Ligands Derived from Carbohydrates for Asymmetric Catalysis

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Received December 11, 2003

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1. Introduction

Discovering efficient methods for gaining access to enantiomerically pure compounds in the development of pharmaceuticals, agrochemicals, and flavors has been a great challenge for chemists. Of the various methods for producing enantiopure compounds, enantioselective homogeneous metal catalysis is an appealing strategy, as 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.[1] Usually with this strategy, a transition-metal complex containing a chiral ligand catalyzes the transformation of a prochiral substrate while dissymmetrically shaping the space around the reaction center so that one stereochemical path is preferentially followed.

To achieve the highest levels of reactivity and selectivity in catalytic enantioselective reactions, several reaction parameters must be optimized. Among them, the selection and design of the chiral ligand is perhaps the most crucial step. One of the simplest ways to obtain chiral ligands is to transform or derivatize natural chiral compounds, thus making tedious optical-resolution procedures unnecessary. In the past few years, impressive results have been obtained using carbohydrate derivative ligands in a wide range of catalytic asymmetric reactions. 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. One of the main limitations of using natural products as precursors for ligands is that often only one of the enantiomers (in the case of carbohydrates, the D-series) is readily available. However, this limitation can be overcome by using pseudo-enantiomer ligands or by suitable ligand tuning, as we will show in this review.

Although there is much relevant literature in this field, there are only a few reviews.[2,3] These reviews either cover mainly narrow or specific areas (one type of ligand or one type of reaction)[2b−g] or describe the

10.1021/cr0306889 CCC: $48.50 © 2004 American Chemical Society
Published on Web 04/09/2004

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transition-metal complexes with carbohydrate ligands.[3] Hence, there is no review which discusses several reactions under the same perspective, providing a global overview of the research done and the possibilities for future research.

This review will cover reports in the literature on the use of carbohydrate derivative ligands in asymmetric catalysis in the most emerging period for this area of research (1996−2003). We will focus on those asymmetric homogeneous reactions for which research has been most active during this period and that have not yet been reviewed.[4]

The review is organized as follows. In section 2 we present a short historical overview of the use of carbohydrate ligands in asymmetric catalysis before 1996. We list the catalysts derived from carbohydrates together with the type of reaction and the best optical yields reported. The aim of this section is to

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show the diversity of structures of sugar ligands and the reactions in which they were applied. In the next sections, we cover the period between 1996 and 2003. To review the carbohydrate derivative ligands we grouped them according to the type of asymmetric catalytic reaction. For each reaction we will present an overview of the state of art and then focus on the catalytic data using carbohydrates for different donor groups. We will also discuss any mechanistic aspects when these are reported.

2. Carbohydrate Ligands in Asymmetric Catalysis: A Historical Overview

In this section we present a short historical overview of the use of carbohydrate ligands in asymmetric catalysis roughly between 1972 and 1995. These ligands were mainly developed for asymmetric hydrogenation. Among these ligands, bidentate phosphorus donors were widely used. These were mainly phosphines, phosphinites, and, to a lesser extent, phosphites, but other donor atoms such as sulfur or nitrogen and monodentate ligands were also applied. All these ligands were synthesized from various sugars including xylose, glucose, galactose, mannitol, and trehalose among others. This led to a wide range of sugar backbones with different electronic and steric properties.

2.1. Phosphine Ligands

The successful early application of the diphosphine DIOP (**1**, derived from tartaric acid) in metal-catalyzed asymmetric hydrogenation[5] led to the design of several types of phosphine ligands (mainly diphosphine ligands) derived from carbohydrates for this process (Figure 1).[6−19] Although in general these new ligands showed lower enantioselectivities than those obtained with DIOP, three of them (ligands **2**, **4,** and **18**) provided better results.

In particular, ligand **2**, also derived from tartaric acid (with a more rigid five-membered chelate ring and the two stereocenters closer to the metal), showed a broad scope in the Rh-catalyzed asymmetric

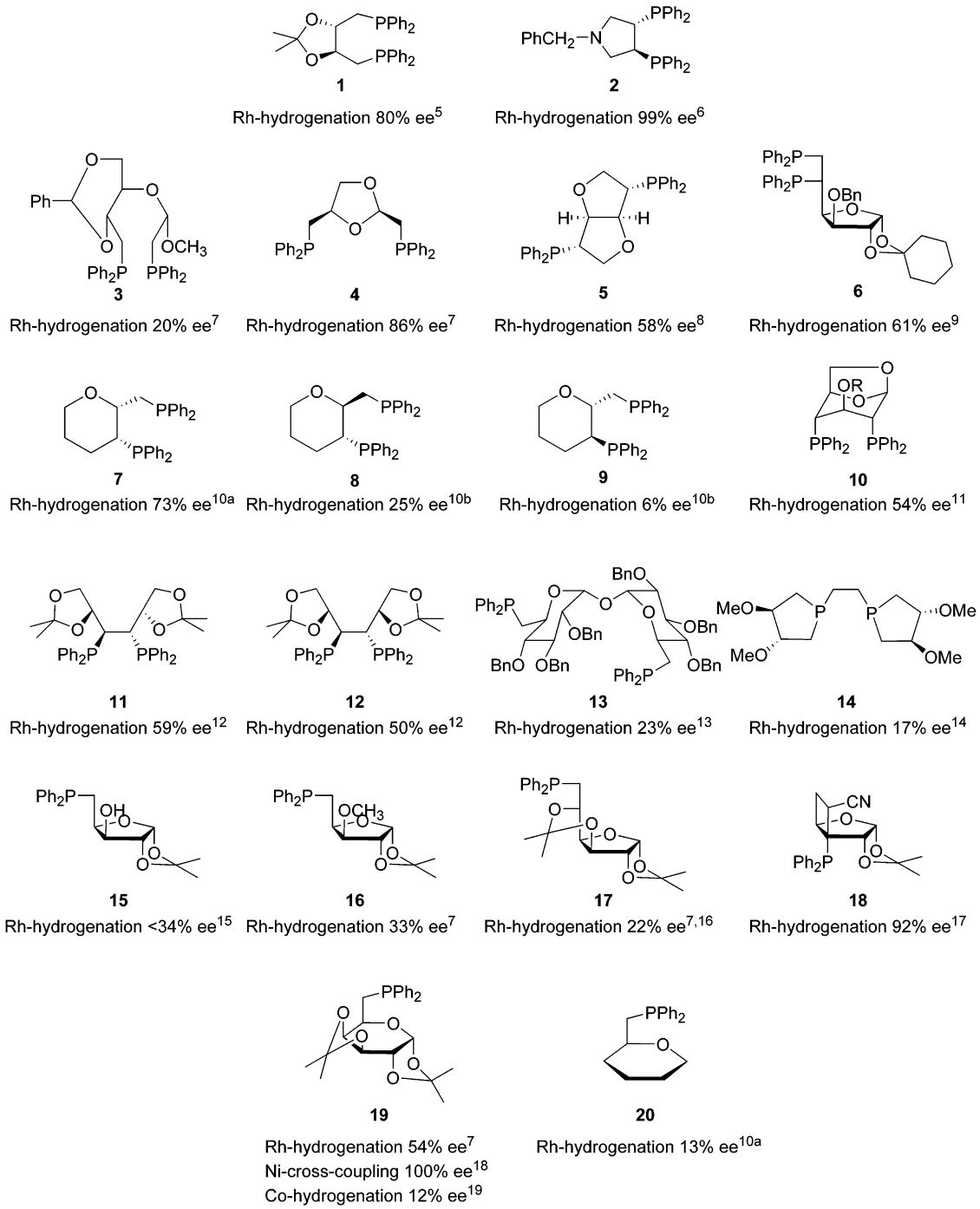


Figure 1. Phosphine ligands derived from carbohydrate between 1972 and 1995. Maximum ee's reported at room temperature.

hydrogenation of several dehydroamino acid derivatives (ee's up to >99%).[6]

The monophosphine **18** constitutes one of the earliest successful applications of monodentate ligands in asymmetric hydrogenation.[17]

Another monophosphine ligand, **19**, was successful in the Ni-catalyzed cross coupling of *sec*-butylmagnesium bromide to bromobenzene.[18]

2.2. Phosphinite Ligands

Phosphinite ligands with carbohydrate backbone were first used in asymmetric catalysis by the groups of Cullen,[20] Thompson,[21] Selke,[22a] and Descotes.[23] These authors studied a wide variety of 2,3-diphenylphosphinite pyranoside ligands **21**−**25** (Figure 2) in the asymmetric hydrogenation of dehydroamino acid derivatives. These ligands were used in the first systematic study into how the configuration of the stereocenters and different substituents in the ligand backbone affect enantiodiscrimination. They found the best enantioselectivities (ee's up to 96.6%) using *β*-glucopyranoside 2,3-diphosphinite ligands **22**, mainly developed by Selke and co-workers.[21,22] RajanBabu and co-workers also successfully applied ligands **22** in the Ni-catalyzed asymmetric hydrocyanation of vinylarenes.[24]

Since the 1980s, other di- and monophosphinite ligands with carbohydrate backbone have also been

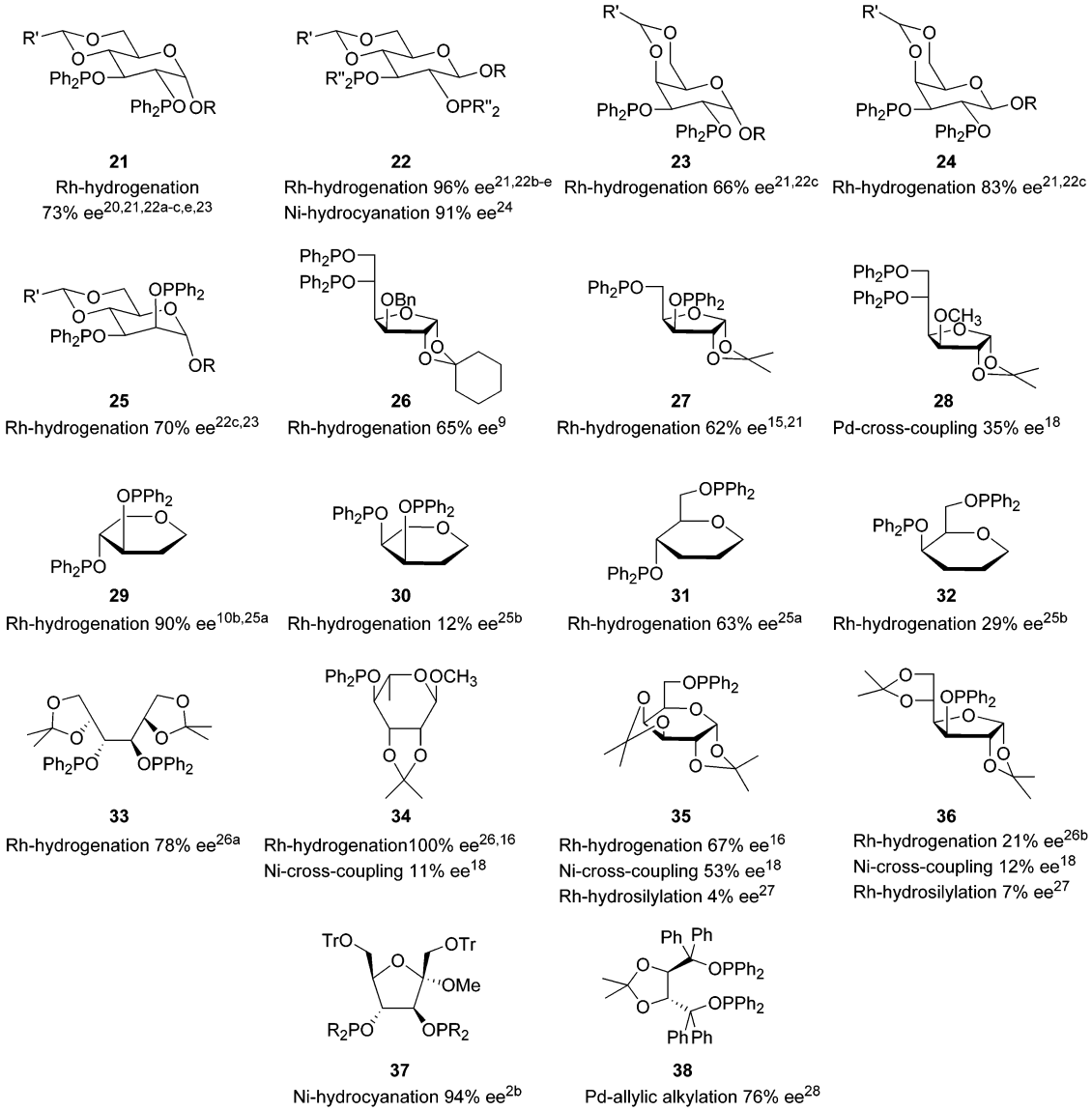


Figure 2. Phosphinite ligands with carbohydrate backbone between 1978 and 1995.

developed, mainly for metal-catalyzed asymmetric hydrogenation, cross-coupling, and hydrocyanation reactions.[2b,25−28] It is worthwhile to note the work of the groups of Šunjić, Yamashita, and RajanBabu. Šunjić and co-workers systematically designed a series of pyranoside ligands **29**−**32** for the Rh-catalyzed hydrogenation.[25] Yamashita and co-workers reported the first monodentate phosphinite ligand **34,** which shows excellent enantioselectivities in the Rh-catalyzed hydrogenation of dimethyl itaconate.[26] RajanBabu and co-workers synthesized a successful series of furanoside diphosphinite ligands **37** for asymmetric hydrocyanation.[2b]

2.3. Phosphite Ligands

Unlike with phosphine and phosphinite carbohydrate ligands, the early application of carbohydrate phosphite ligands in asymmetric catalysis (mainly hydrogenation and hydroformylation) led to low-to-moderate enantioselectivities (Figure 3).[15,29−31]

The use of diphosphite ligands in asymmetric catalysis was first reported by Brunner[15] and Wink.[29] These authors used diphosphite ligands based on D-mannitol (**40**) and tartaric acid (**39**, **41**) in the Rh-catalyzed hydrogenation of enamides and obtained low enantioselectivities (1−34% ee) (Figure 3).

In 1993, Seebach and co-workers developed a series of monophosphite ligands **42**, derived from TADDOL (tetraaryl-1,3-dioxolane-4,5-dimethanol), for the Rh-catalyzed hydroformylation and hydrosilylation reactions but had little success.[30]

In the early 1990s, van Leeuwen and co-workers developed a series of sugar-derived ligands **43**−**49** for the Rh-catalyzed asymmetric hydroformylation of styrene (Figure 3).[31] Catalytic activity strongly depended on the bulkiness of the ligand. The best enantioselectivity (64% ee) was obtained with ligand **45c**.

2.4. Other Ligands

Initially, sulfoxide **50**[32] and several mixed phosphinite−phosphite **51**[15] and phosphine−phosphinite **52**−**53**[15,16] ligands were developed for the Rh-catalyzed asymmetric hydrogenation but with little success (Figure 4).

In 1980, Sharpless and co-workers reported a highly enantioselective Ti-catalyzed epoxidation of allylic alcohols using ligand **54**.[1c,33]

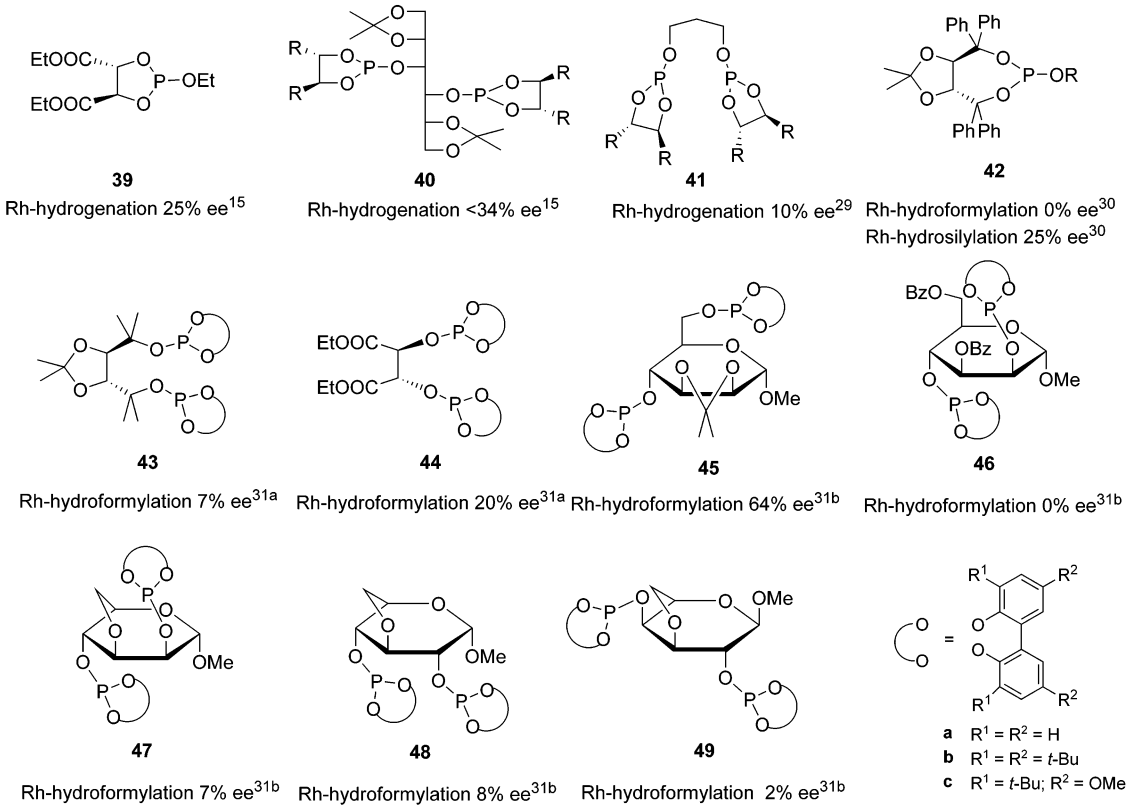


Figure 3. Diphosphite ligands derived from carbohydrate between 1980 and 1995.

In the 1990s, Seebach and co-workers developed a series of successful TADDOLs **55** for the 1,2-addition of several organozinc reagents to aldehydes.[34] Meanwhile, Masaki and co-workers reported promising results in the 1,2-addition of diethylzinc to benzaldehyde with a series of tetrasubstituted pyrrolidines **56** and **57** (Figure 4).[35]

In 1993, Seebach and co-workers reported the successful application of a series of phosphonite ligands **58**, derived from TADDOL, in the Rh-catalyzed hydrosilylation of aromatic ketones.[30]

Spescha introduced a series of thiolate ligands **59**−**62** for the Cu-catalyzed asymmetric 1,4-addition of butylmagnesium halides to 2-cyclohexenone (Figure 4). The best ee's were obtained with glucofuranoside ligand **59**.[36]

In 1995, Collman and co-workers developed threitol-strapped prophyrins **63** for the Mn-catalyzed epoxidation of unfunctionalized alkenes.[37]

3. Asymmetric Hydrogenation

Of all the asymmetric catalytic methods, metal-catalyzed asymmetric hydrogenation using molecular hydrogen to reduce prochiral olefins, ketones, and imines has become one of the most efficient methods for constructing chiral compounds. This process has been widely used in stereoselective organic synthesis, and some processes have found industrial applications.[1] The scope of this reaction has been gradually extended in terms of reactant structure and catalyst efficiency over many years. A large number of chiral ligands, mainly P- and N-containing ligands with either C_2- or C_1-symmetry, have been successfully applied.[1] Diphosphines and, to a lesser extent, diphosphinites have played a dominant role among the P-ligands. However, a group of less electron-rich phosphorus compounds (phosphite and phosphoroamidite ligands) has also recently demonstrated their potential utility in asymmetric hydrogenation.[38]

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. Other donor atoms such as sulfur and monodentate ligands have also exhibited very good catalytic behavior. Some of the results are among the best ever reported.

In this section we summarize the catalytic data reported since 1996 in the metal-catalyzed hydrogenation of C=C and C=N double bonds with carbohydrate ligands.

3.1. Hydrogenation of C=C Double Bonds

The hydrogenation of carbon−carbon double bonds (Scheme 1) is widely used to prepare high-value compounds that can be used as building blocks for asymmetric synthesis. For instance, the hydrogenation of α-dehydroamino acid derivatives (Scheme 1a) and enamides (Scheme 1c) provides access to unnatural amino acids and amines that are useful intermediates for the pharmaceutical and agrochemical industries.[1] The hydrogenation of α-dehydroamino acid derivatives is also a typical reaction for testing the efficiency of new chiral ligands.

In this section we describe the results published for the asymmetric hydrogenation of C=C bonds with ligands derived from carbohydrate.

3.1.1. P-Donor Ligands

3.1.1.1. Phosphine Ligands. A review of the research into carbohydrate phosphine ligands over

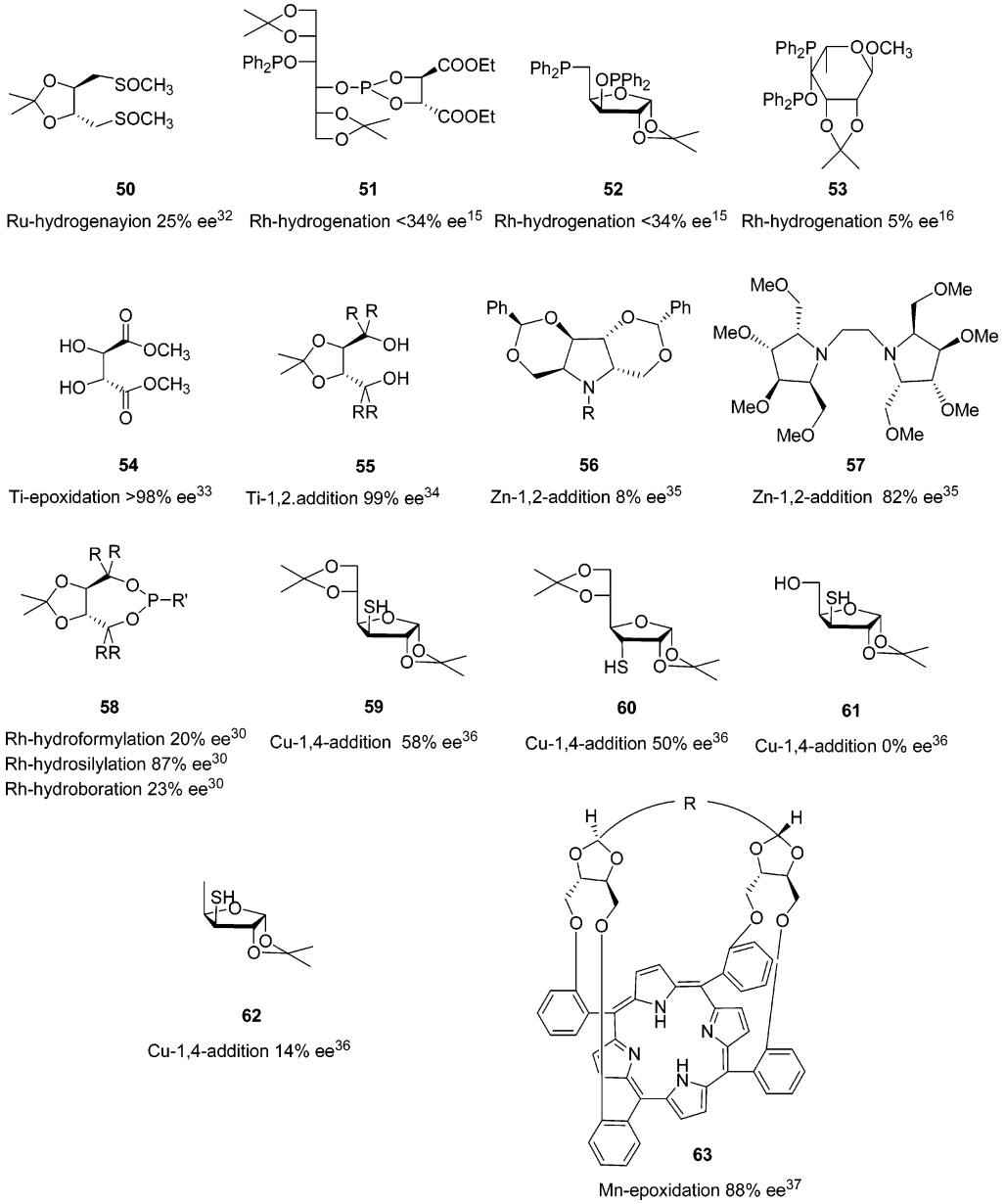


Figure 4. Ligands **50**−**61** developed between 1980 and 1995.

the last seven years reveals three main trends: DIOP derivatives, phospholane ligands derived from carbohydrate, and carbohydrate-based sugar ligands.

Inspired by the early work by Kagan on DIOP chemistry, other research groups have recently developed many diphosphine ligands with a 1,4-dioxane backbone derived from tartrates for asymmetric hydrogenation (Figure 5).[39−41] In this context, the use of ligand **64** in the Rh-catalyzed asymmetric hydrogenation of dehydroamino acids, itaconates, and enamides (Scheme 1) led to similar enantioselectivities but a reversed absolute configuration to that obtained with the DIOP ligand **1** (Figure 1).[39a] However, using DIOP derivative ligands **64e** led to lower enantioselectivities than those of the Rh−DIOP catalytic system in the asymmetric hydrogenation of dehydroamino acid derivatives.[39b,c] In any case, the use of ligand **64** showed that both enantiomers can be obtained by suitably adjusting of the ligand structure. This feature will also be observed in other ligands and highlights the importance of systematically studying variations of the ligand.

An efficient modification of DIOP is found in the recent studies by the groups of RajanBabu and Zhang, which have substantially improved enantioselectivities by increasing the rigidity of the conformational flexibility of the seven-membered chelate ring in the DIOP ligand. Two different strategies were applied: (a) introducing a methyl substituent in the α positions of the phosphine groups, which led to ligands **65**and **66**,[40] and (b) introducing a conformationally rigid 1,4-dioxane backbone, which led to ligands **67** and **68**.[41] These modified DIOP ligands provided excellent enantioselectivities (up to 99%) in the Rh-asymmetric hydrogenation of aryl enamides and MOM-protected *β*-hydroxyl enamides (Scheme 1c).[40,41]

In the past few years the diphospholanes, related to DUPHOS (1,2-bis(2,5-dimethylphospholanyl)benzene), have emerged as a powerful new class of

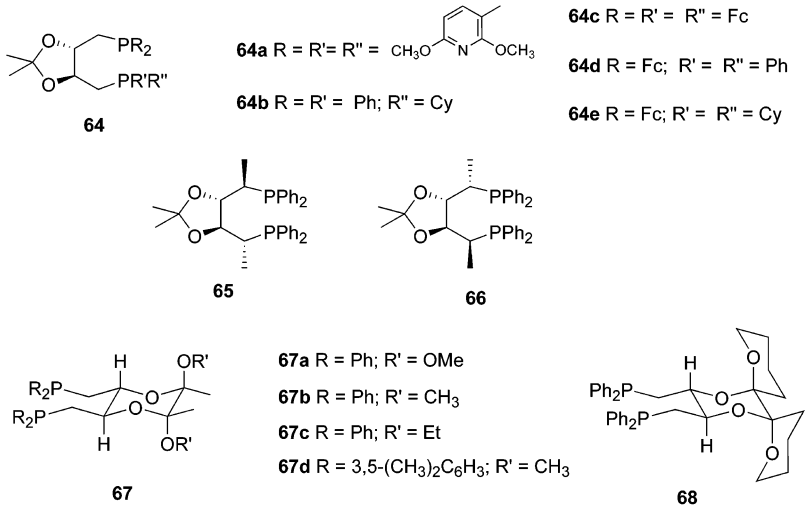
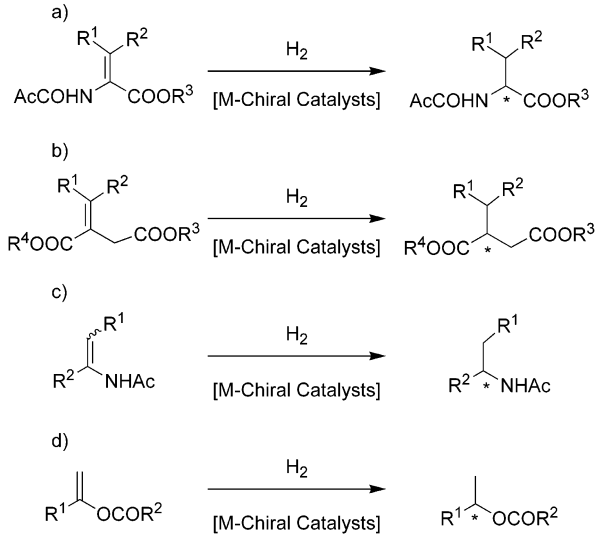


Figure 5. C_2-Modified DIOP diphosphine ligands **64**−**68**.

Scheme 1. Model Metal-Catalyzed Hydrogenation Reactions: (a) Metal-Catalyzed Hydrogenation of α-Dehydroamino Acid Derivatives; (b) Metal-Catalyzed Hydrogenation of Itaconic Acid Derivatives; (c) Metal-Catalyzed Hydrogenation of Enamides; (d) Metal-Catalyzed Hydrogenation of Enolates



ligands for asymmetric hydrogenation.[42−45] These ligands are mainly derived from D-mannitol. In 1987, Brunner and co-workers reported the synthesis of bisphospholane **14** derived from tartaric acid (Figure 1). However, due to the remote position of the chiral centers (*β*-position from the P-atom) from the metal, the Rh-catalytic hydrogenation of prochiral olefins was disappointingly low.[14] Many recent reports have introduced different modifications that have led to highly efficient ligands for this process (Figure 6). In general, this type of ligand maintains the high efficiency of DUPHOS in the Rh-catalyzed hydrogenation.

In particular, Holz and co-workers developed novel diphospholanes **69** and **70a** derived from D-mannitol that have chiral information at both the α- and *β*-positions of the phosphorus atom. These ligands were tested in the Rh-catalyzed hydrogenation of a range of functionalized olefins. In all cases enantioselectivities were high (from 92.6% to 99.1% ee).[42a]

In this context, Zhang and co-workers developed new diphospholanes **70b**,**c**−**72**.[43] Ligands **70b**,**c** and **72** were successfully applied in the Rh-catalyzed asymmetric hydrogenation of dehydroamino acids derivatives, itaconic acid derivatives, enamides, and enolacetates (Scheme 1) (ee's usually >99%). Surprisingly, the isopropylidene-protected diphospholanes **71** did not work in this process. More recently, Rieger and co-workers studied how other substituents in the α-position (R′ groups) affect enantiodiscrimination with ligands **70b**−**f**. Their results indicated that the optimal substituents are generally Me and Et.[44]

Another recent series of diphospholane ligands **73** and **74** were efficiently used in the Rh-catalyzed asymmetric hydrogenation of α- and *β*-amino acid derivatives, itaconates, and an unsaturated phosphonate. Enantioselectivities, which range from 8% to 99% ee, strongly depended on the type of substituent in the oxymethyl group and the bridge connecting the phospholane units. Enantioselectivities were best with ligand **73b**. Ligand **73b** was also successfully applied in the Ru-catalyzed hydrogenation of prochiral *β*-oxo esters (ee's up to 98.8%).[42b]

Ligands with hydroxyl groups **70b**, **70c,** and **73a** also enabled hydrogenation to be carried out in aqueous solution and maintained high enantioselectivities.[46]

Another efficient structural variation combined a phospholane moiety, derived from D-mannitol, with a DIPAMP (bis[(2-methoxyphenyl)phenylphosphino]-ethane) chiral phosphine through an ethylene bridge (Figure 7). These ligands were applied in the Rh-catalyzed hydrogenation of several itaconates with ee's ranging from 80% to 95% (Scheme 1b).[45]

In 2000, a new series of C_1-diphosphine ligands **77**−**79** with furanoside backbone were developed for the Rh-asymmetric hydrogenation of α,*β*-unsaturated carboxylic acid derivatives (dehydroamino acid and itaconic acid derivatives, Scheme 1) (Figure 8).[47] Ligands **78** and **79** differ from ligand **77** at C-5, where a new stereogenic center was introduced. The results indicated that introducing a methyl substituent at C-5 in ligand **77** significantly increased activity (TOF were approximately double for ligands **78** and **79**). Moreover, the configuration of C-5 strongly influ-

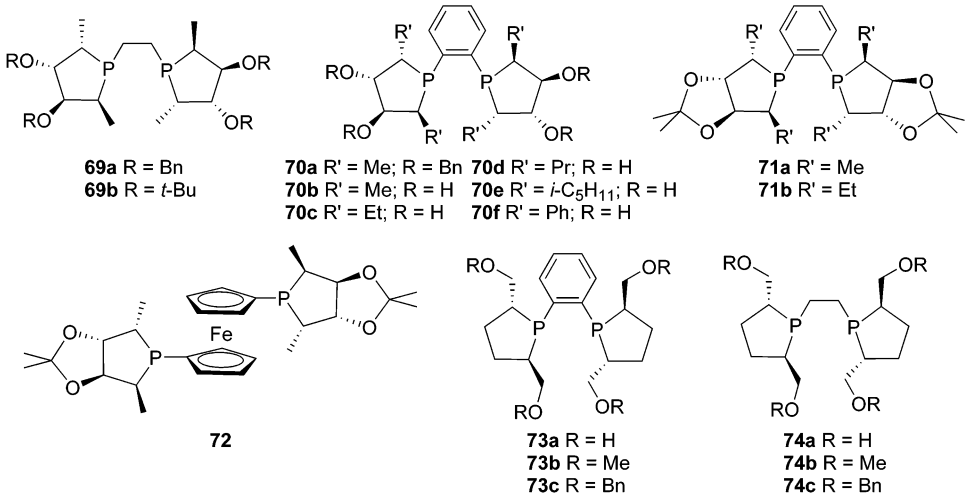


Figure 6. Diphospholane ligands **69**−**74**.

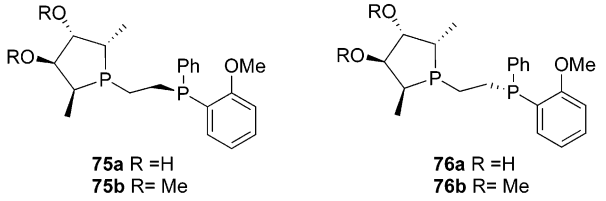


Figure 7. Phosphine−phospholane ligands developed by Brown and co-workers.

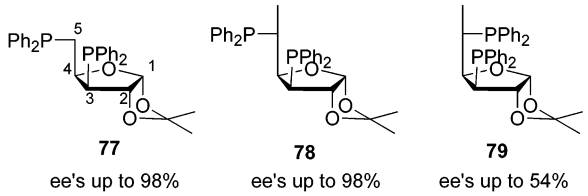


Figure 8. Diphosphine ligands with furanoside backbone derived from D-(+)-xylose and D-(+)-glucose.

enced enantioselectivity. By comparing ligands **78** and **79**, therefore, we can see that the best results were obtained with ligand **78** with an *R*-configuration at C-5.

3.1.1.2. Phosphinite Ligands. In the historical overview, we have seen that pyranoside phosphinite ligand **22** (R = R′ = R″ = Ph; Figure 2), derived from inexpensive D-glucose, was efficient in the Rh-catalyzed asymmetric hydrogenation of dehydrophenylalanines (Scheme 1a; R^1 = Ph, R^2 = H, R^3 = H or Me). However, the scope was limited for the synthesis of substituted phenylalanines and the corresponding heteroatomic derivatives. In this context, RajanBabu and co-workers studied whether further modifications in diphosphinite-type ligand **22** 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 **22** (Figure 9).[48]

The Rh-hydrogenation results showed that there was a major electronic effect with these systems. 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 **22a** and **22b** (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 **22** from the expensive L-glucose, RajanBabu and co-workers developed pseudo-enantiomeric diphosphinite ligands to **22** with the corresponding 3,4-diphosphinite ligands **80**−**84** (Figures 10 and 11).[48] Ligands **80** and **81** provided the highest enantioselectivities in favor to the *R*-enantiomer of the 3,4-diphosphinite series (Figure 11). As before, enantioselectivities were best with electron-rich phosphinites (ee's up to 99% (*R*)). In summary, the sugar−diphosphinite ligand systems developed by RajanBabu appear to be among the most practical ligands for the synthesis of (*S*)-

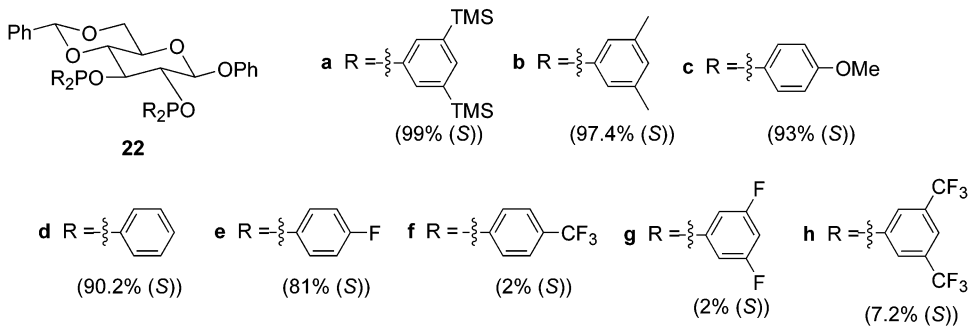


Figure 9. Modifications of diphosphinite ligand **22**. In brackets, the enantioselectivities obtained in the hydrogenation of methyl α-acetamidocinnamate are shown as examples.

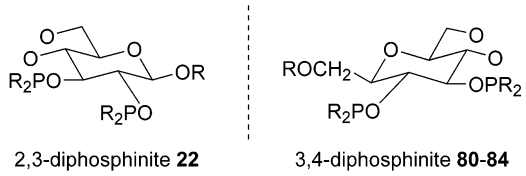


Figure 10. Pseudo-enantiomeric D-glucopyranoside ligands.

and (*R*)-aromatic and heteroaromatic alanine derivatives.

Water-soluble rhodium complexes **85** related to diphosphinite ligands **22** (Figure 12) were effective for the hydrogenation of dehydroamino acid derivatives in aqueous or biphasic media. However, the enantioselectivities were lower than those in organic medium with diphosphinites **22** (ee's up to 90%).[49]

RajanBabu and co-workers also used a series of 3,4-diphosphinite ligands **37** with fructofuranoside backbone (Figure 2; R = Ph, 4-OMe-C_6H_4, 3,5-Me_2−C_6H_3).[48b] However, this backbone was not as efficient as the pyranoside backbone. Therefore, enantioselectivities of up to 57% were obtained in the Rh-catalyzed hydrogenation of substituted phenylalanines (Scheme 1a).

In 1998, Uemura and co-workers developed novel disaccharide diphosphinite ligands **86** and **87** derived from α,α-trehalose (Figure 13). These work as ligands in the Rh-catalyzed asymmetric hydrogenation of α-acetamidoacrylic and cinnamic acid derivatives (Scheme 1a) to afford both enantiomers of amino acids up to 84% ee (*S*) (with ligand **86**) and 72% ee (*R*) (with ligand **87**).[50]

The deprotected-hydroxyl diphosphinite ligand **86** also enabled the hydrogenation of enamides and itaconic acid to be conducted in aqueous solution and enhanced enantioselectivities (ee's up to 99%).[51]

In 1999, Chan and co-workers used the previously mentioned diphosphinite ligand **33** (Figure 2), derived from D-mannitol, in the Rh-catalyzed hydrogenation of α-acetamidoacrylic acid. This provided ee's of up to 96.7%.[52]

Recently, Miethchen and co-workers modified the previously mentioned diphosphinite **21** (Figure 2) with an anellated crown-ether in the 1,4-position (Figure 14) to investigate whether tuning the conformation of the crown ether would affect enantioselectivity in the Rh-catalyzed asymmetric hydrogenation.[53] In several solvents the range of enantioselectivity was lower than with analogous **21**.

More recently a diphosphinite ligand **89**, related to ligand **27** (Figure 2) but with opposite configuration of C-3, has been developed (Figure 15). Unlike ligand **27**, ligand **89** showed good enantioselectivities in the Rh-catalyzed asymmetric hydrogenation of methyl α-acetamidoacrylate (ee's up to 81%).[54] Interestingly, the same authors observed a major metal precursor effect for this system. Thus, with [Ir(cod)(**27**)]BF_4 enantioselectivity was better (ee's up to 78%) than with the rhodium analogue (ee's up to 20%).[54]

3.1.1.3. Phosphite Ligands. A review of the research into carbohydrate phosphite ligands over the last 7 years reveals two main trends: bidentate ligands (mainly two families derived from D-mannitol and D-glucose) and monodentate ligands.

In 1998, Selke et al. reported the use of a series of diphosphite ligands with glucopyranoside backbone **90** in the Rh-catalyzed hydrogenation of methyl (*Z*)-2-*N*-acetamidocinnamate and showed rather low enantioselectivities (ee's up to 13%) (Figure 16).[55] This contrasts with the excellent results obtained with the related diphosphinite ligands **22** (vide supra).

An important breakthrough in the use of phosphite ligands for asymmetric hydrogenation came with the work of Reetz and co-workers. These authors developed a series of C_2-derivative ligands derived from D-mannitol **91** with different phosphite substituents (**a**−**e**) (Figure 17).[56]

These ligands were efficiently applied in the Rh-catalyzed hydrogenation of dimethyl itaconate (Table 1) and methyl *N*-acetamidoacrylate. Results indicated that the sense of enantiodiscrimination is predominantly controlled by the configuration of the binaphthyl moiety (entries 4 and 5). Moreover, they observed a cooperative effect between the stereogenic centers of the ligand backbone and the stereogenic binaphthyl phosphite moieties (entries 4 and 5). This resulted in a matched combination for ligand **91e** (entry 5 and 7).

Reetz et al. also found that ligand **91b** with conformational flexibility in readily epimerizing biphenyl moieties was superior to those with fixed binaphthyl chirality (entry 2 vs entries 4 and 5).

Results obtained in the asymmetric hydrogenation of methyl *N*-acetamidoacrylate followed the same trend as those for dimethyl itaconate, but the enantioselectivities were somewhat lower (ee's up to 88.7%).

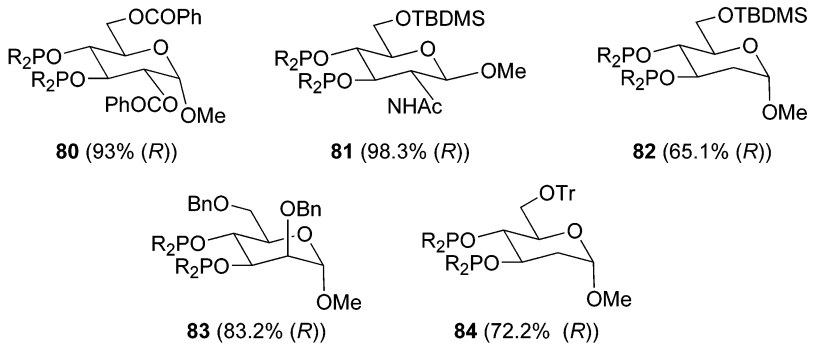


Figure 11. 3,4-Diarylphosphinite ligands **80**−**84**. In brackets, the enantioselectivities obtained in the hydrogenation of methyl α-acetamidocinnamate are shown as examples.

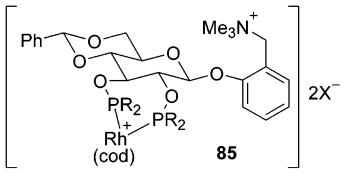
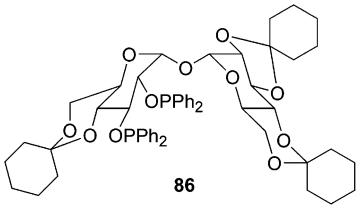


Figure 12. Water-soluble rhodium complexes **85**.



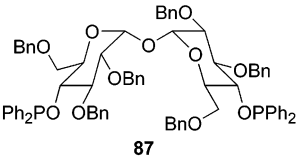


Figure 13. α,α-Trehalose-based diphosphinite ligands **86** and **87**.

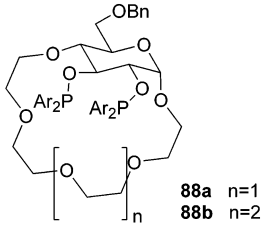


Figure 14. Carbohydrate-based crown ether diphosphinite ligands **88**.

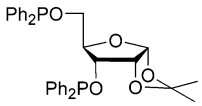


Figure 15. Diphosphinite ligand with furanoside backbone **89**.

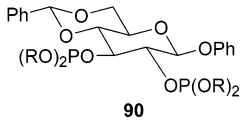


Figure 16. Structure of the diphosphite ligands **90** with glucopyranoside backbone.

The group of Claver and co-workers recently developed a series of highly efficient modular C_1-diphosphite ligands **92**−**97** (Figure 18) with furanoside backbone for the Rh-catalyzed hydrogenation.[57] These ligands are derived from D-(+)-xylose and D-(+)-glucose. The modular construction of these ligands 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 dimethyl itaconate (Table 2). Systematically varying stereocenters C-3 and C-5 at the ligand backbone showed that enantiomeric excesses depended strongly on the absolute configuration of C-3

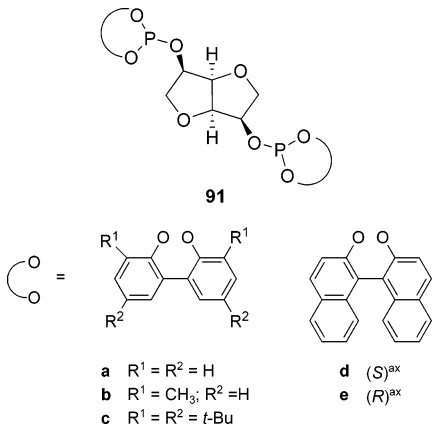


Figure 17. D-Mannite diphosphite ligands developed by Reetz et al.

Table 1. Rh-Catalyzed Hydrogenation of Dimethyl Itaconate Using Phosphite Ligands 91[a]

entry	ligand	*T* (°C)	% conv	% ee
1	**91a**	20	74	38.9 (*R*)
2	**19b**	20	>99	96.8 (*R*)
3	**91c**	20	24	5.2 (*R*)
4[b]	**91d**	20	>99	87.8 (*S*)
5	**91e**	20	>99	94.5 (*R*)
6	**91b**	−10	>99	98.2 (*R*)
7	**91e**	−10	>99	96.2 (*R*)

[a] General conditions: substrate/catalyst= 1000/1; t = 20 h; ligand/rhodium= 1/1; solvent= CH_2Cl_2. P_{H2} = 1 bar. [b] Substrate/catalyst = 250/1.

and slightly on that of the stereocenter carbon C-5. Enantioselectivities were therefore best with ligands **94** with an *R* configuration on both C-3 and C-5 stereocenters.

Varying the chirality at the axial chiral binaphthyl substituents in ligands **94** showed that the sense of the enantiodiscrimination is predominantly controlled by the configuration of the biaryls at the phosphite moieties (entries 6 and 7). Bulky substituents at the *ortho*-positions of the biaryl diphosphite moieties have a positive effect on enantioselectivity. Enantiomeric excess was highest for allofuranoside ligand **94d**, which has *o*-trimethylsilyl substituents in the biphenyl moieties (entries 5 and 13).

It was also found that a methyl substituent on the carbon C-5 significantly increased activity (entries 3−12 vs 1 and 2).

This set of ligands was also applied in the Rh-catalyzed hydrogenation of methyl (*N*)-acetylaminoacrylate and methyl (*Z*)-(*N*)-acetylaminocinnamate. The results followed the same trend as those for dimethyl itaconate, but the activities were somewhat higher.[57c]

In the last few decades it has generally been accepted that enantioselective hydrogenation was more effective in the presence of bidentate ligands. Recently, however, some monophosphorus ligands have been found to be very efficient for the Rh-catalyzed asymmetric hydrogenation.[38,58] Research in this area was initiated by Reetz and co-workers. In connection with the previously described diphosphite ligands derived from D-mannitol **91**, they found that the related monophosphite ligands **98a** and **98b** provided similar enantioselectivities (Figure 19).[59]

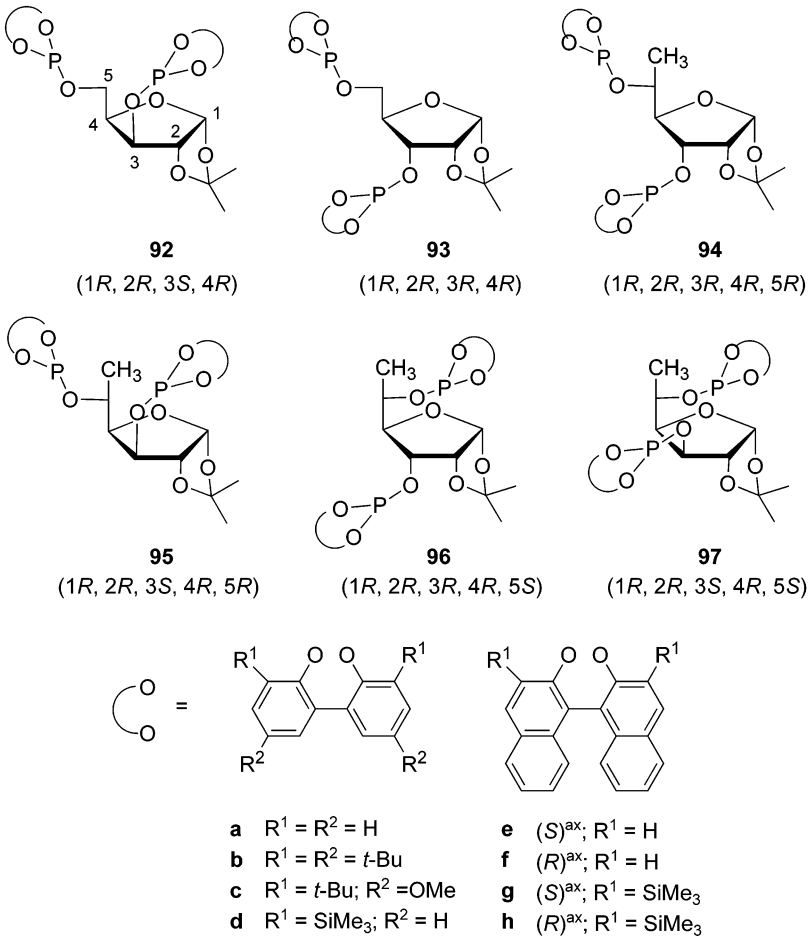


Figure 18. Diphosphite ligands **92**−**97** with furanoside backbone.

Table 2. Rh-Catalyzed Asymmetric Hydrogenation of Dimethyl Itaconate Using Diphosphites 92−97[a]

entry	ligand	% conv (t/h)	% ee
1	**92b**	12 (8)	22 (*R*)
2	**93b**	28 (8)	64 (*R*)
3	**94b**	90 (8)	90 (*R*)
4	**94c**	82 (8)	85 (*R*)
5	**94d**	100 (6)	97 (*R*)
6	**94e**	50 (8)	50 (*S*)
7	**94f**	46 (8)	52 (*R*)
8	**94g**	100 (8)	90 (*S*)
9	**94h**	100 (8)	92 (*R*)
10	**95b**	100 (8)	2 (*R*)
11	**96b**	87 (8)	67 (*R*)
12	**97b**	73 (8)	29 (*R*)
13[b]	**94d**	100 (4)	>99 (*R*)

[a] $[Rh(cod)_2]BF_4$ = 0.01 mmol; ligand/Rh = 1.1; substrate/Rh = 100; CH_2Cl_2 = 6 mL; P_{H2} = 5 bar; T = 25 °C. [b] T = 5 °C; P_{H2} = 30 bar.

Recently, the groups of Reetz[60] and Chen[61] developed new efficient monophosphite ligands for the Rh-catalyzed asymmetric hydrogenation of vinyl carboxylates and enamides, respectively (Figure 20).

The hydrogenation results reported by Reetz and co-workers using ligands **99**−**102** 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 phosphite **99b**, prepared from (*R*)-Binol and a D-(+)-glucose derivative (ee's up to 94%).[60]

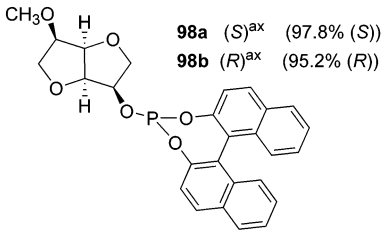


Figure 19. Monophosphite ligands **98**. In brackets, the enantioselectivities obtained in the Rh-catalyzed asymmetric hydrogenation of dimethyl itaconate are shown as examples.

The hydrogenation results reported by Chen and co-workers using ligands **99**, **100**, **103**, and **104** indicate that the enantiomeric excess depends strongly on the configuration of carbon atom C-3. In general, therefore, ligands **100** and **104** with an an *R* configuration produced much higher enantioselectivity than ligands **99** and **103** with 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 best enantioselectivities (up to 99.6% ee) were therefore obtained with ligands **100b** and **104b**.[61]

3.1.1.4. Phosphoroamidite Ligands. In the past few years several monophosphoroamidites derived from carbohydrate have been used for the Rh-catalyzed asymmetric hydrogenation (Figure 21).[44,62] TADDOL-based phosphoroamidite ligands **105** and

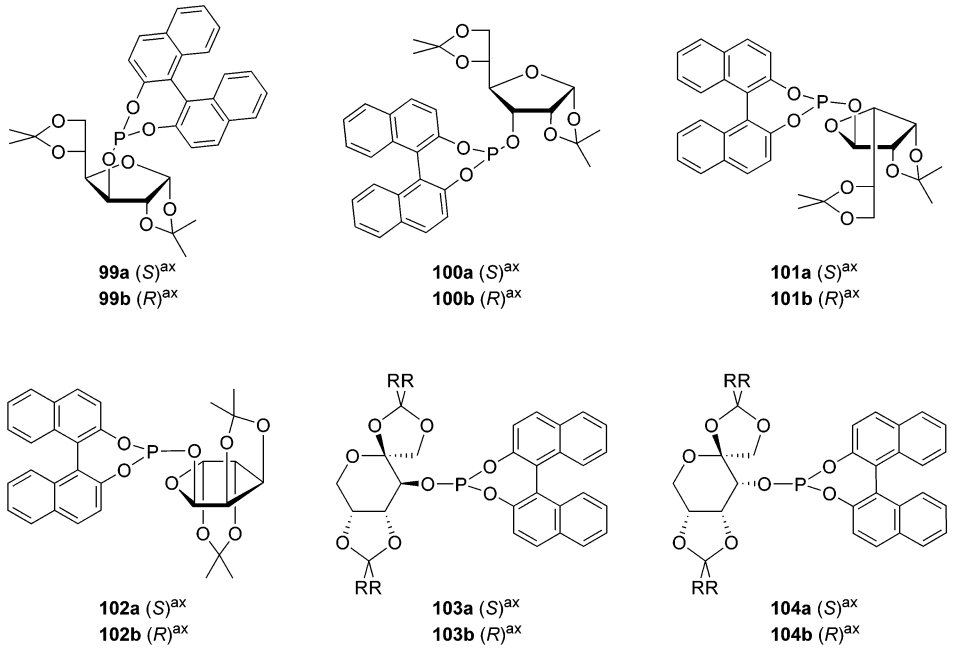


Figure 20. Monophosphites **99**−**104** derived from carbohydrates.

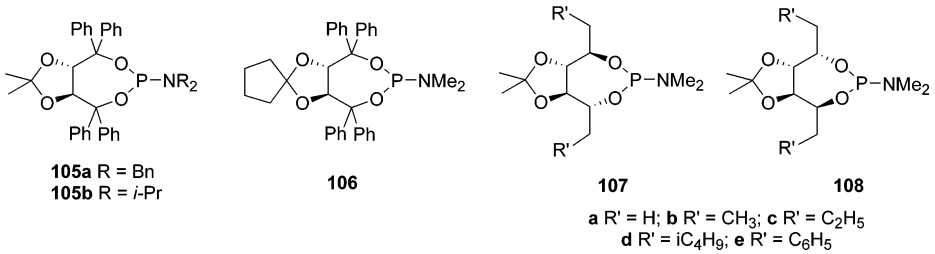


Figure 21. Phosphoroamidite ligands **105**−**108**.

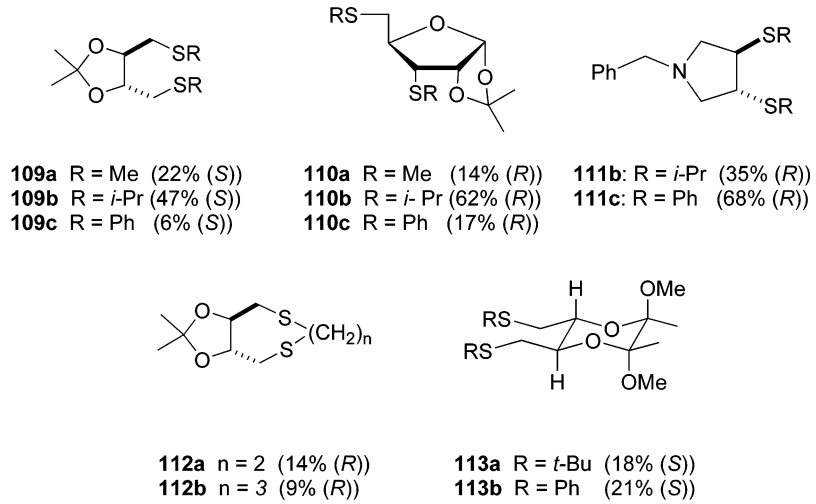
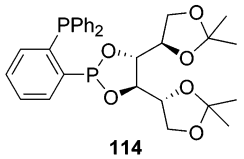


Figure 22. Dithioethers ligands **109**−**113**. Enantioselectivities are shown in brackets.

106 were applied with low enantioselectivity and rates (ee's up to 37%).[62] However, ligands **107** and **108** 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%).[62]

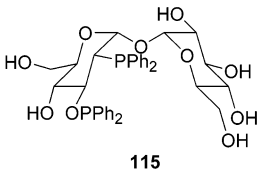
3.1.2. S-Donor Ligands

Chiral dithioethers in asymmetric hydrogenation have been used in a number of studies.[41,63] In particular, ligands **109**−**112** have shown low-to-moderate enantioselectivities (from 6% to 68%) in the enantioselective Ir-catalyzed hydrogenation of itaconic acid under mild conditions (Figure 22). Results indicate that the structure of the ligand backbone, the size of the metal chelate ring, and the R substituents influence the activity and enantioselectivity of the process. The enantiomeric excess is higher for **110**[63c] and **111**,[63b] with a more rigid backbone, than for the derivatives **109**,[63a] which form a more flexible seven-membered chelate ring. However, the results do not show obvious trends based on the R substit-



114

Figure 23. Phosphine−phosphonite ligand derived from D-mannitol.



115

Solvent	%ee
THF	63
CH_2Cl_2	37
$Cl_2CH_2CH_2Cl_2$	69
H_2O	62
H_2O / AcOEt	73

Figure 24. Rh-catalyzed hydrogenation of methyl (*Z*)-α-acetamidocinnamate using phosphine−phosphinite ligand **115**.

uents. For precursors containing ligands **109** and **110**, therefore, enantiomeric excesses are highest when bulky and electron-rich isopropyl substituents are present in the thioether groups; for ligands **111,** enantioselectivity is best with phenyl groups bonded to the sulfur atoms.[63a−c]

Unexpectedly, the bicyclic dithioethers **112**, in which the sulfur inversion is fixed, showed lower activity and enantiomeric excess than the related more flexible ligands **109**.[63d]

Dithioethers **113** related to **109** have recently been described. These ligands have been reported to be more rigid than **109** derivatives due to the presence of the 1,4-dioxane six-membered conformationally rigid ring rather than the flexible 1,3-dioxolane five-membered ring in **109**. These ligands showed low enantioselectivities in the Rh-catalyzed asymmetric hydrogenation of *N*-acetyl-1-phenylethenamine (ee's up to 21%).[41]

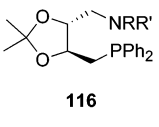
3.1.3. Heterodonor Ligands

Several types of heterodonor carbohydrate ligands have been developed for application in asymmetric hydrogenation catalysis. In particular, phosphite−phosphine, phosphite−phosphoroamidite, and phosphite−oxazoline ligands have produced excellent results.

In 1999, Reetz and co-workers reported a phosphine−phosphonite ligand **114** derived from D-mannitol (Figure 23). This ligand was tested in the Rh-catalyzed asymmetric hydrogenation of dimethyl itaconate with moderate enantioselectivities (ee's up to 60%).[64]

Uemura and co-workers developed a phosphine−phosphinite ligand **115** derived from α,α-trehalose for the Rh-catalyzed asymmetric hydrogenation of enamides in organic and aqueous solution with moderate enantioselectivities (Figure 24).[65]

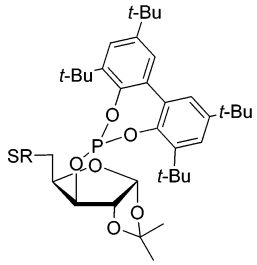
Sinou and co-workers developed a series of phosphine−amino ligands **116** (Figure 25) for the Rh-catalyzed asymmetric hydrogenation of α,*β*-unsaturated amino acids with moderate success. The enantioselectivity is higher in water than in methanol. The best enantioselectivities were obtained using ligand **116b** (ee's up to 60%).[66]



116

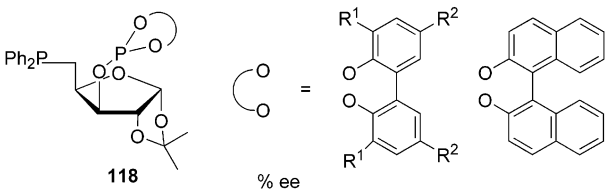
a R= R'= Ph
b R= Ph; R'= Me
c R= Ph; R'= α-naphthyl
d R= 4-OMe-Ph; R'= Me
e R= R'= Bn
f R= H; R'= Ts

Figure 25. Phosphine−amino ligands **116**.



117a R= Me (22% ee)
117b R= *i*-Pr (55% ee)
117c R= Ph (47% ee)

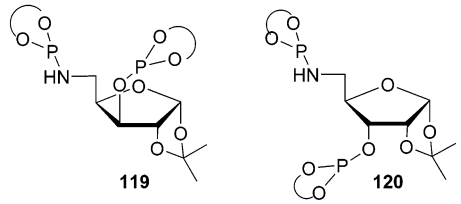
Figure 26. Thioether−phosphite ligands **117** derived from D-(+)-xylose. Enantioselectivities are shown in brackets.



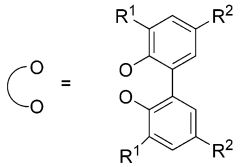
118

		% 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 27. Phosphine−phosphite ligands **118** derived from D-(+)-xylose. Enantioselectivities obtained in the Rh-catalyzed hydrogenation of methyl *N*-acetamidoacrylate are shown as examples.



119 **120**



a $R^1 = R^2 = t$-Bu
b $R^1 = t$-Bu; R^2 = OMe

Figure 28. Phosphite−phosphoroamidite ligands derived from D-(+)-xylose.

Claver and co-workers recently developed a series of phosphite−thioether **117**[67] (Figure 26), phosphite−phosphine **118**[68] (Figure 27), and phosphite−phosphoroamidite **119** and **120**[69] (Figure 28) ligands with furanoside backbone derived from D-(+)-xylose for asymmetric hydrogenation.

Catalytic systems [Ir(cod)(**117**)]BF_4 were the first examples of transition-metal catalysts containing a phosphite−thioether used to hydrogenate prochiral olefins (Figure 26). Moderate enantioselectivities

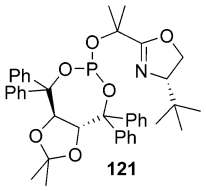


Figure 29. Phosphite−oxazoline ligand **121**.

were achieved in the hydrogenation of methyl α-acetamidocinnamate. The enantiomeric excess is highest for the bulky and electron-rich ligand **117b** (55%).[67]

Phosphite−phosphine ligands **118** were successfully applied in the Rh-catalyzed asymmetric hydrogenation of several α,β-unsaturated carboxylic acid derivatives (ee's up to >99%) under very mild reaction conditions (Figure 27). Varying the biphenyl substituents in the phosphite moiety greatly affected enantioselectivity. The best enantioselectivity was obtained using ligand **118b**, which contains bulky *tert*-butyl groups in the ortho and para positions of the biphenyl moiety. The results also indicate that the sense of enantioselectivity is mainly controlled by the configuration of the phosphite moiety. Both enantiomers can therefore be obtained with high enantioselectivities.[68] It is worth nothing that these phosphite−phosphine ligands showed higher degrees of enantioselectivity and higher reaction rates than their corresponding diphosphine **77** and diphosphite **92** analogues under the same reaction conditions. $^{31}P\{^1H\}$ NMR and kinetic studies on intermediates of the catalytic cycle show that the [Rh(P−P′)(enamide)]BF_4 (P−P′ = phosphite−phosphine) species is the resting state and that the rate dependence is first order in rhodium and hydrogen pressure and zero order in enamide concentration.

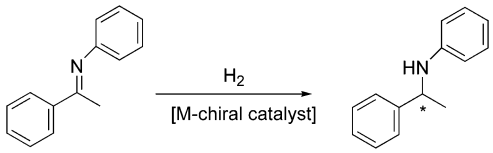
Phosphite−phosphoroamidite ligands **119** and **120** with furanoside backbone were also efficiently used in the Rh-catalyzed asymmetric hydrogenation of α,β-unsaturated carboxylic acid derivatives (Figure 28). The results show that the enantiomeric excesses and activities depend strongly on the absolute configuration of the C-3 stereocenter of the carbohydrate backbone and the substituents in the biphenyl moieties. Therefore, enantioselectivities and activities were best (ee's up to >99%) when using ligand **119a** with *tert*-butyl groups in the ortho and para positions of the biphenyl moieties and an *R* configuration of C-3.[69] These phosphite−phosphoroamidite ligands showed a much higher degree of enantioselectivity and higher reaction rates than their corresponding diphosphite analogues **92** under similar reaction conditions.

Pfaltz and co-workers developed a phosphite−oxazoline ligand **121** for the Ir-catalyzed asymmetric hydrogenation of several unfunctionalized olefins (Figure 29). The conversions were higher than those obtained for related P,N-ligands containing oxazoline, and the enantioselectivity was best in the hydrogenation of (*Z*)-2-(4-methoxyphenyl)but-2-ene (ee's up to 90%).[70]

3.2. Hydrogenation of C=N Double Bonds

The enantioselective hydrogenation of carbon−nitrogen double bonds is a simple and convenient route to synthesizing chiral amines (Scheme 2).

Scheme 2. Model Metal-Catalyzed Asymmetric Hydrogenation of *N*-(1-phenylethylidene)-Benzylamine



However, while many highly enantioselective chiral catalysts have been developed for the asymmetric hydrogenation of C=C, very few effective catalysts are available for the enantioselective hydrogenation of C=N.[1] The most widely used catalyst systems for this process are the diphosphine−rhodium(I) and diphosphine−iridium(I) complexes. Unlike the hydrogenation of C=C double bonds, reports using carbohydrate ligand in this process are scarce.

In this section we describe the results published for the asymmetric hydrogenation of C=N bonds with ligands derived from carbohydrate.

3.2.1. P-Donor Ligands

3.2.1.1. Phosphine Ligands. To our knowledge, only the DIOP ligand and some modifications (Figure 30) developed by Börner and co-workers have been applied in the Rh-catalyzed asymmetric hydrogenation of *N*-(1-phenylethylidene)benzylamine with low-to-moderate enantioselectivities.[71] Their results indicated that enantioselectivity is affected by the use of additives. They found that the best additive (*t*-BuOK) increased enantioselectivity with ligand **1** from 19% to 41% ee.

3.2.1.2. Phosphinite Ligands. To the best of our knowledge, only two chiral catalytic systems based on carbohydrate phosphinite ligands have been reported for the hydrogenation of C=N. In 1999, Börner and co-workers used the previously mentioned ligand **22** (Figure 2, R = R′ = R″ = Ph) and its deprotected dihydroxyl derivative in the Rh-catalyzed asymmetric hydrogenation of *N*-(1-phenylethylidene)benzylamine with low enantioselectivity (ee's up to 28% (*S*)).[71] Recently, the previously reported ligand **27** (Figure 2) was applied in the Ir-catalyzed asymmetric hydrogenation of *N*-(1-phenylethylidene)benzylamine with an enantioselectivity of 57% (*S*).[72]

3.2.1.3. Phosphite Ligands. Little attention has been paid to the use of phosphite ligands for the asymmetric hydrogenation of C=N. Thus far, only two reports are known in the literature. The first one used the previously described diphosphite ligand with β-glucopyranoside backbone **90** (Figure 16, $(OR)_2$ = 3,3′-bis-phenyl-1,1′-biphenyl-2,2′-diol) in the Rh-catalyzed asymmetric hydrogenation of *N*-(1-phenylethylidene)benzylamine with practically null enantioselectivity.[71]

The second one used the previously described xylose-based diphosphite ligands (**92a** and **92b**) in the Ir-catalyzed asymmetric reduction of *N*-(phenyl-

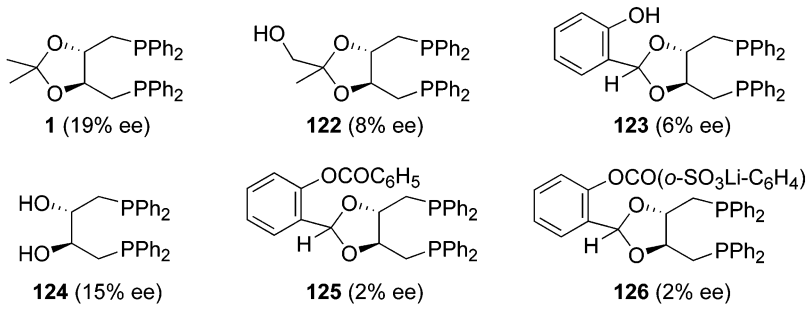


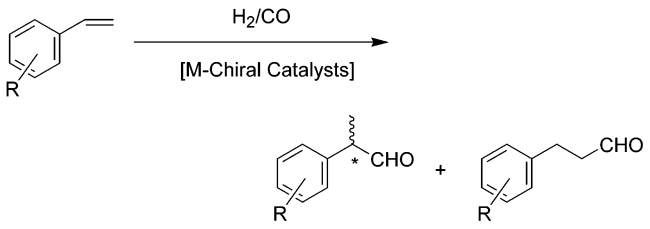
Figure 30. DIOP and its derivatives developed by Börner for the hydrogenation of imines. Enantioselectivities are shown in brackets.

ethylidene)aniline and obtained poor-to-moderate enantioselectivities (ee's up to 46%). Results indicated that enantioselectivity is strongly affected by additives and substituents in the biphenyl moiety. Enantioselectivities were best with bulky ligand **92b** and Bu_4NI as additive.[72]

4. Asymmetric Hydroformylation

The metal-catalyzed asymmetric hydroformylation of alkenes (Scheme 3) has attracted much attention

Scheme 3. Model Metal-Catalyzed Asymmetric Hydroformylation of Styrene (R = H) and Derivatives



as a potential tool for preparing enantiomerically pure aldehydes, which are important precursors for synthesizing biologically active compounds, biodegradable polymers, and liquid crystals.[1c,73] Since the early 1970s, transition-metal complexes based on rhodium and platinum have been used as catalysts in asymmetric hydroformylation.[73] High enantioselectivities have been obtained with Pt/diphosphine catalysts, but these suffer from low chemo- and regioselectivity.[74] In general, Rh/diphosphine catalysts have high catalytic activities and regioselectivities in branched aldehydes, but the ee's do not exceed 60%.[75] During the past decade, two new types of ligands—phosphine−phosphite and diphosphite ligands—have emerged as suitable ligands for the Rh-asymmetric hydroformylation, yielding better activities and selectivities than the phosphine-based catalytic systems.[76]

As far as carbohydrate ligands are concerned, several types of bidentate ligands, mainly phosphorus donors (either homo- or heterodonors), have been reported and used in metal-catalyzed hydroformylation. Some of the results are among the best ever reported.

Here we describe the catalytic data reported since 1996 in the metal-catalyzed asymmetric hydroformylation of olefins with carbohydrate ligands. We also discuss any reported mechanistic aspects according to the hydroformylation results. Among these, it is important to note the thorough studies of the mechanistic aspects for the rhodium-catalyzed hydroformylation reaction. The $[HRh(P-P)(CO)_2]$ (P−P = bidentate ligand) species are known to be the resting state in the hydroformylation reaction.[73d] 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 31), are possible. The presence of only one active diastereoisomeric hydridorhodium carbonyl species with the Rh−diphosphites (**ee**) and Rh−phosphine−phosphite (**ea**) systems precursors is presumably the key to controlling efficient chirality transfer.

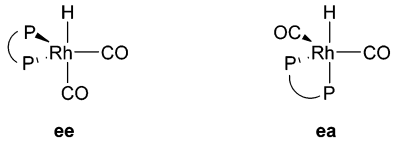


Figure 31. Equatorial−equatorial (**ee**) and equatorial−axial (**ea**) $[HRh(P-P)(CO)_2]$ species.

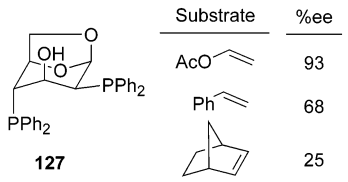


Figure 32. Rh-catalyzed asymmetric hydroformylation of olefins using ligand **127**.

4.1. P-Donor Ligands

4.1.1. Phosphine Ligands

Thus far, only two families of carbohydrate−phosphine ligands have been reported for the hydroformylation of olefins.

In 2000, Liu and co-workers designed a new diphosphine ligand **127** related to **10** with a pyranoside backbone for the Rh-catalyzed asymmetric hydroformylation of olefins (Figure 32).[77] This ligand has shown excellent enantioselectivities in the hydroformylation of vinyl acetate, while low-to-moderate ee's were obtained for styrene and norbornene. The rather high enantioselectivity in the hydroformylation of vinyl acetate is explained in terms of the hydrogen bonding between the OH group in the

ligand and the carbonyl group of the vinyl acetate.

The previously described furanoside phosphine ligands **77**−**79** (Figure 8) were also applied in the Rh-catalyzed asymmetric hydroformylation of styrene derivatives.[78] In general, they led to high regioselectivities (roughly 97%) in branched aldehyde and moderate enantioselectivities (ligands **77**, **78**, and **79** afforded 51% (*S*), 58% (*S*), and 44% (*S*) ee, respectively). As in the hydrogenation reaction, activities were improved when a methyl substituent was introduced at C-5 of the sugar backbone. It is worth nothing that there was a cooperative effect between stereocenters C-3 and C-5, which resulted in a matched combination for ligand **78**. The characterization of the rhodium complexes [$HRh(CO)_2$(PP)] (PP = **77**−**79**) formed under hydroformylation conditions by high-pressure NMR (HP NMR) shows that introducing a methyl substituent at C-5 induces a strong coordination preference, so ligands **78** and **79** have only one diastereoisomer with equatorial−axial (**ea**) coordinated diphosphine, while for [$HRh(CO)_2$(**77**)] there was equilibrium between two equatorial−axial diastereoisomers. However, this strong coordination preference only minimally affected enantioselectivity.[78]

4.1.2. Phosphinite Ligands

Thus far, only RajanBabu and co-workers have reported the use of sugar-based diphosphinite ligands in asymmetric hydroformylation. They used the previously mentioned ligands **22a**−**h** (Figure 9) in the metal-catalyzed asymmetric hydroformylation of several olefins (metal = Rh, Ir, Pt, and Co).[79] The best results were obtained in the hydroformylation of 2-vinylnaphthalene derivatives using a rhodium catalyst precursor. In contrast with Rh-catalyzed hydrogenation, in Rh-catalyzed hydroformylation enantioselectivities were best with diphosphinite ligands with electron-withdrawing aryl substituent groups on the phosphorus. There was also a remarkable solvent effect on enantioselectivity. Enantioselectivities were therefore best with ligand **22h** and Et_3SiH as a solvent (ee's up to 72% ee).

4.1.3. Phosphite Ligands

Thus far, only two families of carbohydrate−phosphite ligands have been reported for the hydroformylation of olefins.

Selke and co-workers also used the previously described diphosphite ligands **90** (Figure 16) with β-D-glucopyranoside backbone in the Rh- and Pt-catalyzed asymmetric hydroformylation of vinyl acetate, allyl acetate, and *p*-methoxystyrene. In general, good regioselectivities in branched product (>90%) and low-to-moderate enantioselectivities (ee's up to 36%) were obtained.[55]

An important breakthrough in this area came with the use of the previously mentioned tunable furanoside diphosphite ligands **92**−**97** (Figure 18) in the Rh-catalyzed hydroformylation of vinyl arenes.[31b,80] These ligands show both excellent enantioselectivities (up to 93%) and regioselectivities (up to 98.8%) under mild conditions (Table 3).

Table 3. Rh-Catalyzed Asymmetric Hydroformylation of Styrene Using Diphosphites 92−97[a]

entry	ligand	TOF[b]	% 2-PP[c]	% ee
1	**92c**	5	97	60 (*S*)
2	**93c**	5	97	61 (*R*)
3	**94b**	14	97.1	46 (*R*)
4	**94c**	13	97.2	58 (*R*)
5	**95b**	19	98.4	74 (*S*)
6	**95c**	18	98.6	90 (*S*)
7	**96b**	16	98.7	76 (*R*)
8	**96c**	17	98.3	89 (*R*)
9	**97b**	15	97.4	52 (*S*)
10	**97c**	12	97.6	64 (*S*)
11	**94d**	10	98.1	62 (*R*)
12	**95d**	11	98.8	93 (*S*)

[a] [$Rh(acac)(CO)_2$] = 0.0135 mmol; ligand/Rh = 1.1; substrate/Rh = 1000; toluene = 15 mL; $P_{H2/CO}$ = 10 bar; T = 20 °C; P_{CO}/P_{H2} = 0.5. [b] TOF in mol styrene × mol Rh^{1-} × h^{-1} determined after 1 h reaction time. [c] Regioselectivity for 2-phenylpropanal.

Unlike the hydrogenation process, hydroformylation shows (a) that the level of the enantioselectivity is influenced by a cooperative effect between stereocenters C-3 and C-5; accordingly, ligands **95** and **96** provide better enantioselectivities than ligands **94** and **97** (Table 3, entries 6 and 8 vs 4 and 10); and (b) that the absolute configuration of the product is governed by the configuration at the stereogenic center C-3. Accordingly, ligands **92**, **95**, and **97**, with an *S* configuration at C-3, gave (*S*)-2-phenylpropanal (Table 3, entries 1, 5, 6, 9, 10, 12) while ligands **93**, **94,** and **96**, with an *R* configuration at C-3, gave (*R*)-2-phenylpropanal (Table 3, entries 2−4, 7, 8, 11).

From points a and b it can be concluded that both the *S* and *R* enantiomers of the product can be obtained with excellent enantioselectivity. These results are among the best ever reported for the asymmetric hydroformylation of vinyl arenes.[76] There was also an influence on the substituents in the biaryl phosphite moieties. Thus, ligands **95c**,**d** and **96c**,**d** with either methoxy substituents or trimethylsilyl groups always produced the best enantioselectivities.

As in the hydrogenation, activities and enantioselectivities were best when a methyl substituent was introduced at C-5 of the sugar backbone.

The characterization of the rhodium complexes formed under hydroformylation conditions by NMR techniques and in situ IR spectroscopy showed that there is a relationship between the structure of the [$HRh(CO)_2$(PP)] (PP = **92**−**97**) species and their enantiodiscriminating performance. In general, enantioselectivities were highest with ligands with a strong bis-equatorial (**ee**) coordination preference, while an equilibrium of species with bis-equatorial (**ee**) and equatorial−axial (**ea**) coordination modes considerably reduced the ee's.[80b,c]

4.2. Heterodonor Ligands

Several types of heterodonor carbohydrate ligands have been developed for application in the asymmetric hydroformylation catalysis but with little success.

In 1996, Börner and co-workers developed a series of chiral phosphine−phosphite ligands, **128**−**132**,

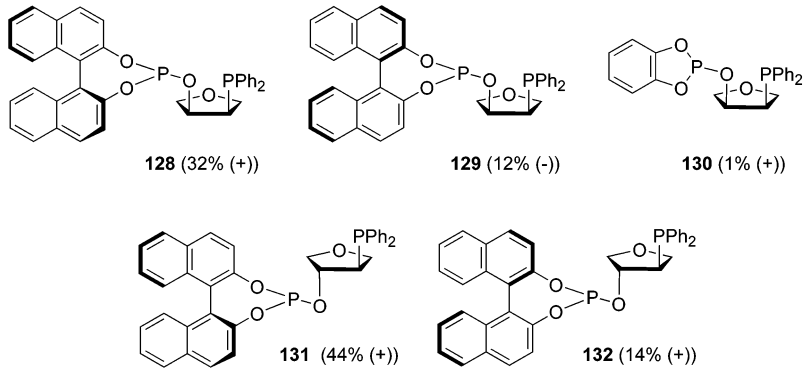


Figure 33. Furanoside phosphine−phosphite ligands **128**−**132**. Enantiomeric excess and absolute configuration are shown in brackets.

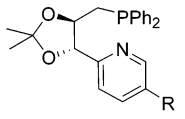


Figure 34. Mixed P,N-ligand **133** derivatives of 2,2-dimethyl-1,3-dioxolane.

with axial and central chirality for the Rh-catalyzed asymmetric hydroformylation of allyl acetate (Figure 33).[81] Their results clearly indicated that both central and axial chirality are responsible for the stereochemical outcome of this reaction. Enantioselectivities of up to 44% ee were obtained using ligand **131**.

Chelucchi and co-workers developed the first phosphine−pyridine derivatives of 2,2-dimethyl-1,3-dioxolane (Figure 34) for the Rh- and Pt-catalyzed asymmetric hydroformylation of styrene with low-to-moderate enantioselectivities (ee's up to 31%).[82]

The previously reported phosphine−amino ligands **116** (Figure 25) were also applied in the Rh-catalyzed hydroformylation of vinylarenes with low success (ee's up to 23%).[83] To elucidate the coordination mode of the P−N ligands, NMR studies were performed under catalytic conditions. Results showed that species with monodentate ligands were present in the catalytic solution. There was no evidence to suggest that chelated P,N-species were also present. This could explain the low enantiomeric excess obtained with this and the Cheluchi systems.

Recently, Claver and co-workers also used the previously mentioned series of phosphite−thioether **117**[67] (Figure 26), phosphite−phosphine **118**[84] (Figure 27), and phosphite−phosphoroamidite **119** and **120**[85] (Figure 28) ligands with furanoside backbone in the Rh-catalyzed asymmetric hydroformylation of styrene and derivatives.

Phosphite−thiother ligands **117** were applied with practically null enantioselectivity.[67] To determine the coordination mode of the P−S ligands, NMR studies were performed under catalytic conditions. Results indicated that under hydroformylation conditions the thioether moiety is not coordinated in the mononuclear hydride−rhodium complexes. This could explain the low enantiomeric excess obtained with this system and other thioether systems.[86]

Phosphite−phosphine ligands **118**[84] and phosphite−phosphoroamidite ligands **119** and **120**[85] generally showed low-to-moderate enantioselectivities in the Rh-catalyzed asymmetric hydroformylation of styrene (ee's up to 65%). As previously observed for the diphosphite ligands **92**−**97**, enantioselectivity was best when bulky substituents were present in the ortho positions of the biphenyl moieties.

5. Asymmetric Allylic Substitution

Palladium-catalyzed allylic substitution is one of the catalytic homogeneous reactions that has attracted the most attention in recent decades (and for which the catalytic cycle is well established). This is partly because this process is an efficient synthetic tool for the formation of carbon−carbon and carbon−heteroatom bonds, which is one of the main objectives in modern organic synthetic chemistry.[1c,87]

Two model Pd-catalyzed allylic substitutions are pictured in Scheme 4. *rac*-(*E*)-1,3-Diphenylprop-2-enyl is widely used as a substrate for alkylation reactions with dimethyl malonate (Scheme 4a) or for amination reactions with benzylamine (Scheme 4b) as nucleophile.

Since the first enantioselective catalytic process described by Trost in 1977, many catalytic systems have been tested and these have provided excellent enantiomeric excesses. Among the chiral ligands, bidentate nitrogen and phosphorus donors are widely used.[87,88] However, other donor atoms such as sulfur or selenium and monodentate ligands have also exhibited very good catalytic behavior.[89] As far as carbohydrate ligands are concerned, they have only very recently shown their huge potential as a source of highly effective chiral ligands in this process. Several types of ligands, mainly heterodonors, have been developed for this process. Some of the results are among the best ever reported.

In this section we describe the results published for the palladium-catalyzed allylic substitution since 1996.

5.1. P-Donor Ligands

5.1.1. Phosphine Ligands

The previously reported furanoside ligands **77**−**79** (Figure 8) were applied in the Pd-catalyzed asymmetric allylic substitution reactions.[90,91] Unlike the hydrogenation and hydroformylation processes, the results in the allylic alkylation of dimethyl malonate to (*E*)-1,3-diphenylprop-2-enyl acetate showed that

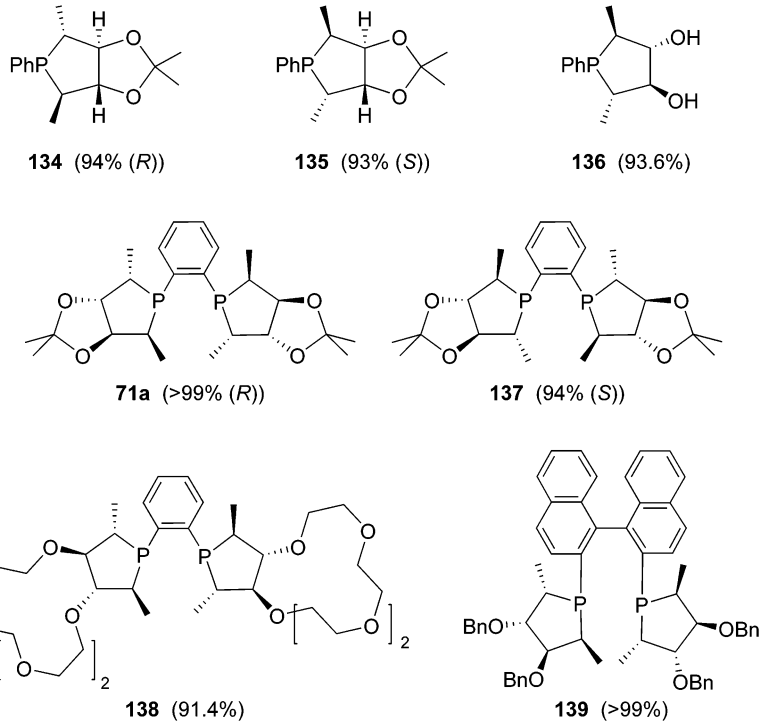
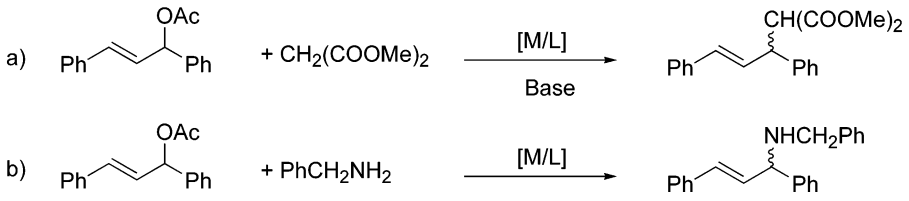


Figure 35. C_2-Phospholane ligand **71a** and **134**−**139**. Enantioselectivities are shown in brackets.

Scheme 4. Model Allylic Substitution Reactions: (a) Dimethyl Malonate (alkylation) and (b) Benzylamine (amination)



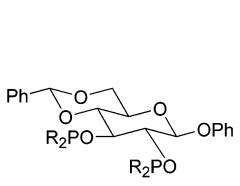
the configuration of C-5 has no relevant influence on enantiodiscrimination (ee's up to 61%).[91] Moreover, for ligand **75** there was a strong solvent effect and enantioselectivities increased to 78% when THF was used.[90]

The groups of RajanBabu and Zhang recently independently reported the use of monophospholane ligands **134**−**136**, diphospholanes **137**−**139**, and previously reported **71a** in the Pd-catalyzed allylic alkylation of dimethyl malonate to (*E*)-1,3-diphenylprop-2-enyl acetate (Figure 35).[92] In general, high enantioselectivities were achieved. Interestingly, the sense of asymmetric induction appears to be dictated by the absolute stereochemistry of the P-carrying carbons. Both enantiomers of the product can therefore be obtained.

RajanBabu also reported the use of DIOP and its derivatives **65** and **66** (Figure 5) in the Pd-catalyzed allylic alkylation of dimethyl malonate to (*E*)-1,3-diphenylprop-2-enyl acetate.[92a] Their results show that introducing a methyl substituent in the α positions of the phosphine groups in the DIOP ligand improved enantioselectivity from 0% to 63% ee when ligand **66** was used.

5.1.2. Phosphinite Ligands

Thus far, only RajanBabu and co-workers have reported the use of carbohydrate-based diphosphinite ligands for the allylic substitution reaction (Figures 36 and 37).[93] They applied the previously mentioned ligands **22** (Figure 36) in the Pd-catalyzed asymmetric allylic alkylation of diethyl malonate to 1,3-diphenylprop-2-enyl acetate with low-to-moderate enantioselectivities (ee's up to 59%).[93a] Interestingly, the results indicate an unprecedented electronic effect. Electron-withdrawing and electronic-rich diphosphinite ligands therefore lead to products with



R	%ee
Ph	0
3,5-*bis*-TMS-C_6H_3	16 (*R*)
3,5-*bis*-*t*-Bu-4-OMe-C_6H_2	25 (*R*)
3,5-*bis*-CF_3-C_6H_3	39 (*R*)
4-F-C_6H_4	17 (*S*)
3,5-*bis*-F-C_6H_3	41 (*S*)
4-CF_3-C_6H_4	55 (*S*)
Et	18 (*R*)
Cy	59 (*R*)

Figure 36. Pd-catalyzed asymmetric allylic alkylation of diethyl malonate to 1,3-diphenylprop-2-enyl acetate using ligands **22**.

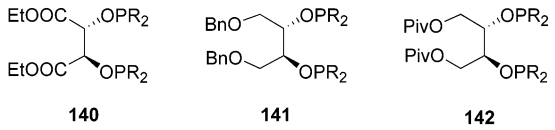


Figure 37. Diphosphinite ligands **140**−**142**.

opposite stereochemistry. Moreover, sterically bulky substituents have the same effect as electron-rich ones.

Diphosphinite ligands **140**−**142**, derived from tartaric acid, were also used in the Pd-catalyzed asymmetric allylic alkylation of diethyl malonate to 1,3-diphenylprop-2-enyl acetate.[93b] The electronic effects with these ligands were similar to those with ligands **22**, but enantioselectivities were up to 77% (Figure 37).

5.1.3. Phosphite Ligands

To our knowledge there is only one example of the application of diphosphite ligands to the Pd-catalyzed asymmetric allylic substitution reactions.[57d,91,94] The series of previously reported furanoside diphosphite ligands **92**−**96** (Figure 18) were also successfully applied in the Pd-catalyzed allylic substitution of diethyl malonate (ee's up to 95%) and benzylamine to 1,3-diphenylprop-2-enyl acetate (ee's up to 97%) (Table 4).

Table 4. Pd-Catalyzed Allylic Substituion Using Ligands 92−96[a]

entry	ligand	time (h)	% conv[b]	% ee[c]
1	**92a**	22	95	20 (*S*)
2	**92b**	1.5	83	90 (*S*)
3	**93b**	1.5	100	1 (*R*)
4	**93c**	22	11	5 (*R*)
5	**94b**	0.25	100	64 (*R*)
6	**94c**	0.32	100	45 (*R*)
7	**95b**	0.08	100	84 (*S*)
8	**95c**	0.17	100	95 (*S*)
9	**96b**	60	100	52 (*S*)
10[d]	**92b**	20	60	97 (*R*)

[a] All reactions were run at room temperature. Diphenylallyl acetate/palladium = 100. Malonate/palladium = 300. Ligand/palladium = 1. Diphenylallyl acetate/dimethyl malonate= 0.5. [b] Conversion determined by GC. [c] Enantiomeric excesses determined by HPLC. [d] Diphenylallyl acetate/palladium = 100. Ligand/palladium = 1. Diphenylallyl acetate/benzylamine = 0.5. Ligand/palladium = 1.

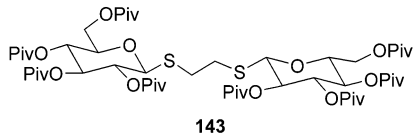
Results indicated that enantiomeric excesses depended strongly on the absolute configuration of the stereocenter carbon C-3 of the carbohydrate backbone. This behavior is similar to the results for asymmetric hydrogenation, except that the stereochemistry in the carbon atom C-3 that provides good enantioselectivities is reversed (vide supra). Ligands **92** and **95** therefore provided the highest enantiomeric excess in asymmetric allylic alkylation. Note that introducing a stereogenic center in C-5 had a positive effect on activity, though enantioselectivity was unaffected. This contrasts with the results from the hydroformylation and hydrogenation reactions (vide supra). These authors also concluded that the nucleophilic attack, which is generally accepted as the enantiodiscrimination step, takes place trans to the carbon atom C-5.

5.2. S-Donor Ligands

To date, chiral dithioether ligands have been shown to provide low to good enantioselectivities in Pd-catalyzed allylic alkylation.[89]

Among the previously reported ligand backbones based on tartaric acid **109**, **111**, and **112** (Figure 22), the five-membered ligand **111** afforded the best enantioselectivity (81% (*S*)) in the allylic substitution of diethyl malonate to 1,3-diphenylprop-2-enyl acetate.[89,95]

Recently, Khiar and co-workers used a combinatorial approach to find the best dithioether ligand **143** (Figure 38), from a library of 64 potential ligands



143

Figure 38. Dithioether ligand **143**.

(four linkers × four sugar residues × four protective groups), for the Pd-catalyzed allylic alkylation of diethyl malonate to 1,3-diphenylprop-2-enyl acetate (ee's up to 90%).[96] Dynamic NMR spectroscopy of a Pd(II) complex has shown that there is an efficient stereochemical control of the sulfur configuration upon coordination to the palladium.

5.3. Heterodonor Ligands

5.1.1. P–S Ligands

Different combinations of P,S-donor ligands such as phosphine−thioether, phospholane-thioether, phosphine−oxathiane, and phosphite−thioether have been studied. They have generally proven to be effective in enantioselective Pd-catalyzed allylic substitutions.

The ferrocenylphosphine−thiosugar ligand **144** (Figure 39) with multiple stereogenic units afforded

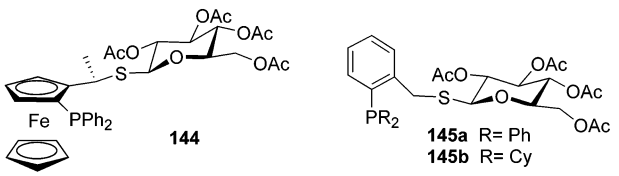
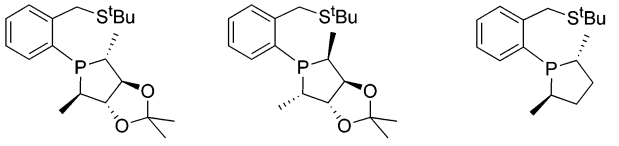


Figure 39. Thiother−phosphine ligands **144** and **145**.

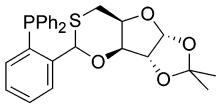
an ee of 88% in the palladium allylic substitution of diethyl malonate to 1,3-diphenylprop-2-enyl acetate.[97a] However, when the thiosugar moiety was the sole stereogenic unit on P,S-ligand (ligands **145**) (Figure 39), enantioselectivities were only moderate (ee's up to 64%).[97b]

Phospholane−thioether ligands **146**−**148** have been used in the Pd-catalyzed substitution of dimethyl malonate to 1,3-diphenylprop-2-enyl acetate with enantioselectivities up to 60% (Figure 40).[92a]



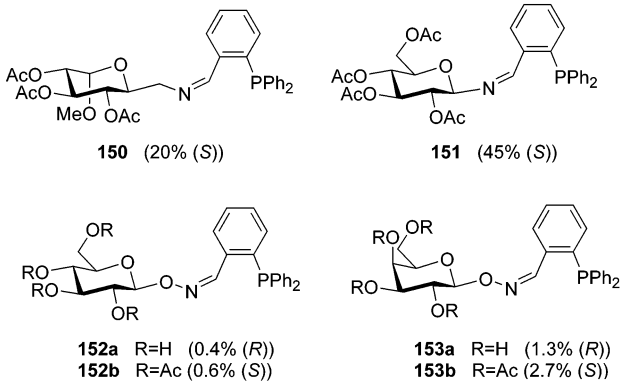
146 (44% (*S*)) **147** (60% (*R*)) **148** (31% (*S*))

Figure 40. Phospholane−thioether ligands **146**−**148**. Enantioselectivities are shown in brackets.



149

Figure 41. Phosphine−oxathiane ligand **149**.



150 (20% (*S*)) **151** (45% (*S*))

152a R=H (0.4% (*R*)) **152b** R=Ac (0.6% (*S*)) **153a** R=H (1.3% (*R*)) **153b** R=Ac (2.7% (*S*))

Figure 42. Bidentate P,N-ligands **150**−**153**. This figure also shows the enantioselectivities obtained in the Pd-catalyzed asymmetric allylic alkylation of dimethyl malonate to 1,3-diphenylprop-2-enyl acetate.

Recently, a phosphine−oxathiane ligand **149**, derived from D-(+)-xylose, has been developed for the Pd-catalyzed allylic substitution reactions (Figure 41). Good enantioselectivities have been obtained in the addition of dimethyl malonate to 1,3-diphenylprop-2-enyl acetate (ee's up to 91%) and in the addition of benzylamine to 1,3-diphenylprop-2-enyl acetate (ee's up to 94%).[98]

Previously reported phosphite−thioether ligands **117** (Figure 26) with a furanoside backbone have been applied in the model enantioselective palladium-catalyzed allylic alkylation and amination substitutions providing up to 58% and 67% ee, respectively.[94] In this case, both functionalities had similar donor properties, but the catalytic results indicate that the thioether moiety hardly affected the enantioselectivity. It was then assumed that the nucleophilic attack took place trans to the thioether group.

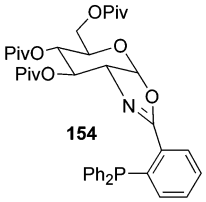
5.3.2. P–N Ligands

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.

The previously reported phosphine−amino ligands **116** (Figure 25) and phosphine−pyridine ligands **133** (Figure 34) have also been used in Pd-catalyzed asymmetric alkylation. The former gave enantioselectivities of up to 75%,[99] whereas the latter ligands provided low enantioselectivities (ee's up to 9%).[82]

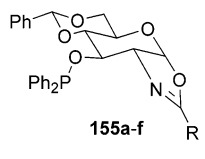
The groups of Ruffo[100] and Brunner[101] recently developed a series of P,N-ligands derived from D-mannose and D-glucose for the Pd-catalyzed asymmetric alkylation with low-to-moderate enantioselectivities (Figure 42).

An important breakthrough in the use of P,N-donor ligands for the Pd-catalyzed asymmetric allylic alkylation came with the work of the groups of Kunz,[102] Uemura,[103] and Pfaltz.[70]



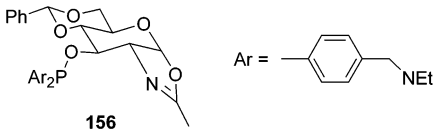
154

Figure 43. Phosphine−oxazoline ligand **154** developed by Kunz and co-workers.



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

Figure 44. Phosphinite−oxazoline ligands **155**. This figure also shows the enantioselectivities obtained in the Pd-catalyzed asymmetric allylic alkylation of dimethyl malonate to 1,3-diphenylprop-2-enyl acetate.



156

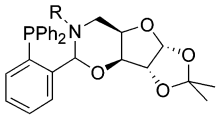
Figure 45. Water-soluble ligand **156**.

Kunz and co-workers developed a phosphine−oxazoline ligand **154** 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 43).[102] These results are in line with a nucleophilic attack trans to the phosphorus atom.

Uemura and co-workers developed a series of phosphinite−oxazoline ligands **155** also derived from D-glucosamine for the Pd-catalyzed allylic substitution reactions (Figure 44).[103] The results of the allylic alkylation of diethyl malonate to 1,3-diphenylprop-2-enyl acetate indicated that the best enantioselectivity was obtained with the smallest substituent on oxazoline (R = Me, ligand **155a**). Their results indicate that the nucleophilic attack took place trans to the phosphorus atom through an *endo* π-allyl Pd intermediate. Moreover, there was an unfavorable interaction between the R substituents on the oxazoline ring and the Ph group of the π-allyl moiety, which explains why the enantioselectivities obtained with ligand **155a** were best. Moreover, ligand **155a** was also effective for the Pd-catalyzed amination of ethyl 1,3-diphenylprop-2-enyl carbonate (ee's up to 94% (*R*)).

Water-soluble ligand **156** (Figure 45), related to **155a**, were effective for the Pd-catalyzed allylic alkylation of different nucleophiles to 1,3-diphenylprop-2-enyl acetate in aqueous or biphasic media (ee's up to 85%).[104]

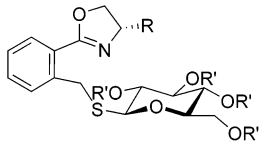
Pfaltz and co-workers used the previously reported phosphite−oxazoline ligand **121** (Figure 29) for the Pd-catalyzed allylic alkylation of several substrates.[70] This ligand showed good enantioselectivities in the reaction of 3-aryl-2-propenyl acetates (ee's up to 94%), whereas enantioselectivity was low in the reaction of 1,3-diphenylprop-2-enyl acetate (ee's up to 20%).



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

157

Figure 46. Phosphine−oxazinane ligands **157**. This figure also shows the enantioselectivities obtained in the Pd-catalyzed asymmetric allylic alkylation of dimethyl malonate to 1,3-diphenylprop-2-enyl acetate.



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

158a-d

Figure 47. Phosphinite−oxazoline ligands **158**. This figure also shows the enantioselectivities obtained in the Pd-catalyzed asymmetric allylic alkylation of dimethyl malonate to 1,3-diphenylprop-2-enyl acetate.

A series of phosphine−oxazinane ligands **157**, derived from D-xylose, have recently been developed for the Pd-catalyzed allylic alkylation (Figure 46). In general, enantioselectivities were low to moderate. The best enantioselectivity was obtained with ligand **157b**.[98]

5.3.3. P–P′ Ligands

Previously reported phosphine−phosphite ligands **118** (Figure 27) with a furanoside backbone have been used in the model enantioselective Pd-catalyzed allylic alkylation and amination substitutions providing up to 42% and 66% ee, respectively.[94] The authors also concluded that the nucleophilic attack takes place trans to the phosphine group.[94]

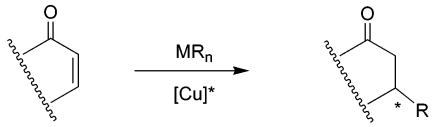
5.3.4. N–S Ligands

Thioglucose-derived ligands **158a**−**d** containing a chiral oxazoline moiety (Figure 47) used as chiral ligands in palladium-catalyzed allylic alkylation of diphenylprop-2-enyl acetate have provided some of the best results achieved in this reaction with mixed N,S-donor ligands.[105] Mild size effects of the thiosugar substituents on enantioselectivity were observed. The success of this kind of system seems to lie in the combination of thiosugar function with the proximity of all stereogenic units to the palladium allylic fragment because the Pd−N distance is shorter that the Pd−P distance in related phosphino−thiosugar palladium complexes.

6. Asymmetric 1,4-Addition

The enantioselective conjugate addition of organometallic reagents to α,β-unsaturated substrates, in particular, the addition of organocuprates to enones, is an attractive method to form a C−C bond and simultaneously introduce a new stereogenic center (Scheme 5).[106] These additions are key steps, for instance, in the synthesis of numerous biologically active compounds including steroids, prostaglandins, and terpens. A number of successful methods for enantioselective 1,4-addition based on chiral auxiliaries or stoichiometric organometallic reagents have

Scheme 5. Cu-Catalyzed 1,4-Addition of Organometallic Reagents to Enones



been widely studied, but few highly enantioselective catalytic processes have been reported. Excellent enantioselectivities have recently been obtained in the copper-catalyzed Michael addition of Grignard and diorganozinc reagents to enones and other α,β-unsaturated carbonyl compounds using phosphoroamidites,[107] amido−phosphine,[108] phosphite−oxazolines,[109] diphosphite,[110] and Schiff-based[111] ligands.

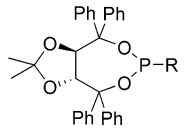
Several types of carbohydrate ligands, mainly monodentate phosphorus donors, have been used with excellent enantioselectivities. Others, such as bidentate phosphite and heterodonor N−S ligands, have also exhibited very good catalytic behavior.

Here we summarize the catalytic data reported since 1996 in the copper-catalyzed 1,4-addition of organometallic reagents to α,β-unsaturated compounds.

6.1. P-Ligands

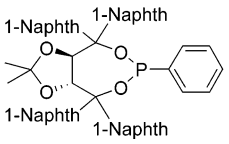
6.1.1. Phosphonite Ligands

Alexakis and co-workers developed a series of phosphonite ligands **159**−**161**, derived from (−)-TADDOL, with an exocyclic carbon framework (Figure 48).[112] These ligands were applied in the Cu-

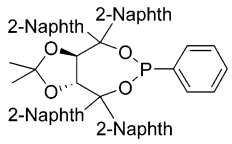


	R	%ee
a	*n*-Bu	48 (*S*)
b	*t*-Bu	17 (*S*)
c	Ph	50 (*S*)
d	2-MeO-C_6H_4	2 (*S*)
e	Fc	33 (*S*)

159



160 33 (*S*)

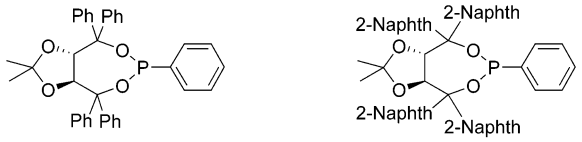


161 45 (*S*)

Figure 48. Phosphonite ligands **159**−**161** derived from (−)-TADDOL. This figure also shows the enantioselectivities obtained in the Cu-catalyzed 1,4-addition of diethylzinc to 2-cyclohexenone.

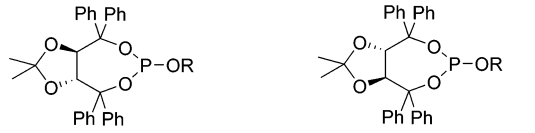
catalyzed 1,4-addition of diethylzinc to 2-cyclohexenone with low-to-moderate enantioselectivities (Figure 48). Their results indicate that the presence of bulky substituents has a negative effect on enantioselectivity and that the best enantioselectivities were obtained with ligands **159a** and **159c** (ee's up to 50%). These ligands were also applied in the diethylzinc addition to chalcone and benzalacetone with low enantioselectivities (ee's up to 8%)

Alexakis also used phosphonite ligands **162** and **163** (Figure 49), derived from (+)-TADDOL, in the asymmetric conjugate addition of diethylzinc to nitroolefins[113] and alkylidene malonates[114] with moderate-to-good enantioselectivities. Ligand **162** appears to



162 **163**

Figure 49. Phosphonite ligands **162** and **163** derived from (+)-TADDOL.



164 **165**

R = alkyl, cyclohexanyl, substituted cyclohexanyl, aryl

R= substituted cyclohexanyl

Figure 50. Basic structure of phosphite ligands **164** and **165**.

be the optimal choice for the diethylzinc addition to aryl nitro-olefins (ee's up to 86%).

6.1.2. Phosphite Ligands

The previously mentioned phosphite furanoside ligands **92**−**96** (Figure 18) were also applied in the Cu-catalyzed 1,4-addition of diethylzinc to cyclohexenone.[115] Results show that enantioselectivity depends strongly on the absolute configuration of the C-3 stereogenic center and in the biaryl substituents, while the sense of enantiodiscrimination is predominantly controlled by the configuration of the biaryl groups of the phosphite moieties. The best enantioselectivities were obtained with ligands **92h** and **94g** with ee's of 81% (*R*) and 84% (*S*), respectively. Interestingly, both enantiomers of the product can be obtained. Note that introducing a stereogenic center in C-5 had a positive effect on activity, while enantioselectivity was unaffected.

Alexakis and co-workers developed a series of phosphite ligands **164** and **165**, derived from (−)-TADDOL and (+)-TADDOL, with an exocyclic alcohol (Figure 50). These ligands were applied in the Cu-catalyzed 1,4-addition of diethylzinc to 2-cyclohexenone (ee's up to 96%),[112,116] benzalacetone (ee's up to 35%),[112,116] chalcone (ee's up to 50%),[112,116] nitro-olefins (ee's up to 96%),[113] and alkylidene malonates (ee's up to 73%)[114] (Figure 50).

For the addition to α,β-unsaturated ketones, the use of ligands with an achiral alcohol in the exocyclic position provided low enantioselectivity (Figure 51, ligands **164a**−**d**). Enantioselectivity was increased by using ligands with a chiral exocyclic alcohol if the right combination of the configuration of both chiral sources (TADDOL and alcohol) was chosen (Figure 51, ligands **164e** and **164f**). Moreover, these ligands generally provided low enantioselectivity for the addition to acyclic enones (ee's up to 50%).

6.1.3. Phosphoramidite Ligands

In the past few years mono- and diphosphoroamidite ligands, derived from TADDOL, have been developed for the Cu-catalyzed 1,4-addition of diethylzinc to several substrates (Figure 52).

The bidentate phosphoroamidite ligands **166** have been applied in the Cu-catalyzed conjugated addition of diethyl zinc to 2-cyclohexenone and 2-cyclopentenone with low-to-moderate enantioselectivity (ee's up to 38% for cyclohexenone and 18% for cyclopentenone).[117] Ligand **166a** has also been applied in several aromatic nitro-olefins using a multisubstrate approach with moderate enantioselectivities (ee's from 27% to 60%).[118]

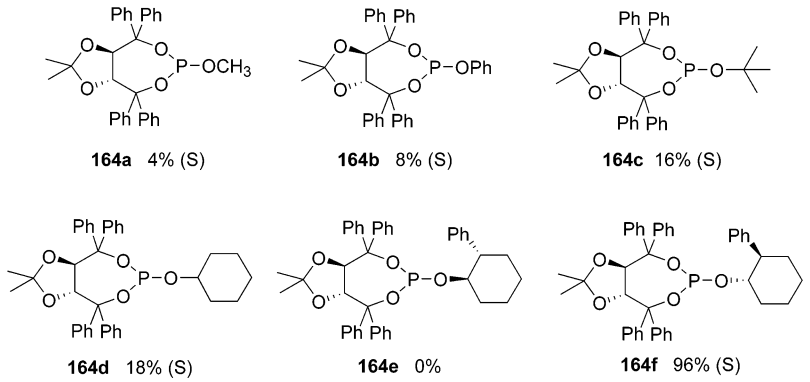
The series of monophosphoroamidite ligands **167** and **168** have been applied in the Cu-catalyzed conjugated addition of diethyl zinc to 2-cyclohexenone, benzalacetone, chalcone, and nitro-olefins with poor to moderate enantioselectivity.[112,113,116] Interestingly, ligand **168c** with the small methylamino group was among the best for α,β-unsaturated ketones (49%). However, results were poor with nitro-olefins (ee's up to 13%). For the latter substrates, ligand **168b** gave better enantioselectivities (ee's up to 56%).[118] Feringa and co-workers observed an unexpected improvement in enantioselectivity in the Cu−**168b**-catalyzed addition of diethyl zinc to cyclohexenone when using powdered molecular sieves (ee's up to 71%).[117b]

6.2. Nitrogen Ligands

To our knowledge, there is only one report of application of imines and amides (Figure 53) as chiral ligands to the Cu-catalyzed conjugated addition of diethyl zinc to 2-cyclohexenone.[119] These ligands displayed high activities but low enantiomeric excess (10−15%).

6.3. Heterodonor Ligands

The groups of Seebach and Alexakis developed a series of heterodonor O−S, N−S, and N−P ligands



164a 4% (S) **164b** 8% (S) **164c** 16% (S)

164d 18% (S) **164e** 0% **164f** 96% (S)

Figure 51. Selected phosphite ligands **164** in the Cu-catalyzed asymmetric addition of diethylzinc to cyclohexenone.

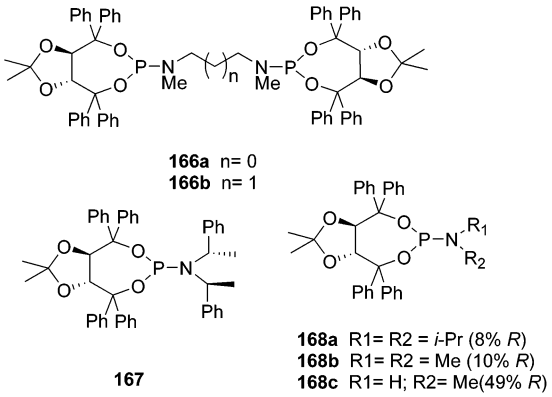


Figure 52. Phosphoroamidite ligands **166**−**168** derived from TADDOL. This figure shows the enantioselectivities obtained in the diethyl zinc addition to benzalacetone.

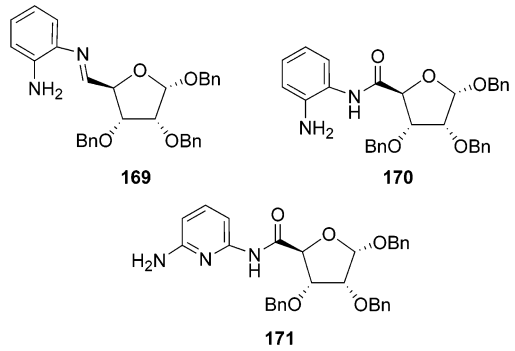


Figure 53. Nitrogen ligands **169**−**171**.

derived from TADDOL for the Cu-catalyzed 1,4-addition of organometallic reagents to cyclic and lineal enones (Figure 54).[112,116,120] The best enantioselectivities were obtained with **173** in the Cu-catalyzed addition of butylmagnesium chloride to cycloheptanone (ee's up to 84%).[120] Ligands **174** and **175** provided low-to-moderate enantioselectivities (ee's up to 38%).[112,116]

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.

Thioether−hydroxyl furanoside ligands **176** (Figure 55) were used in the conjugate addition to 2-cyclohexenone (ee's up to 62%) and to *E*-non-3-en-2-one (ee's up to 34%). Results indicated that conversions were higher for electron-rich ligand **176b**, while enantioselectivities were better with ligand **176c**.[121]

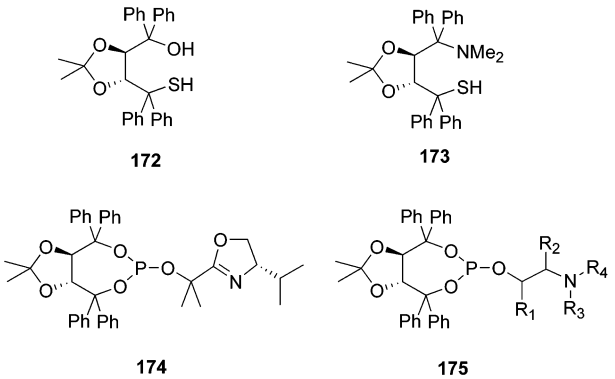


Figure 54. Heterodonor ligands **172**−**175** derived from TADDOL.

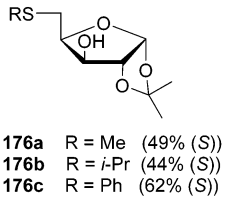


Figure 55. Furanoside ligands **176**. This figure shows the enantioselectivities obtained in the diethyl zinc addition to 2-cyclohexenone.

Amino−phosphite furanoside ligands **177** and **178** (Figure 56) were applied in the conjugate addition

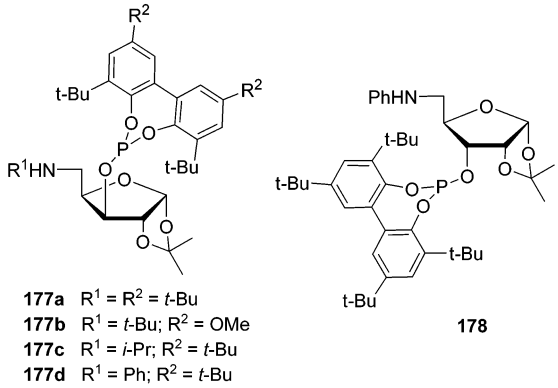


Figure 56. Amino−phosphite ligands **177** and **178**.

of diethyl zinc to 2-cyclohexenone. Results showed that the configuration of the stereogenic carbon atom C-3 at the ligand backbone and the different substituents at the amino group strongly affected activity and enantioselectivity. The best enantioselectivities were obtained with ligand **177d**, which has an *R*-configuration at C-3 and a phenyl substituent on the amino group (ee's up to 63%).[122]

Previously reported phosphite−thioether ligands **117** (Figure 26) and ligands **179** (Figure 57) were

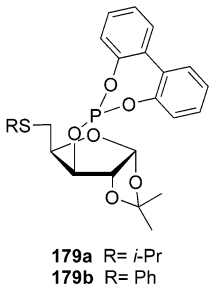


Figure 57. Thioether−phosphite ligands **179**.

tested in the Cu-catalyzed conjugate addition of diethyl zinc to 2-cyclohexenone. Results indicated that enantioselectivity was strongly affected by the substituents in the thioether moiety and in the biaryl phosphite moiety. Enantioselectivities were best for ligand **179b**.[123]

The previously mentioned furanoside phosphine−phosphite **118**[123] (Figure 27) and phosphite−phosphoroamidite **119** and **120**[122] ligands (Figure 28) were also tested in the Cu-catalyzed conjugate addition of diethyl zinc to 2-cyclohexenone with low-to-moderate enantioselectivities (ee's up to 63%).

7. Other Processes

7.1. Asymmetric 1,2-Addition

The enantioselective 1,2-addition of organometallic reagents (mainly diorganozinc) to aldehydes is one of the most important synthetic procedures for obtaining enantiopure secondary alcohols. The fact that this reaction can also be promoted by $Ti(O^iPr)_4$ has increased the possibility of inducing asymmetric induction by increasing the number of ligands that can be used. Many chiral ligands (β-amino alcohols, diols, hydroxy sulfonamides, among others) have been successfully applied for many years.[1c] As far as carbohydrate ligands are concerned, the TADDOL derivatives have played a predominant role. This is very well documented in the review by Seebach and co-workers.[124] Other sugar backbones have also been successfully applied in this process. The work done by the groups of Kim, Bauer, and Zheng is of particular interest (Figure 58).

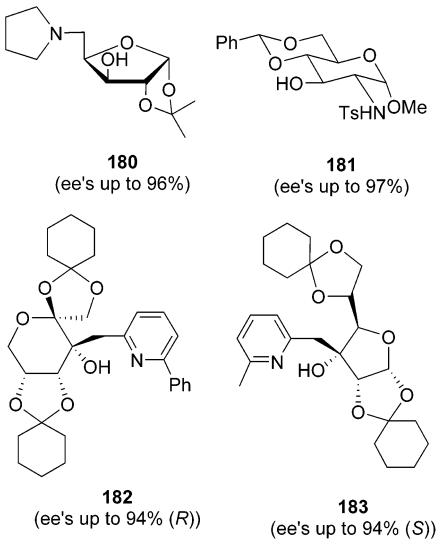


Figure 58. Carbohydrate-based ligands successfully applied in the asymmetric 1,2-addition.

In 1996, Kim and co-workers developed a series of furanoside β-amino alcohols, derived from D-(+)-xylose, for the asymmetric addition of diethyl zinc to several aldehydes. Ligand **180** provided high yields and enantioselectivities for aromatic aldehydes (ee's up to 96%).[125]

More recently, Bauer and co-workers developed a-hydroxy sulfonamide ligands derived from D-glucosamine for the Ti-catalyzed asymmetric addition of diethyl zinc to several aldehydes. Ligand 181 provided high yields and enantioselectivities for aromatic and aliphatic aldehydes (ee's up to 97%).[126]

Zheng and co-workers developed a series of pseudoenantiomeric pyridyl alcohols derived from D-fructose and D-glucose for the asymmetric addition of diethyl zinc to several aldehydes. Both enantiomers can be obtained in good yields and enantioselectivities using ligands **182** and **183 (**ee's up to 94%).[127]

7.2. Asymmetric Heck Reaction

The enantioselective Pd-catalyzed arylation or vinylation of olefins is a powerful method to synthesize both tertiary and quaternary chiral carbon centers. High enantioselectivities have been reached by using bidentate ligands, usually diphosphines and phosphine−oxazoline ligands.[1c] To our knowledge, only two kinds of carbohydrate derivative ligands **155** (Figure 44) and **166a** and **168b** (Figure 52) have been efficiently applied in the Pd-catalyzed Heck reaction.

The previously reported pyranoside phosphinite−oxazoline ligands **155** (Figure 44) were successfully applied in the Pd-catalyzed enantioselective arylation of 2,3-dihydrofuran (ee's up to 96%). This set of ligands was also applied in the phenylation of *trans*- and *cis*-crotyl alcohols with low enantioselectivity (ee's up to 17%).[128]

Phosphoroamidite ligands **166a** and **168b** were applied in the Pd-catalyzed intramolecular Heck reaction of cyclohexadienone monoacetals with high enantioselectivities (ee's up to 96%). Results indicate that the extra flexibility and rotational freedom obtained by using monodentate ligand **168b** instead of bidentate ligand **166a** has a beneficial effect on enantioselectivity.[129]

7.3. Asymmetric Hydroboration

The asymmetric hydroboration of alkenes is one of the most valuable synthetic techniques in organic synthesis because the organoboranes formed are readily converted into various kinds of organic compounds. Diphosphines have played a dominant role in the catalytic version of this process.[1c] To our knowledge, there is only one report of the successful application of carbohydrate ligands in the Rh-catalyzed hydroboration of styrene. The phosphine−phosphite ligand **184** (Figure 59), derived from TADDOL, provided an enantioselectivity of 91%.[130]

7.4. Asymmetric Hydrosilylation

In the last few decades, the asymmetric Rh-catalyzed hydrosilylation of ketones has been recognized as a versatile method to provide optically active secondary alcohols. For many years, a large number of chiral ligands, mainly P- and N-containing compounds possessing either C_1- or C_2-symmetry, have been used successfully in asymmetric Rh-catalyzed hydrosilylation.[1c]

As far as carbohydrate ligands are concerned, only monodentate TADDOL-based phosphonite ligands developed by the groups of Scharf and Seebach have been successfully used in this process.[131]

Scharf and co-workers have taken advantage of the previously successfully applied phosphonite ligand **162** to investigate the effect of introducing a confor-

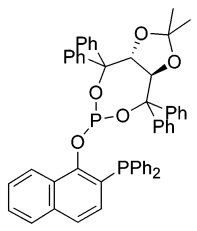
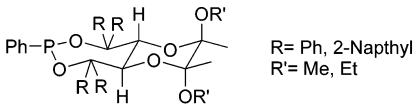


Figure 59. Phosphine−phosphite ligand **184**.

mationally rigid 1,4-dioxane backbone with ligands **185** (Figure 60).[132] Disappointingly, the use of these



185

Figure 60. Phosphonite ligands **185**.

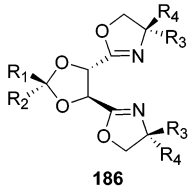
ligands resulted in similar enantioselectivities (ee's up to 86%).

Seebach and co-workers applied the previously reported ligand **121** (Figure 29) for the Rh-catalyzed asymmetric hydrosilylation of several ketones with high enantioselectivities (ee's up to 95%).[133]

7.5. Asymmetric Cyclopropanation

Asymmetric catalytic cycloaddition of electrophilic metal carbenes to prochiral olefins is a facile method for highly enantioselective cyclopropane synthesis. Cyclopropanes play an important role as starting material and intermediates in organic synthesis because they can be easily converted to a variety of useful products by cleavage of the three-membered ring.[1c] High enantioselectivities have been reached by using bidentate nitrogen ligands, usually bis-oxazoline ligands.[1c,134]

As far as carbohydrate ligands are concerned, they have been scarcely used.[135] To our knowledge, only the tartrate-derived bis-oxazoline ligands **186** (Figure 61) developed by the groups of Anderson and Knight



186

Figure 61. Tartrate-derived bis-oxazoline ligands **186**.

have been successfully used in the Cu-catalyzed cyclopropanation of olefins (ee's up to 96%).[135a−c]

8. Concluding Remarks and Perspectives

Carbohydrate ligands have undoubtedly become some of the most versatile ligands for enantioselective catalysis. Excellent control of selectivity, based on the properties of the ligand, has been demonstrated. This means that by appropriate ligand tuning (i) a ligand can be selected for each particular reaction and (ii) both enantiomers of the product are accessible. For industrial applications, however, the productivity of the catalysts needs to be further improved to achieve high turnover numbers and frequencies. Hopefully the efficiency of the catalyst can be increased and the search for improved ligand systems will be greatly assisted by combinatorial screening methods, for which the readily available carbohydrate ligands may prove to be well suited. Finally, it is predicted that many new applications will be discovered in the years to come.

9. Acknowledgment

Financial support from the Spanish Ministerio de Educación, Cultura y Deporte, and the Generalitat de Catalunya (CIRIT) is gratefully acknowledged.

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CR0306889