated on the hydroformylation of styrene and other vinylarenes (Scheme 6).[xi] The conversion into enantiomerically pure (*S*)-2-phenylpropanol derivatives is

of considerable interest because it is a straightforward route to enantiomerically pure non-steroidal anti-inflammatory drugs (Figure 39). Oxidation of the branched aldehydes provides the desired enantiopure 2-arylpropionic acids, such as cetoprofen, fenoprofen, naproxen and ibuprofen. In the last few years, however, researchers have become significantly more interested in the asymmetric hydroformylation of vinyl acetate, unsaturated nitriles and heterocyclic substrates.[xi]



Scheme 6. Metal-catalyzed asymmetric hydroformylation of vinylarenes.

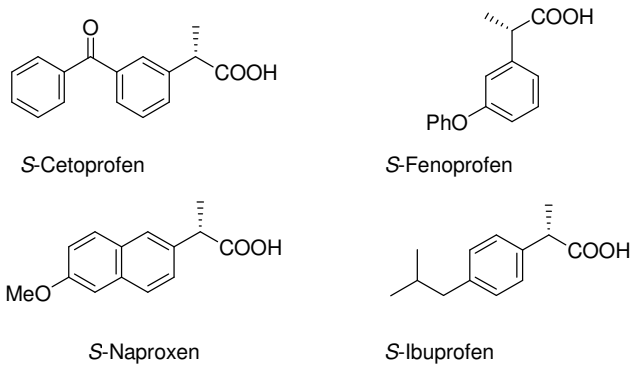


Figure 39. Enantiomerically anti-inflammatory drugs produced via asymmetric hydroformylation.

Typically, catalysts for this process are complexes of a transition metal atom (M) that enables the formation of mononuclear metal-carbonyl hydride species. These complexes may be modified by additional ligands (L). The general composition is represented by the structure $HM(CO)_xL_n$. In the last few years, transition-metal complexes based on rhodium and platinum have exclusively been applied in asymmetric hydroformylation. The best results, however, have been achieved with the rhodium systems.[xi]

1.4.1. Mechanism

The accepted mechanism for the Rh-catalyzed hydroformylation of olefins is illustrated in Figure 40.[i,xie,f]

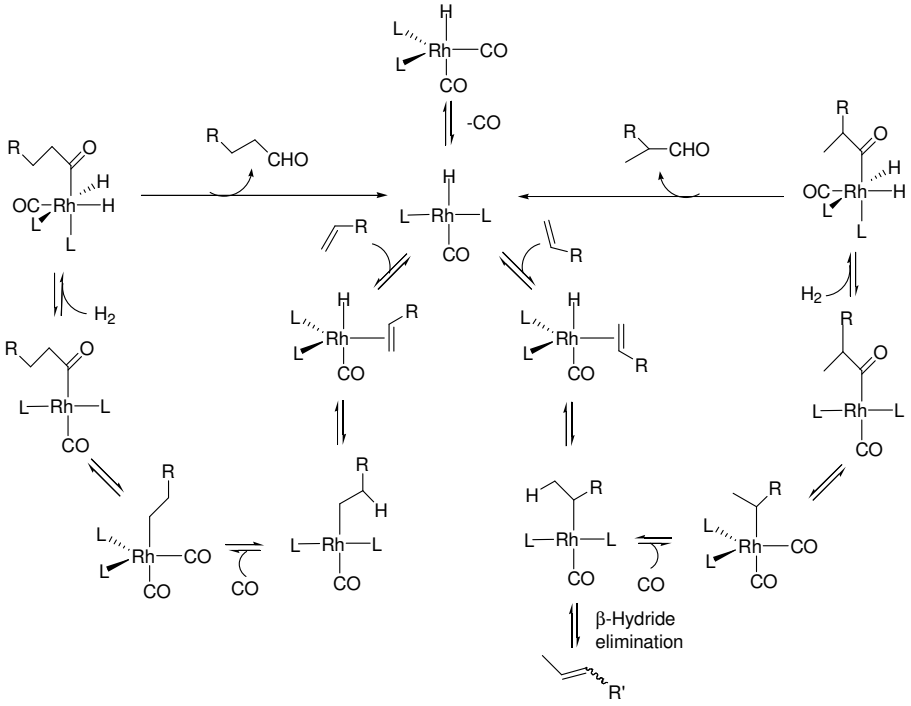


Figure 40. Accepted mechanism for the Rh-catalyzed hydroformylation of olefins.

The catalytic cycle begins with the dissociation of a carbon monoxide molecule from the catalyst precursor $[HRhL_2(CO)_2]$ (18-electron) intermediate, which has a trigonal bipyramidal structure. Next, the alkene substrate is added to a vacant coordination site of the metal, which generates a π-bonded alkene rhodium complex. The hydride then migrates towards alkene and a 1,2-insertion or 2,1-insertion takes place and a linear or branched rhodium alkyl complex is formed. The rhodium-alkyl complexes can also undergo β-hydride elimination, which, in the case of the branched alkyl complex, can lead to isomerized alkenes. In the

insertion step, a 16-electron species is formed. This rhodium alkyl species is electronically unsaturated and reacts with carbon monoxide to generate an 18-electron species. At low temperature and a sufficiently high carbon monoxide pressure, the insertion reaction is usually irreversible, so the regioselectivity of the reaction is fixed in this reaction step. The preference for the hydride migration to form the linear and branched alkyl toward the β-hydride elimination is a key step in the determination of the regioselectivity. There is then the migratory insertion of the alkyl group to one of the coordinated carbon monoxides, the oxidative addition of molecular hydrogen, the reductive elimination of the product aldehyde, and the regeneration of the species $[HRhL_2(CO)_2]$, which completes the catalytic cycle.

Asymmetric hydroformylation with transition metals is based on the modification of the catalytic system by bidentate phosphorus chiral ligands, which, to obtain high enantioselectivities, must be coordinated throughout the catalytic steps. The solution structures of the trigonal bipyramidal hydrodorhodium complexes with bidentate phosphorus ligand (P-P) $[HRh(P\text{-}P)(CO)_2]$, which are the resting states in the hydroformylation reaction, have been analyzed in detail.[xi] These complexes are generally assumed to have a trigonal bipyramidal structure. Two isomeric structures of these complexes are possible. These contain the bidentate ligand coordinated in a bis-equatorial (**ee**) or an equatorial-axial (**ea**) fashion (Figure 41). In certain cases, ^{31}P and ^{1}H NMR spectroscopy studies at variable temperature, together with IR studies, establish a relation between the results from catalysis, the coordination mode of the bidentate phosphorus ligand to the rhodium, and the selectivity of the hydride rhodium intermediates.[xi] The excellent selectivities obtained using some diphosphite and phosphine-phosphite ligands (see below) have been mainly attributed to the presence of only one active diastereoisomeric hydridorhodiumcarbonyl species.[xi] To design and synthesise chiral ligands is therefore a fundamental research subject in asymmetric hydroformylation.

ee **ea**

Figure 41. Equatorial-equatorial (**ee**) and equatorial-axial (**ea**) [HRh(P-P)$(CO)_2$] species.

1.4.2. Ligands

Since the early 1970s, transition metal complexes based on rhodium and platinum have been used as catalysts in asymmetric hydroformylation.[xi] High enantioselectivities have been obtained with Pt/diphosphine catalysts, but these suffer from low chemo- and regioselectivity.[xiii] In general, Rh/diphosphine catalysts have high catalytic activities and regioselectivities in branched aldehydes, but the ee's do not exceed 60%. Only in the case of the rhodium catalyst containing ferrocenylethyldiphenylphosphine was an enantioselectivity of up to 76% obtained with a very low conversion rate.[xiv] In the last decade, two new types of ligands (phosphine-phosphite and diphosphite ligands) have emerged as suitable for the Rh-asymmetric hydroformylation, yielding better activities and selectivities than the phosphine-based catalytic systems (Figure 42).[xv,xie,f] The presence of only one active diastereoisomeric hydridorhodiumcarbonyl species with the Rh-diphosphites (**ee**) and Rh-phosphine-phosphite (**ea**) system precursors is presumably the key to controlling efficient chirality transfer. So far BINAPHOS is the most versatile ligand for this process, providing high enantioselectivities in a wide range of both functionalized and internal alkenes.[xv]

As far as carbohydrate ligands are concerned, several types of bidentate ligands, mainly phosphorus donors (either homo or heterodonors), have been used in metal-catalyzed hydroformylation, but only one family of diphosphite ligands has provided excellent enantioselectivities.**¡Error! Marcador no definido.**

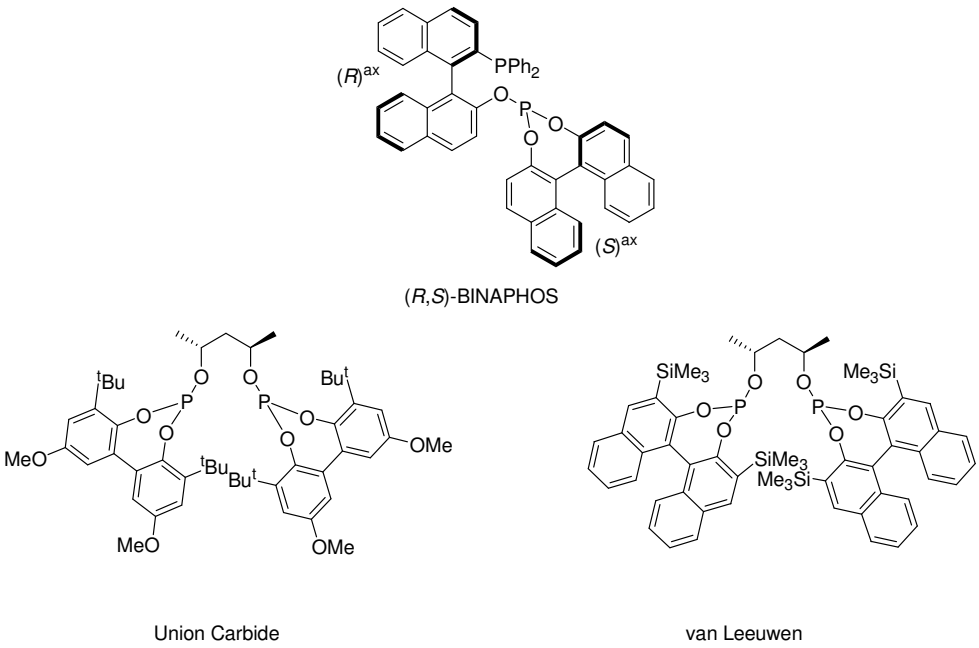


Figure 42. Most successful ligands developed for asymmetric hydroformylation.

In the next section we present the most relevant catalytic data on the metal-catalyzed asymmetric hydroformylation of olefins with carbohydrate ligands. We also discuss any reported mechanistic aspects according to the hydroformylation results.

2 1.4.2.1. P-donor ligands

Phosphine ligands

So far, only two families of carbohydrate-phosphine ligands have been reported for the hydroformylation of olefins[xvi] and the best results were obtained with the pyranoside diphosphine ligand **77**.[xvia] This ligand showed excellent enantioselectivities in the hydroformylation of vinyl acetate but low-to-moderate enantioselectivities for styrene and norbornene (Figure 43). The rather high enantioselectivity in the hydroformylation of vinyl acetate is explained by the

hydrogen bonding between the OH group in the ligand and the carbonyl group of the vinyl acetate.

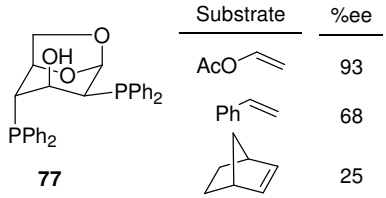


Figure 43. Rh-catalyzed asymmetric hydroformylation of olefins using ligand **77**.

Phosphinite ligands

So far only RajanBabu and coworkers have reported using sugar-based diphosphinite ligands **19a-h** (Figure 7) in the metal-catalyzed asymmetric hydroformylation of several olefins (metal= Rh, Ir, Pt and Co). The best results were in the hydroformylation of 2-vinylnaphthalene derivatives using a rhodium catalyst precursor (ee's up to 72% ee).[xvii]

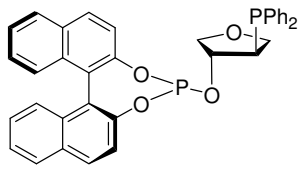
Phosphite Ligands

So far, only two families of carbohydrate-phosphite ligands have been reported for the hydroformylation of olefins.[xviii] However, the best results were obtained with the furanoside diphosphite ligands **24**-**29** (Figure 11) in the Rh-catalyzed hydroformylation of vinyl arenes.[xviiic-f] These ligands show excellent enantioselectivities (up to 93%) and excellent regioselectivities (up to 98.8%) under mild conditions. The hydroformylation results suggest that the level of enantioselectivity is influenced by a cooperative effect between stereocenters C-3 and C-5. The enantioselectivities were therefore best with ligands **27** and **28**. Also, the absolute configuration of the product outcome is governed by the configuration at the stereogenic center C-3. Both enantiomers of the product can therefore be obtained with high enantioselecitivities. The characterization of the rhodium complexes formed under hydroformylation conditions showed that there is a relationship between the structure of the [HRh(P-P)$(CO)_2$] (P-P=**24**-**29**) species and

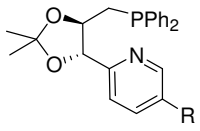
their enantiodiscriminating performance. Enantioselectivities were generally highest with ligands with a strong bis-equatorial (**ee**) coordination preference, and were considerably lower with an equilibrium of species with bis-equatorial (**ee**) and equatorial-axial (**ea**) coordination modes.

3 1.4.2.2. Heterodonor ligands

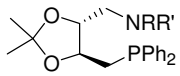
Several types of heterodonor carbohydrate ligands have been applied in asymmetric hydroformylation catalysis, but with little success (Figure 44).[xix]



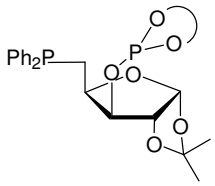
78 (ee's up to 45%)



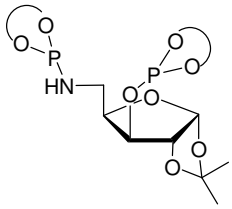
79 (ee's up to31%)



80 (ee's up to 23% ee)



81 (ee's up to 65%)



82 (ee's up to 65%)

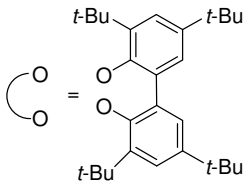


Figure 44. Heterodonor ligands **78**-**82** tested in asymmetric hydroformylation and their enantiomeric excesses.

1.5. References

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Objectives

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

The more specific aims are:

1. To synthesize new chiral diphosphinite and thioether-phosphinite ligands (Figure 1), with furanoside backbone, from inexpensive D-(+)-xylose. The modular construction of these ligands enables us to study the effect of: (a) the configuration of the C-3 of the carbohydrate backbone, (b) the introduction of a thioether moiety in C-5 and (c) the steric and electronic properties of thioether substituents in order to improve the selectivity of these reactions. We therefore studied the effect of the stereogenic carbon atom C-3 on the sugar backbone with diphosphinite ligands whose configuration of C-3 is opposite. Thioether-phosphinite ligands provided an insight into the effect of a thioether moiety at the carbon atom C-5.

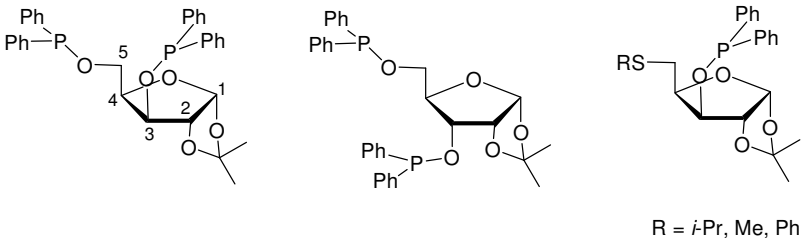


Figure 1. Furanoside ligands synthesized in this thesis.

2. To synthesize and characterize Rh and Ir complexes containing these ligands and their intermediates for the hydrogenation and hydroformylation reactions.

3. To apply these ligands in the asymmetric 1,4-addition of organocuprates to enones and asymmetric hydroformylation of vinyl arenes.

3. Furanoside diphosphinite and thioether-phosphinite ligands in asymmetric 1,4-addition

3.1. Background

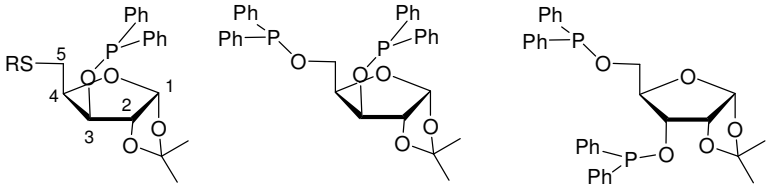
Most of the chiral ligands developed for highly enantioselective 1,4-addition of organozinc reagents to α,β–unsaturated compounds are P-donor and mixed P,N-donor ligands. Most phosphorus ligands are of the phosphite and phosphoramidite type. To our knowledge, diphosphinite and thioether-phosphinite ligands have not been applied before in this process. More research is therefore needed to study the possibilities offered by other classes of ligands in this process.

As we discussed in the introduction (Chapter 1), in the last few decades carbohydrates have been widely used in asymmetric catalysis. However, their full potential in providing chiral ligands has hardly been studied in 1,4-addition. Only a few highly enantioselective 1,4-additions, have been reported using these systems.

In this chapter, we report the application of the furanoside diphosphinite and thioether-phosphinite ligands in copper-catalyzed asymmetric 1,4-addition to 2-cyclohexenone. These applications show that activity and selectivity (chemo- and enantioselectivity) depend strongly on the type of functional group at the C-5 position of the carbohydrate backbone, the steric properties of the substituent in the thioether moiety, the catalyst precursor and the alkylating agent. Good enantioselectivities (up to 72%) and activities (TOF up to > 1225 mol product x (mol catalyst precursor x h) $^{-1}$) combined with excellent selectivity in 1,4 product were obtained.

3.2. Thioether-phosphinite and diphosphinite ligands derived from D-xylose for the copper-catalyzed asymmetric 1,4-addition to 2-cyclohexenone

We have tested their thioether-phosphinite (**1**-**3**) and diphosphinite (**4** and **5**) counterparts (Figure 1) in the enantioselective copper-catalyzed 1,4-addition to 2-cyclohexenone. To our knowledge, diphosphinite and thioether-phosphinite ligands have not applied before in this process.



1 R = *i*-Pr
2 R = Me
3 R = Ph

4 **5**

Figure 1. Furanoside thioether-phosphinite (**1**-**3**) and diphosphinite (**4** and **5**) ligands.

3.2.2. Results and Discussion

3.2.2.1. Ligands design

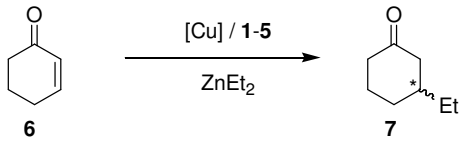
Ligands **1**-**5** consist of chiral 1,2-*O*-protected xylo- and ribo-furanoside backbones, which determines their underlying structure and either thioether (ligands **1**-**3**) or phosphinite (ligands **4** and **5**) groups at C-5 position.

We studied the influence of various substituents at the thioether groups using ligands **1**-**3**, which have the same phosphinite moiety.

We then used ligands **4** and **5** to study how a phosphinite moiety rather than the thioether functionality affected catalytic performance. We also studied how the configuration of the C-3 stereogenic center of the ligand backbone affected by comparing ligands **4** and **5**, which have opposite configuration at C-3.

3.2.2.2. Asymmetric conjugate 1,4-addition of ZnEt2

In a first set of experiments, we tested furanoside ligands **1**-**5** in the copper-catalyzed conjugate addition of diethylzinc to 2-cyclohexenone **6** (eq. 1). The latter was chosen as a substrate because this reaction has been performed with a wide range of ligands with several donor groups enabling the direct comparison of the efficiency of the various ligands systems.[¡Error! Marcador no definido.] The catalytic system was generated *in situ* by adding the corresponding ligand to a suspension of catalyst precursor. The results are shown in Table 1.



(1)

The effect of several reaction parameters, such as solvent, ligand-to-copper ratio and catalyst precursor, were studied using ligand **1** (entries 1-8).

Our results showed that the efficiency of the process depended on the nature of the solvent (entries 1-3). Therefore, the selectivity (chemoselectivity in 1,4-product and enantioselectivity) was best when dichloromethane was used.

Adding one-fold excess of ligand led to higher chemoselectivity in 1,4-product and enantioselectivity (entry 4). However, the outcome of the reaction was not affected when a greater excess of ligand was added (entry 5).

Varying the catalyst precursor showed an effect on the selectivity of the process (entries 6-8). The best trade-off between chemoselectivities and enantioselectivities was therefore achieved with the catalyst precursors CuCN and $[Cu(MeCN)_4]BF_4$. Interestingly, the sense of the asymmetric induction obtained with these catalyst precursors was the opposite of that for the catalyst precursor $Cu(OTf)_2$. The nature of the catalyst precursor is therefore also important in determining enantioselectivity.

Under the optimised conditions, we then studied how the thioether substituents affected the catalytic performance with ligands **2** and **3**. Using ligand **2** with a methyl substituent in the thioether moiety showed lower enantioselectivity (entries 9 and 10). Using ligand **3** with a phenyl substituent in the thioether moiety showed the lowest asymmetric induction (entry 11 and 12).

Table 1. Cu-catalyzed asymmetric 1,4-addition of diethylzinc to 2-cyclohexenone **6** using ligands **1**-**5**.[a]

Entry	Ligand	Solvent	Catalyst precursor	% Conv (h)[b]	1,4-Product(%)[c]	% ee [d]
1	**1**	CH_2Cl_2	$Cu(OTf)_2$	100 (2)	55	25 (*S*)
2	**1**	Toluene	$Cu(OTf)_2$	100 (2)	45	10 (*S*)
3	**1**	THF	$Cu(OTf)_2$	100 (2)	45	12 (*S*)
4[e]	**1**	CH_2Cl_2	$Cu(OTf)_2$	100 (2)	60	34 (*S*)
5[f]	**1**	CH_2Cl_2	$Cu(OTf)_2$	100 (2)	59	33 (*S*)
6[e]	**1**	CH_2Cl_2	CuI	100 (2)	100	55 (*R*)
7[e]	**1**	CH_2Cl_2	CuCN	100 (2)	100	64 (*R*)
8[e]	**1**	CH_2Cl_2	$[Cu(MeCN)_4]BF_4$	100 (2)	100	63 (*R*)
9[e]	**2**	CH_2Cl_2	CuCN	100 (2)	85	26 (*R*)
10[e]	**2**	CH_2Cl_2	$[Cu(MeCN)_4]BF_4$	100 (2)	100	53 (*R*)
11[e]	**3**	CH_2Cl_2	CuCN	100 (2)	98	2 (*R*)
12[e]	**3**	CH_2Cl_2	$[Cu(MeCN)_4]BF_4$	100 (2)	100	15 (*R*)
13	**4**	CH_2Cl_2	CuCN	97 (1.30)	38	17 (*S*)
14	**4**	CH_2Cl_2	$[Cu(MeCN)_4]BF_4$	97 (1)	69	25 (*S*)
15	**5**	CH_2Cl_2	$[Cu(MeCN)_4]BF_4$	96 (1)	68	29 (*S*)
16[e,g]	**1**	CH_2Cl_2	CuCN	63 (2)	100	72 *(R)*

[a] Reaction conditions: catalyst precursor (0.025 mmol), ligand (0,025 mmol), $ZnEt_2$ (3.5 mmol), substrate (2.5 mmol), solvent (6 ml), room temperature.[b] Measured by GC using undecane as internal standard. Reaction time in hours shown in parentheses. [c] Chemoselectivity in 1,4-product determined by GC using undecane as internal standard. [d] Determined by GC using Lipodex-A column. Absolute configuration drawn in parentheses. [e]L/Cu = 2. [f]L/Cu = 4. [g]T = 0ºC.

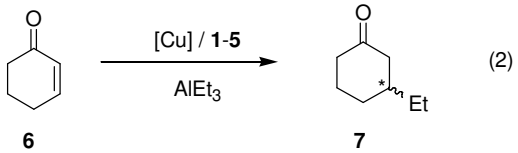
The influence of the phosphinite moiety rather than the thioether functionality was studied with ligands **4** and **5** (entries 13-15). In general, these ligands led to lower enantioselectivities and chemoselecitivities with higher

activities. Interestingly, the sense of asymmetric induction was the opposite of that obtained with the catalytic systems Cu/**1**-**3**. Also, if we compare the results obtained with ligands **4** and **5** we can see that the configuration of C-3, of the carbohydrate backbone, had no effect in the catalytic performance of the process (entries 14 and 15)

Finally, we also studied how the temperature affected the outcome of the reaction with ligand **1**. Lowering the temperature to 0ºC increased enantioselectivity (up to 72%) (entries 7 *vs* 16). This phenomenon was also observed for related furanoside Cu-thioether-phosphite systems. **¡Error! Marcador no definido.**

3.2.2.3. Asymmetric conjugate 1,4-addition of $AlEt_3$

Michael additions of organolitium, Grignard and diorganozinc reagents to enones have been widely studied in the last decade but very little attention has been paid to trialkylaluminium reagents.**¡Error! Marcador no definido.**,**¡Error! Marcador no definido.** Bearing in mind the positive effect when we used triethylaluminium rather than diethylzinc as the alkylating reagent, we also studied the use of triethylaluminium.**¡Error! Marcador no definido.** Table 2 shows the results of the copper-catalyzed conjugate addition of trialkylaluminium to 2-cyclohexenone **6** (eq. 2) using the thioether- phosphinite (**1**-**3**) and diphosphinite (**4** and **5**) ligands. The catalytic system was generated *in situ* by adding the corresponding ligand to a suspension of catalyst precursor.



6 **7** (2)

Our preliminary investigations into the solvent effect, the ligand-to-copper ratio and catalyst precursor using ligand **1** (Table 2, entries 1-7) indicated that the

optimum trade-off between chemoselectivities and enantioselectivities was obtained when dichloromethane was used as solvent, the ligand-to-copper ratio was 2 and $Cu(OTf)_2$ and $[Cu(MeCN)_4]BF_4$ were used as catalyst precursor (entries 4 and 7).

Under optimised conditions, the results with ligands **1**-**3** (Table 2, entries 4, 7-11) indicate that the chemoselectivities and enantioselectivities followed a different trend to those for the copper-catalyzed conjugate addition of diethylzinc to 2-cyclohexenone **6** (Table 1, entries 7-12). Enantioselectivity was therefore best with ligand **3**, which contains a phenyl substituent in the thioether moiety, while ligand **1** provided the lowest asymmetric induction in this case. Note that with ligands **2** and **3** the best catalyst precursor was $[Cu(MeCN)_4]BF_4$.

In general, diphosphinite ligands **4** and **5** showed much higher reaction rates (TOF up to > 1225 mol product x (mol catalyst precursor x h)$^{-1}$) but lower enantioselectivities than the Cu-thioether-phosphinite ligand systems (entries 12-16). Unlike thioether-phosphinite ligands, with diphosphinite ligands excess of ligand decreased activity, chemoselectivity and enantioselectivity (entries 14 vs 15). The same effect was observed by decreasing the catalyst loading (entry 16). If we compare entries 13 and 14, we can see that the configuration at C-3 affected the product outcome. Therefore, ligand **5**, with an *R* configuration of C-3, obtained a better enantioselectivity than the catalytic system Cu/**4**.

We studied how temperature affected the outcome of the reaction with ligand **3**. Lowering the temperature to 0ºC increased enantioselectivity (up to 48%) (entries 11 *vs* 17).

If we compare the results of using $AlEt_3$ with the results of using $ZnEt_2$, we can conclude that with thioether-phosphinite ligands activity was higher but enantioselectivity was lower using $AlEt_3$. However, for diphosphinite ligands $AlEt_3$ produced much higher activities and chemoselectivity in 1,4-product than $ZnEt_2$ with similar enantioselectivity.

Table 2. Cu-catalyzed asymmetric 1,4-addition of triethylaluminium to 2-cyclohexenone **6** using ligands **1**-**5**.[a]

Entry	Ligand	Solvent	Catalyst precursor	% Conv (min)[b]	1,4-Product(%)[c]	% ee [d]
1	**1**	CH_2Cl_2	$Cu(OTf)_2$	100 (20)	65	9 (*R*)
2	**1**	Toluene	$Cu(OTf)_2$	100 (20)	60	8 (*S*)
3	**1**	THF	$Cu(OTf)_2$	100 (20)	55	3 (*R*)
4[e]	**1**	CH_2Cl_2	$Cu(OTf)_2$	100 (20)	100	9 (*R*)
5[e]	**1**	CH_2Cl_2	CuI	100 (20)	95	1 (*R*)
6[e]	**1**	CH_2Cl_2	CuCN	100 (20)	94	5 (*S*)
7[e]	**1**	CH_2Cl_2	$[Cu(MeCN)_4]BF_4$	100 (20)	100	10 (*R*)
8[e]	**2**	CH_2Cl_2	$Cu(OTf)_2$	100 (20)	95	15 (*S*)
9[e]	**2**	CH_2Cl_2	$[Cu(MeCN)_4]BF_4$	100 (20)	100	33 (*S*)
10[e]	**3**	CH_2Cl_2	$Cu(OTf)_2$	100 (20)	95	27 (*R*)
11[e]	**3**	CH_2Cl_2	$[Cu(MeCN)_4]BF_4$	100 (20)	100	36 (*S*)
12	**4**	CH_2Cl_2	$Cu(OTf)_2$	91 (5)	48	12 (*S*)
13	**4**	CH_2Cl_2	$[Cu(MeCN)_4]BF_4$	94 (5)	100	24 (*S*)
14	**5**	CH_2Cl_2	$[Cu(MeCN)_4]BF_4$	97 (5)	100	32 (*S*)
15[e]	**5**	CH_2Cl_2	$[Cu(MeCN)_4]BF_4$	91 (10)	65	14 (*S*)
16[f]	**5**	CH_2Cl_2	$[Cu(MeCN)_4]BF_4$	93 (10)	62	20 (*S*)
17[e,g]	**3**	CH_2Cl_2	$[Cu(MeCN)_4]BF_4$	100 (60)	100	48 (*S*)

[a] Reaction conditions: catalyst precursor (0.025 mmol), ligand (0,025 mmol), $AlEt_3$ (3.5 mmol), substrate (2.5 mmol), solvent (6 ml), room temperature.[b] Measured by GC using undecane as internal standard. Reaction time in minutes shown in parentheses. [c] Chemoselectivity in 1,4-product determined by GC using undecane as internal standard. [d] Determined by GC using Lipodex-A colmn. Absolute configuration drawn in parentheses. [e] L/Cu = 2. [f] L/Cu = 0.5. [g] T= 0ºC.

3.2.4. Experimental Section

3.2.4.1. General Comments

All syntheses were performed using standard Schlenk techniques under argon atmosphere. Solvents were purified by standard procedures. Thioether-

phosphinites **1**-**3** and diphosphinites **4** and **5** prepared by previously described methods. All other reagents were used as commercially available.

3.2.4.2. Typical procedure for the catalytic conjugate addition of diethylzinc to 2-cyclohexenone (6).

In a typical procedure, a solution of copper-catalyst precursor (0.025 mmol) and furanoside ligand (0.025 ml) in dichlorometane (3 mL) was stirred for 30 minutes at room temperature. After cooling to 0 ºC, diethylzinc (1 M sol. in hexanes, 3.5 mL, 3.5 mmol) was added. A solution of 2-cyclohexenone (0.24 mL, 2.5 mmol) and undecane as GC internal standard (0.25 mL) in dichlorometane (3 mL) was then added at the corresponding reaction temperature. The reaction was monitored by GC. The reaction was quenched with HCl (2 M) and filtered twice through flash silica. Conversion, chemoselectivity and enantioselectivity were obtained by GC using a Lipodex-A columm.

3.2.4.3. Typical procedure for the catalytic conjugate addition of triethylaluminium to 2-cyclohexenone (6).

In a typical procedure, a solution of copper-catalyst precursor (0.025 ml) and furanoside ligand (0.025 ml) in dichlorometane (3 mL) was stirred for 30 minutes at room temperature. Triethylaluminium (1 M sol. in hexanes, 3.5 mL, 3.5 mmol) was added at the corresponding temperature. A solution of 2-cyclohexenone (0.24 mL, 2.5 mmol) and undecane as GC internal standard (0.25 mL) in dichlorometane (3 mL) was then added. The reaction was monitored by GC. The reaction was quenched with HCl (2 M) and filtered twice through flash silica. Conversion, chemoselectivity and enantioselectivity were obtained by GC using a Lipodex-A columm.

4. Furanoside diphosphinite ligands in asymmetric hydroformylation

4.1. Background

Most of the chiral ligands developed for asymmetric hydroformylation are P-donor ligands. Of these, phosphine-phosphite and diphosphite ligands have provided the catalytic systems with the best selectivity (see Chapter 1). Most research has therefore been devoted to studying these systems and less has been done with diphosphinite ligands. However, some phosphinite ligand systems have also provided promising results for this process (Figure 1; enantioselecitivies up to 75%). This encourages further research into phosphinite ligands.

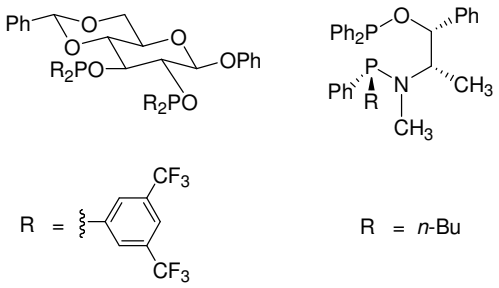


Figure 1. Most successful phosphinite ligands developed for asymmetric hydroformylation.

Unlike in the previous chapters, we did not apply the thioether-phosphinite ligands to asymmetric hydroformylation. The phosphite-thioether ligands that have been developed for this process provide low enantioselectivity. This was demonstrated by NMR studies under hydroformylation conditions, which indicated that the thioether is not coordinated in mononuclear hydride-rhodium complexes.

In this chapter, we report the application of furanoside diphosphinites in the Rh-catalyzed asymmetric hydroformylation of several vinyl arenes. We also report, for the first time, the structure in solution of the species formed under hydroformylation conditions with these diphosphinite ligands.

4.2. Asymmetric hydroformylation of vinyl arenes catalyzed by furanoside diphosphinites-Rh(I) complexes.

We report here the use of previously described furanoside diphosphinite ligands **2** and **3** (Figure 1) in the asymmetric Rh-catalyzed hydroformylation of several vinyl arenes. We also discuss for the first time the structures in solution of the important intermediate species [HRh(P-P)$(CO)_2$] formed under hydroformylation conditions using diphosphinite ligands.

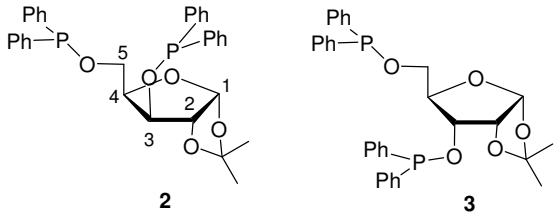


Figure 1. Diphosphinite ligands **2** and **3**.

4.2.2. Results and Discussion

6.2.2.1. Asymmetric hydroformylation of vinyl arenes

Diphosphinites **2** and **3** were tested in the rhodium-catalyzed asymmetric hydroformylation of several vinyl arenes under several reaction conditions. In a first set of experiments, we used ligands **2** and **3** in the rhodium-catalysed

asymmetric hydroformylation of styrene, which is widely used as a model substrate.

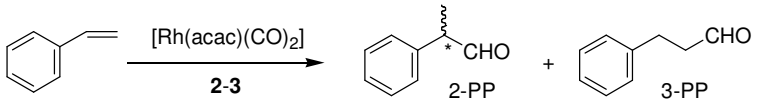
The catalysts were prepared *in situ* by adding the corresponding diphosphinite ligand to [Rh(acac)$(CO)_2$] as a catalyst precursor. The conversion and selectivity results are summarized in Table 1. Hydrogenated or polymerized products of styrene were not observed.

The effects of several reaction parameters (i.e. CO/H_2 pressure, ligand-to-rhodium ratio, CO/H_2 pressure ratio, solvents and temperature) were investigated for the catalytic precursor containing ligand **2**.

Activity and selectivity to the branched aldehyde improved when the pressure was raised from 10 bar to 30, while the enantioselectivity remained the same (entry 1 vs. 2). However, further increasing the *syn* gas pressure had a positive effect on the activity, while the regio- and enantioselectivity were unaffected (entry 3).

Varying the ligand-to-rhodium ratio showed that this catalyst system is highly stable under hydroformylation conditions and no excess of ligand is needed (entries 2, 4 and 5). After identical catalyst preparation, we carried out a hydroformylation experiment under a lower CO/H_2 pressure ratio (entry 6). Our results clearly show that higher partial pressures of H_2 lead to higher initial turnover frequencies. Moreover, if we compare entries 2 and 6, we can see that both regio- and enantioselectivity are hardly affected by changes in the H_2 partial pressure.

Table 1. Asymmetric hydroformylation of styrene catalysed by [Rh(acac)$(CO)_2$] / diphosphinite **2**-**3**.[a]



Entry	Ligand	P (bar)	CO/H_2[b]	TOF[c]	%Conv (h)[d]	%2-PP[e]	%ee[f]
1	**2**	10	1	15	39 (24)	68	2 (*R*)

2	**2**	30	1	77	85 (8)	90	3 (*R*)
3	**2**	60	1	434[g]	62 (1)	90	3 (*R*)
4[h]	**2**	30	1	78	86 (8)	90	3 (*R*)
5[i]	**2**	30	1	78	86 (8)	91	3 (*R*)
6	**2**	30	0.5	90	84 (5)	90	4 (*R*)
7[j]	**2**	30	0.5	30	73 (24)	90	5 (*R*)
8[k]	**2**	30	0.5	16	24 (8)	90	3 (*R*)
9[l]	**2**	30	0.5	18	54 (24)	90	8 (*R*)
10	**3**	30	0.5	67	85 (8)	90	10 (*R*)

[a] Reaction conditions: T = 40 ºC, styrene (9.1 mmol), $Rh(acac)(CO)_2$ (0.013 mmol), ligand/Rh = 1.1, toluene (15 mL). [b] pCO/pH_2 ratio. [c] TOF in mol styrene × mol Rh^{-1} × h^{-1} determined after 5 h reaction time by GC. [d] % Conversion of styrene. [e] Regioselectivity in 2-phenylpropanal. [f] % Enantiomeric excess measured by GC. [g] TOF measured after 1 h. [h] Ligand/Rh = 2. [i] Ligand/Rh = 4. [j] THF as solvent. [k] Et_3SiH as solvent. [l] T = 20 ºC.

The type of solvent was important for the activity of the process but had little effect on regioselectivity or enantioselectivity (entries 7 and 8 vs 6). This contradicts with the results of RajanBabu and coworkers for the asymmetric hydroformylation of vinylarenes using diphosphinite ligands. These authors found a notable positive effect on enantioselectivity when Et_3SiH was used as a solvent.[¡Error! Marcador no definido.a-c]

Lowering the temperature to 20 ºC led to an increase in enantioselectivity (up to 8%) (entry 6 vs 9).

The use of ligand **3**, whose configuration of carbon atom C-3 is opposite, led to lower activity and slightly higher enantioselectivity than catalyst system Rh/**2** (entry 6 *vs* 10). In both cases, the major enantiomer of the product was the same. This behaviour contrasts with that of related diphosphite ligands, for which the absolute configuration of the stereogenic carbon atom C-3 controlled the configuration of the hydroformylation product.[¡Error! Marcador no definido.f]

We then applied these diphosphinite ligands **2** and **3** in the Rh-catalyzed asymmetric hydroformylation of other vinyl arenes (Table 2).

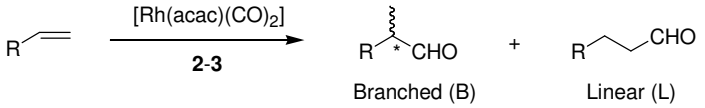
The presence of a fluoro substituent in the *para* position of the substrate hardly affected conversion, regioselectivity and enantioselectivity (Table 2 entries 1 and 7 vs 2 and 8). However, the presence of *para*-methoxy- (entries 3 and 9) and naphthyl (entries 4,5,10 and 11) substituents of the substrate had a clear positive effect on enantioselectivities (up to 55%). In the hydroformylation of substrates 2-vinylnaphthalene and 6-methoxy-2-vinylnaphthalene, the positive effect was also in the regioselectivity of the process (up to 99).

Again, the use of ligand **3** hardly affected the conversion, regioselectivity and enantioselectivity of the process (entries 1-5 vs 7-11).

Interestingly, in the hydroformylation of substrates *para*-methoxystyrene, 2-vinylnaphthalene and 6-methoxy-2-vinylnaphthalene, activity, regio- and enantioselectivity improved when the *syn* gas pressure was raised from 30 bar to 60 bar (entries 12-14).

Lowering the temperature to 20 ^{o}C led to an increase in enantioselectivity (up to 63%) (entries 6 and 15).

Table 2. Asymmetric hydroformylation of vinyl arenes catalysed by [Rh(acac)(CO)$_2$] / diphosphinite **2**-**3**.[a]



Entry	Ligand	R	TOF[b]	%Conv (h)[c]	%Regio[d]	%ee[e]
1	**2**	C_6H_5	90	84 (5)	90	4 (*R*)
2	**2**	4-F-C_6H_4	78	100 (8)	92	2 (*R*)
3	**2**	4-OMe-C_6H_4	49	55 (8)	90	55 (*S*)
4	**2**	2-Naphthyl	67	48 (5)	97	53 (*S*)
5	**2**	6-OMe-2-Naphthyl	27	29 (8)	99	53 (+)
6[f]	**2**	2-Naphthyl	8.6	22 (18)	97	59 (*S*)
7	**3**	C_6H_5	67	85 (8)	90	10 (*R*)
8	**3**	4-F-C_6H_4	79	100 (8)	91	4 (*R*)
9	**3**	4-OMe-C_6H_4	56	56 (8)	90	54 (*S*)

10	**3**	2-Naphthyl	71	51 (5)	97	53 (*S*)
11	**3**	6-OMe-2-Naphthyl	28	31 (8)	99	53 (+)
12[g]	**2**	4-OMe-C_6H_4	118	42 (2.5)	95	57 (*S*)
13[g]	**2**	2-Naphthyl	274	98 (2.5)	99	58 (*S*)
14[g]	**2**	6-OMe-2-Naphthyl	154	55 (2.5)	99	59 (+)
15[f, g]	**2**	2-Naphthyl	91	32 (2.5)	99	63 (*S*)

[a] Reaction conditions: T = 40 ºC, P= 30 bar, substrate (9.1 mmol), $Rh(acac)(CO)_2$ (0.013 mmol), ligand/Rh = 1.1, toluene (15 mL). pCO/pH_2 = 0.5. [b] TOF in mol substrate × mol Rh^{-1} × h^{-1} determined after 5 h reaction time by GC. [c] % Conversion of substrate. [d] Regioselectivity in branched aldehyde. [e] % Enantiomeric excess measured by GC. [f] T = 20 ºC. [g] Pressure = 60 bar. TOF measured after 1h.

To sum up, if we compare ligands **2** and **3** with ligand **1b**, which has the same substituent in the phosphinite moiety, we can see that the furanoside backbone is more effective in transferring the chirality than the pyranoside backbone. With readily available diphenyl diphosphinite ligands **2** and **3**, it therefore obtains, under milder conditions, similar enantiomeric excesses to the best one reported in the literature for the diphosphinite ligand system **1a**, which has electron deficient aryl groups at phosphorus.[¡Error! Marcador no definido.a-c] In addition, the regioselectivity in the branched product obtained with the catalytic systems containing ligands **2** and **3** is higher than with ligands **1**.

4.2.2.2. Characterization of [HRh(P-P)$(CO)_2$] complexes.

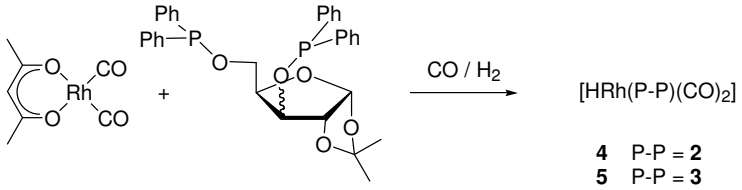
As commented in Chapter 1, the [HRh(P-P)$(CO)_2$] (P-P = bidentate ligand) species are known to be the resting state in the hydroformylation reaction. [¡Error! Marcador no definido.] These complexes are generally assumed to have a trigonal bipyramidal structure. Two isomeric structures of these complexes, containing the bidentate ligand coordinated in a bis-equatorial (**ee**) or an equatorial-axial (**ea**) fashion (Figure 2), are possible. The presence of only one active diastereoisomeric hydridorhodiumcarbonyl species with the Rh-diphosphites (**ee**) and Rh-phosphine-

phosphite (**ea**) systems precursors is presumably the key to controlling efficient chirality transfer.[¡Error! Marcador no definido.]

Figure 2. Equatorial-equatorial (**ee**) and equatorial-axial (**ea**) [HRh(P-P)$(CO)_2$].

To obtain information about the structures in solution of [HRh(P-P)$(CO)_2$] species formed under hydroformylation conditions (PP = diphosphinite ligands **2** and **3**), we used high pressure NMR (HP-NMR) and high pressure IR (HP-IR).

These [HRh(P-P)$(CO)_2$] (PP = **2** and **3**) species were prepared *in situ* under hydroformylation conditions by adding 1.1 equivalent of diphosphinite ligand to the catalyst precursor [Rh(acac)$(CO)_2$] (Scheme 2). The spectroscopic data are summarized in Table 3.



Scheme 2. Preparation of complexes **4-5**.

Table 3. Selected ^{1}H and ^{31}P NMR data for [HRh(P-P)$(CO)_2$] complexes **4-5**.[a]

Complex	δ P_1	δ P_2	$^{1}J_{Rh-P1}$	$^{1}J_{Rh-P2}$	$^{2}J_{P1-P2}$	δ H	J_{H-X}
4	126.0	126.7	155.4	160.9	72.8	-9.28 (bd)	3.9
5	125.5	126.3	155.3	160.9	72.5	-9.62 (bd)	4.5

[a] Prepared in toluene-d_8. δ in ppm. Coupling constants in Hz. (bd= broad doublet). X=Rh, P.

At room temperature, the $^{31}P\{^{1}H\}$ NMR spectra of complexes **4** and **5** showed an eight sharp line spectrum due to the two non-equivalent coordinated phosphorus atoms and a rhodium atom (ABX system). The same NMR pattern was observed at low temperature (298-193 K). The simulation of these signals affords the two phosphorus atoms located at 126.0 ($^{1}J_{Rh-P1}$ = 155.4 Hz, $^{2}J_{P1-P2}$ = 72.8 Hz) and 126.7 ($^{1}J_{Rh-P2}$ = 160.9 Hz, $^{2}J_{P1-P2}$ = 72.8 Hz) for complex **4** and at 125.5 ($^{1}J_{Rh-P1}$ = 155.3 Hz, $^{2}J_{P1-P2}$ = 72.5 Hz) and 126.3 ($^{1}J_{Rh-P2}$ = 160.9 Hz, $^{2}J_{P1-P2}$ = 72.5 Hz) for complex **5**. The large values for the $^{1}J_{P-Rh}$ are characteristic of phosphinite ligands coordinated in an equatorial position.[xix]

For both complexes, the ^{1}H NMR spectra in the hydride region revealed a broad doublet. This indicates that both the J_{Rh-H} and the J_{P-H} coupling constants are small. No better resolution was found even at temperatures as low as 193 K. However, these small values of the phosphorus-hydride coupling constants ($^{2}J_{P-H} \leq$ 3.9 Hz for complex **4** and $^{2}J_{P-H} \leq$ 4.5 Hz for complex **5**) are typical of a trigonal bipyramidal (TBP) hydridorhodium dicarbonyl species with bis-equatorially (**ee**) coordinating phosphorus.[xix] Small *cis* phosphorous-hydride coupling are characteristic of phosphinite ligands coordinated in an equatorial position.[¡Error! Marcador no definido.a] Large J_{P-H} constants have already been reported for a phosphinite ligand in an axial position.[¡Error! Marcador no definido.b]

We confirmed the presence of only equatorial-equatorial species by carrying out the HP-IR spectroscopy. For complex **4**, the spectrum showed two bands in the carbonyl region at 1972 (m) and 2040 (s) cm^{-1} that are characteristic of phosphorous ligands coordinated in an equatorial position.[¡Error! Marcador no definido.] If an equilibrium between equatorial-equatorial and equatorial-axial isomers occurs, two sets of carbonyl frequencies originating from the two isomers should be observed.[xix]

In summary, NMR data indicate trigonal bipyramidal (TBP) hydridorhodium dicarbonyl species with equatorial-equatorial coordinating diphosphinites. Further

evidence is provided by IR *in situ* measurements. Moreover, the formation of only one diastereoisomer was confirmed by variable temperature NMR.

6.2.3. Conclusions

Diphosphinite ligands **2** and **3** were tested in the Rh-catalyzed asymmetric hydroformylation of several vinyl arenes. High regioselectivities in branched aldehyde (up to 99%) and moderate enantioselectivities (up to 63%) were obtained. The results showed a remarkable substrate effect on enantioselectivity. Thus, the presence of *para*-methoxy and naphthyl substituents in the substrate had a positive effect on enantioselectivities.

The characterization of the rhodium complexes formed under hydroformylation conditions by NMR techniques and in situ IR spectroscopy showed that the hydridorhodium dicarbonyl species exist in one diastereosiomeric equatorial-equatorial form. However, this strong coordination preference did not allow high enantioselectivity.

4.2.4. Experimental Section

4.2.4.1. General comments

All experiments were carried out under argon atmosphere. All the solvents were dried using standard methods and distilled prior to use**.** Compounds **2**-**3** were prepared as previously described (Chapter 3, Section 3.2.4.2). ^{1}H and $^{31}P\{^{1}H\}$ NMR spectra were recorded on a Varian Gemini 400 MHz spectrometer. Chemical shifts are relative to $SiMe_4$ (^{1}H) as internal standard or H_3PO_4 (^{31}P) as external standard. Gas chromatographic analyses were run on a Hewlett-Packard HP 5890A instrument (split/splitless injector, J&W Scientific, Ultra-2 25 m column, internal diameter 0.2 mm, film thickness 0.33 mm, carrier gas: 150 kPa He, F.I.D. detector)

equipped with a Hewlett-Packard HP 3396 series II integrator. Hydroformylation reactions were carried out in a home-made 100 mL stainless steel autoclave.[xix] Enantiomeric excesses were measured after the aldehydes had been oxidised to their corresponding carboxylic acids[xix] with a Hewlett-Packard HP 5890A gas chromatograph (split/splitless injector, J&W Scientific, FS-Cyclodex β-I/P 50 m column, internal diameter 0.2 mm, film thickness 0.33 mm, carrier gas: 100 kPa He, F.I.D. detector).

4.2.4.2. Hydroformylation of vinyl arenes

In a typical experiment, the autoclave was purged three times with CO. The solution was formed from [Rh(acac)$(CO)_2$] (0.013 mmol), diphosphinite (0.014 mmol) and the corresponding substrate (9.1 mmol) in toluene (15 mL). The autoclave was then pressurized with *syn* gas and heated to the reaction temperature, and the reaction mixture was stirred. During the reaction, several samples were taken out of the autoclave. After the desired reaction time, the autoclave was cooled to room temperature and depressurized. The reaction mixture was analyzed by gas chromatography.

4.2.4.3. *In situ* HP-NMR hydroformylation experiments

In a typical experiment, a sapphire tube (d = 10 mm) was filled under argon with a solution of [Rh(acac)$(CO)_2$] (0.030 mmol) and ligand (molar ratio PP/Rh =1.1) in toluene-d8 (1.5 mL). The HP-NMR tube was purged twice with CO and pressurized to the appropriate pressure of CO/H_2. After a reaction time of 1 hour shaking at the desired temperature, the solution was analyzed.

4.2.4.4. High-pressure IR experiments

These experiments were performed in an SS 316 50 mL autoclave equipped with IRTRAN windows (ZnS, transparent up to 70 cm^{-1}, 10 mm i.d. optical path

length 0.4 mm), a mechanical stirrer, a temperature controller, and a pressure device. In a typical experiment, a degassed solution of [Rh(acac)$(CO)_2$] (0.013 mmol) and diphosphinite ligand (0.014 mmol) in methyltetrahydrofuran (15 mL) was introduced into the high-pressure IR autoclave. The autoclave was purged twice with CO, pressurized to 30 bar of CO/H_2 and heated to 40°C. The autoclave was placed in the IR spectrometer and the spectra were recorded.

Conclusions

1. Chapter 3. *Furanoside diphosphinite and thioether-phosphinite ligands in asymmetric hydrogenation*. The conclusions of this chapter can be summarized as follows:

- In the asymmetric hydrogenation of prochiral olefins with catalyst precursors based on diphosphinite we observed important effects of the metal source, the absolute configuration of the C-3 stereocenter of the carbohydrate backbone and the substrate structure. The catalytic Rh-ribofuranoside and Ir-xilofuranoside diphosphinite systems therefore provide ee's up to 78%, while the Rh-xilofuranoside and Ir-ribofuranoside diphosphinite systems provide ee's only up to 15%. Results for methyl *N*-acylaminoacrylates were satisfactory, while enantiomeric excesses for methyl *N*-acetamidocinnamate and dimethyl itaconate were low.
- Asymmetric hydrogenation with catalyst precursors containing the thioether-phosphinite ligand shows that 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 along with the metal Rh had a positive effect on enantioselectivity. Results for α-acylaminoacrylate derivatives were satisfactory (up to 96% ee), while enantiomeric excesses for itaconic acid derivatives were lower (up to 64% ee).

If we compare these results with those from the catalyst precursor containing the previous diphosphinite ligands, we find that introducing a thioether substituent in C-5 improves enantioselectivity.

Our detailed structural studies of the complexes $[M(cod)(P\text{-}SR)]BF_4$ (M=Rh, Ir) and $[IrH_2(cod)(P\text{-}SR)]BF_4$ shows that the axial disposition of the sulfur substituents is crucial for high enantioselectivities because it fixes the orientation of the P-phenyl substituent in an edge-on/face-on relationship.

The characterization of the iridium *cis*-dihydridoiridium(III) complexes indicates that only one isomer was present for complexes $[IrH_2(cod)(P\text{-}SPh)]BF_4$ and $[IrH_2(cod)(P\text{-}SMe)]BF_4$. However, for complex $[IrH_2(cod)(P\text{-}S\textit{i}\text{-}Pr)]BF_4$, which contains the more hindered substituent on sulfur, two isomers were detected. Interestingly, despite this lack of selectivity, $[IrH_2(cod)(P\text{-}S\textit{i}\text{-}Pr)]BF_4$ provided the best enantioselectivities.

2. Chapter 4. *Furanoside diphosphinite and thioether-phosphinite ligands in asymmetric allylic substitution*. The conclusions of this chapter can be summarized as follows:

- Using diphosphinite ligands as chiral auxiliaries in the asymmetric allylic alkylation provided good activity (TOF > 200 mol product x (mol catalyst precursor x h)$^{-1}$) but low enantioselectivity (ee's up to 31%). Our results show that the absolute configuration at carbon C-3 of the carbohydrate backbone controlled the sense of enantioselectivity and that the nucleophilic attack takes place *trans* to the phosphinite moiety attached to C-5.
- Asymmetric allylic substitution with catalyst precursors containing the thioether-phosphinite ligand shows that enantiomeric excesses depend strongly on the steric properties of the substituent in the thioether moiety and the substrate structure. A bulky group in the thioether moiety had a positive effect on enantioselectivity. Results for the linear

substrate were satisfactory (ee's up to 93%), while enantiomeric excesses for the cyclic substrate were low (up to 51%).

If we compare these results with those from the catalyst precursor containing the previous diphosphinite ligands, we find that introducing a thioether substituent in C-5 improves enantioselectivity (from 31% to 93% ee) while activities remain constant.

The strong *trans* influence of the phosphinite moiety, together with the effect of the thioether moiety on enantioselectivity, confirms that the nucleophilic attack takes place at the allyl terminus located *trans* to C-3 (phosphinite moiety). This contrasts with the diphosphinite ligands where the nucleophilic attack was *trans* to the phosphinite moiety attached to C-5. This different behavior can be responsible for the better enantioselecitivities obtained with the thioether-phosphinite ligands. If we examine the models for the Pd-allyl intermediate, we can see that for these thioether-phosphinite ligands the nucleophilic attack preferably takes place on the *exo*-diastereoisomer.

3. Chapter 5. *Furanoside diphosphinite and thioether-phosphinite ligands in asymmetric 1,4-addition*. The conclusions of this chapter can be summarized as follows:

Using diphosphinite and thioether-phosphinite ligands as chiral auxiliaries in the asymmetric Cu-catalyzed asymmetric 1,4-addition to 2-cyclohexenone provides good enantioselectivities (up to 72% ee) and activity (TOF up to > 1225 mol product x (mol catalyst precursor x h)$^{-1}$) combined with excellent chemo- and regio-selecitivity in 1,4 product. Our results show that activity and selectivity (chemo- and enantioselectivity) depend strongly on the type of functional group at the C-5 position of the carbohydrate backbone, the steric properties of the substituent in the thioether moiety, the catalyst precursor and the alkylating agent. Enantioselectivity was best with the catalyst precursor containing the thioether-phosphinite ligand, which has an isopropyl substituent in the thioether moiety.

However, activity was best with the diphosphinite ligands. Triethylaluminium has a positive effect on activities but enantioselectivities are better with diethylzinc.

4. Chapter 6. *Furanoside diphosphinite ligands in asymmetric hydroformylation*. The conclusions of this chapter can be summarized as follows:

Using diphosphinite ligands as chiral auxiliaries in the asymmetric Rh-catalyzed asymmetric hydroformylation of several vinyl arenes provides high regioselectivities in branched aldehyde (up to 99%) and moderate enantioselectivity (up to 63% ee). Our results showed that substrate had a remarkable effect on enantioselectivity. The presence of *para*-methoxy and naphthyl substituents in the substrate therefore had a positive effect on enantioselectivities.

Our detailed structural studies of the complexes $[HRh(P\text{-}P)(CO)_2]$ (P-P = diphosphinite ligand) showed that the hydridorhodium dicarbonyl species exist in one diastereosiomeric equatorial-equatorial form. However, this strong coordination preference did not allow for high enantioselectivity.