CHEMICAL REVIEWS

REVIEW

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Phosphite-Containing Ligands for Asymmetric Catalysis

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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 by which enantiopure compounds can be produced, enantioselective 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]

To achieve the highest levels of reactivity and selectivity in catalytic enantioselective reactions, several reaction parameters must be optimized, the most crucial of which is perhaps the design of the chiral ligand.[2] In this context, in the early 1990s, phosphites emerged as suitable ligands for asymmetric Rh-catalyzed hydroformylation[3] and Cu-catalyzed 1,4-additions.[4] In recent years, their use has been successfully extended to other catalytic reactions. Noteworthy are the important breakthroughs achieved using phosphite-containing ligands in the asymmetric hydrogenation of functionalized and unfunctionalized olefins, asymmetric allylic substitution, and the Heck reaction, among others. Phosphite ligands are extremely attractive for catalysis because they are easy to prepare from readily available alcohols, which enables us to synthesize and screen series of chiral ligands in the search for high activities and selectivities for each particular reaction. Another advantage of phosphite ligands is that they are less sensitive to air and other oxidizing agents than phosphines. Furthermore, they are amenable to parallel synthesis, even in solid phase synthesis. On the other hand, phosphites are prone to decomposition reactions such as hydrolysis, alcoholysis, and the

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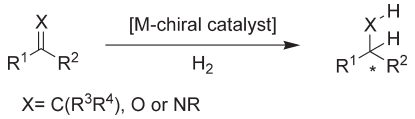
Scheme 1. Asymmetric Hydrogenation of C═C, C═O, and C═N Double Bonds



Arbuzov reaction. In many instances, these side reactions can be suppressed, however, when bulky aryl phosphites are used.

This review will cover the literature reports on the use of phosphite-based ligands in asymmetric catalysis in the past decade, the most active period in this area of research. We will focus on the asymmetric reactions that were most frequently studied during this period. Below, a variety of catalytic reactions containing phosphite-based ligands that have been applied in asymmetric catalysis will be presented and mechanistic aspects discussed. For each particular reaction, we will pay special attention to the key ligand parameters needed for high selectivity. For each reaction, we will also provide the reader with an overview of the state of the art.

2. ASYMMETRIC HYDROGENATION

The asymmetric hydrogenation of prochiral compounds catalyzed by chiral transition-metal complexes has been widely used in stereoselective organic synthesis, and several processes have found industrial applications (Scheme 1).[1] For many years, both the reactant scope and the catalyst efficiency of this reaction have been gradually extended. For the hydrogenation of functionalized olefins and ketones, rhodium and ruthenium complexes containing phosphorus and nitrogen chiral ligands have proved to be the best catalysts.[1] Excellent activities and enantioselectivities have been achieved during recent decades for the asymmetric hydrogenation of dehydroamino acids and other functionalized alkenes and ketones. For the hydrogenation of unfunctionalized olefins and imines, iridium complexes containing P,N ligands have become the most successful catalysts.[1] Although significant progress has been made in this area in recent years, asymmetric hydrogenations remain a challenge for many of these substrates.

Numerous chiral ligands, mainly P- and N-containing ligands with either C_2- or C_1-symmetry, have been successfully applied.[1] Diphosphines have played a dominant role among the P-ligands, but recently phosphite ligands—a group of less electron-rich phosphorus compounds—have received considerable attention. In this section, we report the opportunities that phosphite-containing ligands provide for improving the performance of asymmetric hydrogenation.

2.1. Di- and Monophosphite Ligands

2.1.1. Diphosphite Ligands. The first reports on the use of diphosphite ligands in asymmetric hydrogenation were published by the groups of Brunner,[5] Wink,[6] Kolich,[7] and Selke[8] and concerned low-to-moderate enantioselectivities in the hydrogenation of the enamides, 2-(4-isobutylphenyl)acrylic acid, and methyl (*Z*)-2-*N*-acetamidocinnamate (Figure 1).

An important breakthrough in the use of phosphite ligands for asymmetric hydrogenation came with the work of Reetz and coworkers,[9] who developed a series of C_2 ligands **1** derived from dianhydro-D-mannitol with different phosphite substituents (**a**−**e**) (Figure 2). These ligands were efficiently applied in the Rh-catalyzed hydrogenation of dimethyl itaconate and methyl *N*-acetamidoacrylate (ee's up to 98.2% and 88.7%, respectively).

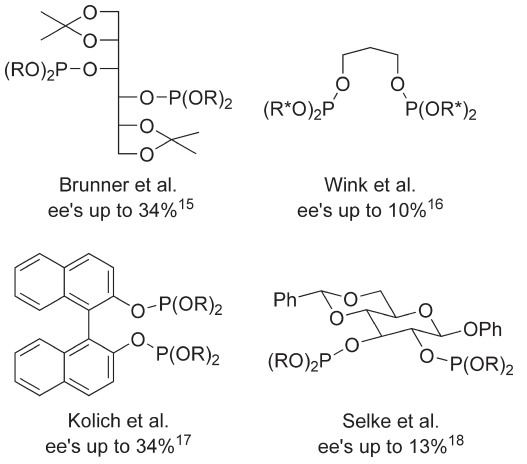


Figure 1. Structure of the first phosphite ligands used in the asymmetric hydrogenation reaction. This figure also shows the best enantioselectivities obtained.

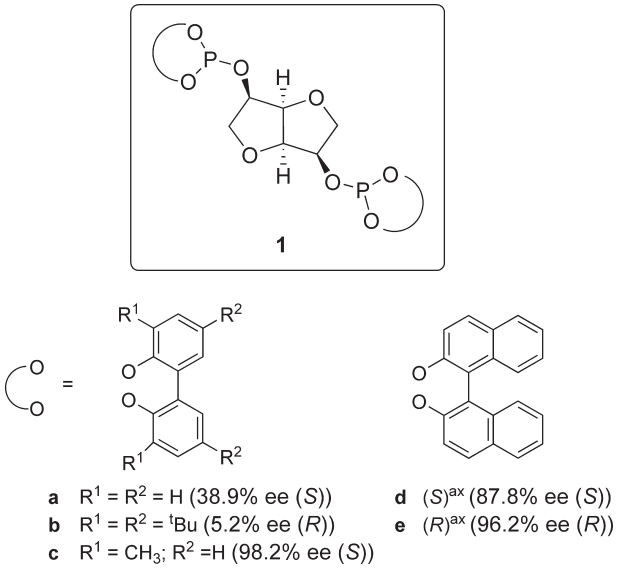


Figure 2. D-Mannite diphosphite ligands developed by Reetz et al. The enantioselectivities obtained in the reduction of dimethyl itaconate are shown in parentheses.

The results indicated that the sense of enantiodiscrimination is predominantly controlled by the configuration of the binaphthyl moiety. There was also a cooperative effect between the stereogenic centers of the ligand backbone and the stereogenic binaphthyl phosphite moieties. This resulted in a matched combination for ligand **1e** (ee's up to 96.2%). They also found that ligand **1c** with conformational flexibility in readily epimerizing biphenyl moieties proved superior to those with fixed binaphthyl chirality (ee's up to 98.2% ee).

These excellent pioneering results led to the recent development of other diphosphite ligands.[10]

In this context, a series of highly modular C_1-diphosphite ligands **2**−**7** (Figure 3), with a furanoside backbone, were developed for Rh-catalyzed hydrogenation.[10a−10c] These ligands are derived from D-(+)-xylose and D-(+)-glucose. Excellent enantioselectivities (ee's up to >99%) and activities were achieved in the Rh-catalyzed hydrogenation of several dehydroamino acid

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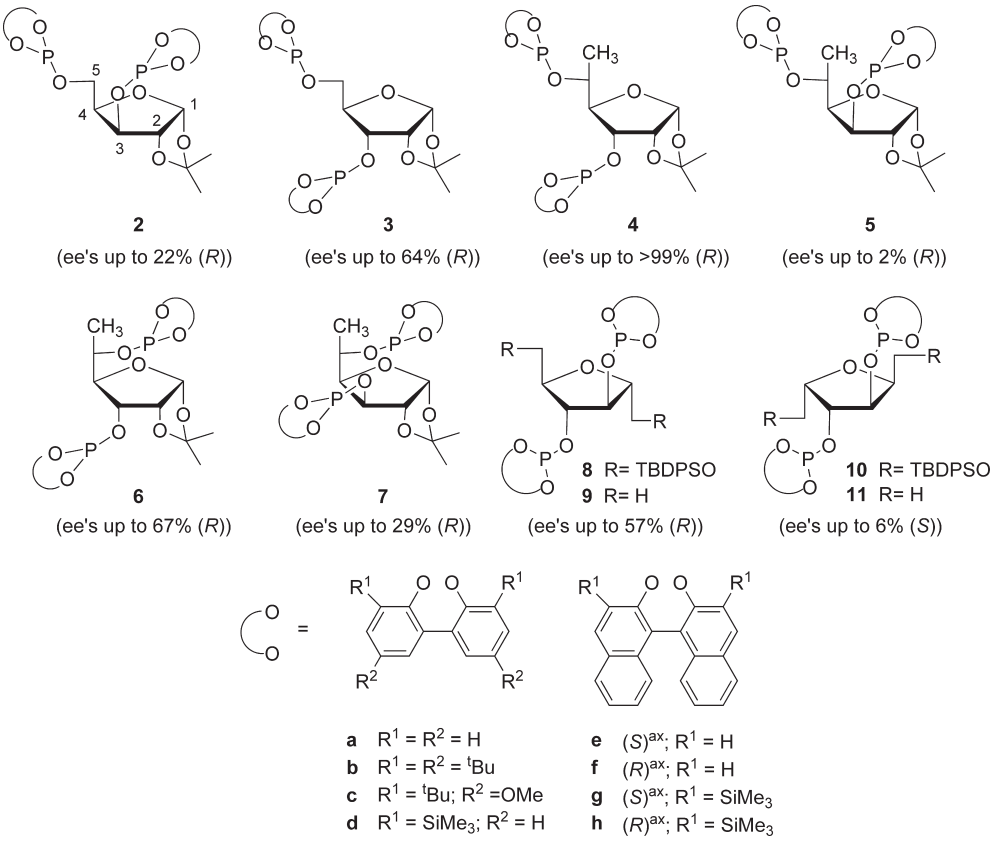

Figure 3. Representative furanoside diphosphite ligands **2**−**11**. The enantioselectivities obtained in the reduction of methyl *N*-acetamidoacrylate are shown in parentheses.

derivatives. Systematic variation of stereocenters C-3 and C-5 at the ligand backbone showed that enantiomeric excesses depended strongly on the absolute configuration of C-3 but only slightly on that of stereocenter C-5. Enantioselectivities were therefore best with ligands **4d** with (*R*) configuration on both C-3 and C-5 stereocenters. Ligands **2** were also applied in the Ir-catalyzed asymmetric hydrogenation of imines with moderate success (ee's up to 46%).[10e] Ru-nanoparticles stabilized with ligands **2** were used in the asymmetric hydrogenation of arenes. Although activities and diastereoselectivities were good, levels of enantioselectivity were not significant.[10f] More recently, C_2-symmetric furanoside diphosphite ligands **8**−**11** (Figure 3), derived from D-glucosamine and D-glucitol, have been used in the Rh-catalyzed asymmetric hydrogenation of methyl acetamidoacrylate with enantioselectivities up to 57%.[10g]

Matt and co-workers successfully applied diphosphite ligand **12** (Figure 4), built on a cyclodextrin scaffold, in the Rh-catalyzed asymmetric hydrogenation of dimethyl itaconate with ee's up to 83.6%.[10h]

Beller,[10i] Vogt,[10j] and Lyubimov,[10k,l] with their respective groups, have also contributed to the development of new diphosphite ligands for the Rh-catalyzed hydrogenation of dehydroamino acid derivatives with moderate success (Figure 5).

More recently, Takacs and co-workers used click chemistry to develop diphosphite ligands **17**−**20** with macrocyclic chelates (Figure 6).[10m] They were successfully applied to the Rh-catalyzed asymmetric hydrogenation of enamides and itaconates (ee's up to 97%). Spectroscopic data and mass spectral analyses, as well as the results obtained using related monophosphites and

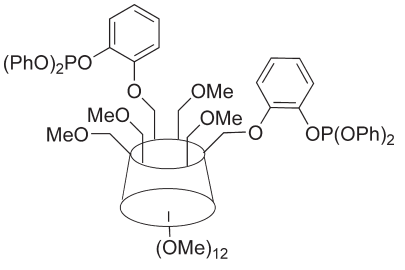

Figure 4. Cyclodextrine-based diphosphite ligand **12** developed by Matt et al.

the lack of a nonlinear effect, suggest that the 16-membered P,P-macrocyclic Rh(I) chelate is formed, which is responsible for the catalytic activity.

Recently, van Leeuwen and Reek reported a new concept in the design of ligands for asymmetric catalysis. They used a template-induced formation of chelating ligands by the selective self-assembly of two monodentate phosphite ligands using either a rigid zinc(II)-salphen template (Figure 7a)[10n−10p] or urea-based ligands, self-assembled through hydrogen bonding interactions (Figure 7b).[10q,10r] The results using the zinc(II)-salphen template indicated that the rigidity of the template is not an important factor in the improvement of enantioselectivity. Enantioselectivities up to 89% were obtained in the Rh-catalyzed hydrogenation of α-methylcinnamic acid.[10n−10p] The supramolecular urea-based homobidentate approach has been more successful for asymmetric hydrogenation. High enantioselectivities

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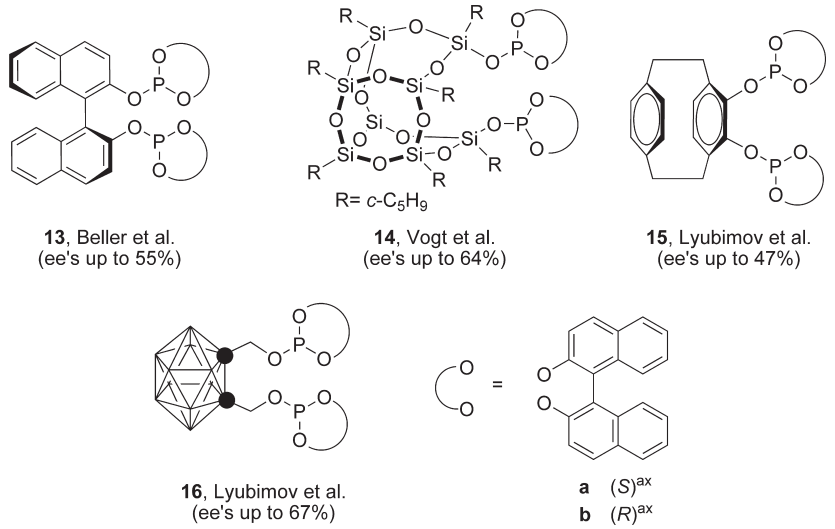

Figure 5. Diphosphite ligands **13**−**16**. The best enantioselectivities obtained in the reduction of methyl-(*Z*)-acetamidocinnamate are shown in parentheses.

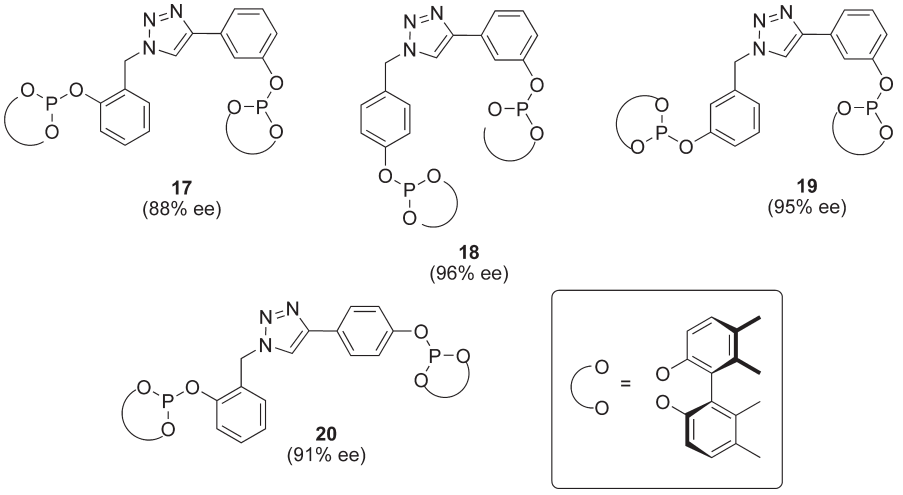

Figure 6. Macrocyclic diphosphite ligands **17**−**20** developed by Takacs et al. The enantioselectivities obtained in the reduction of *N*-[1-(4-chlorophenyl)ethenyl]acetamide are shown in parentheses.

have been therefore achieved for enamides, acrylate, and α- and β-dehydroamino acid derivatives (ee's up to 96%).[10q,r]

2.1.2. Monophosphite Ligands. For more than 30 years, bidentate chiral ligands were considered superior to monodentate ligands in metal-catalyzed asymmetric hydrogenation, as chelation was believed to be necessary to impart sufficient rigidity to the metal complex for chirality to be efficiently transferred.[1] Recently, chiral monodentate phosphorus ligands were reported to lead to excellent results in the asymmetric hydrogenation of several functionalized substrates.[1b,2] In the past few years, therefore, the use of monophosphite ligands in this process has been extensively studied.

Reetz and co-workers initiated research in this area.[11] They found that the monophosphite ligands **23a** and **23b** related to the diphosphite ligands derived from mannitol **1** described above (Figure 2) provided similarly high enantioselectivities (Figure 8, ee's up to 97.8%).

Reetz's work established the basis for further research on monodentate ligands. Over the years, a large library of binol-based monophosphite ligands has been developed, containing several modifications in the ligand design (Figure 9), most of which vary the alcohol unit (R) with ligands **24**.[11,12] These ligands were applied to the asymmetric Rh-catalyzed hydrogenation of α- and β-dehydroamino acid derivatives, itaconates, and enamides. The results indicated that enantioselectivities for each substrate type can be excellent if the appropriate alcohol unit is chosen (Figure 10). Mechanistic studies indicated that two monodentate P-ligands are attached to rhodium and the lock-and-key mechanism holds, in which the thermodynamics of Rh/olefin complexation with the formation of the major and minor diastereomeric intermediates dictates the stereochemical outcome.[12b] The major diastereomer leads to the favored enantiomeric product, which is opposite to the state of affairs in classical Rh-catalyzed olefin hydrogenation based on chiral chelating diphosphines (*anti* lock-and-key mechanism as proposed by Halpern).

This type of ligand was also modified by introducing a new substituent at the *ortho* position of the binaphthol moiety with ligand **25** (Figure 11). This ligand provided enantioselectivities up to 97% in the Rh-catalyzed hydrogenation of methyl 2-acetamidoacrylate.[13]

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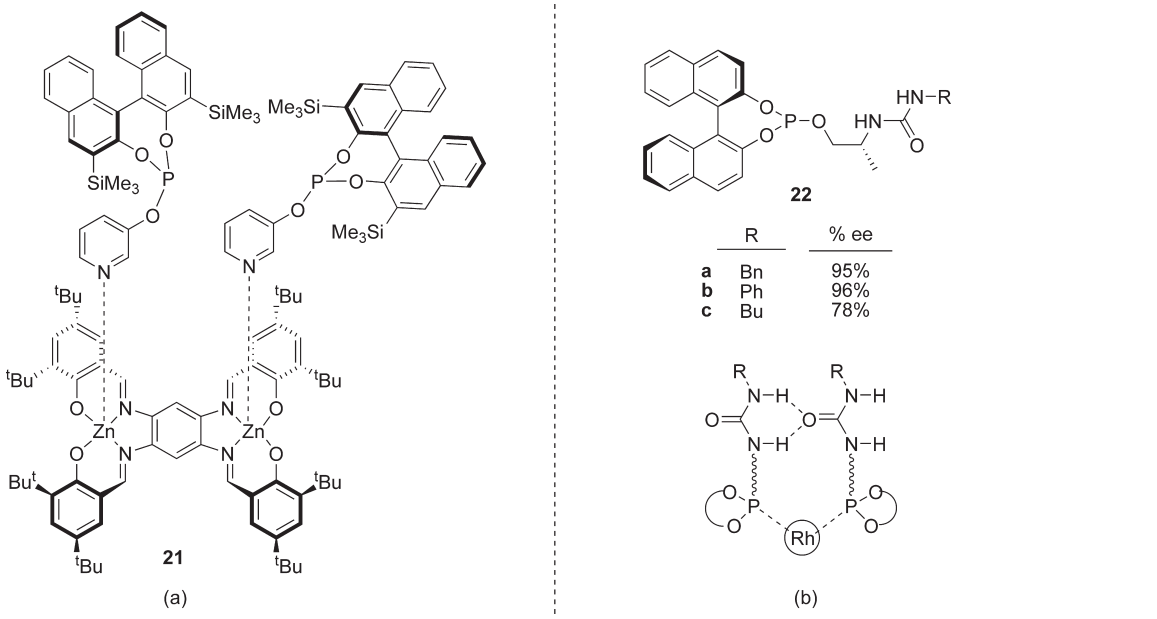

Figure 7. Representative examples of supramolecular bidentate phosphite ligands. (a) Zn-template-assisted phosphite ligand approach. (b) Urea self-assembled phosphite ligand approach. Enantioselectivites obtained in the reduction of (*E*)-methyl 2-(acetamidomethyl)-3-phenylacrylate are also shown.

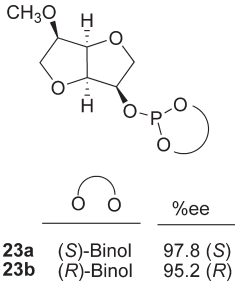

Figure 8. Monophosphite ligands **23** developed by Reetz et al. This figure also shows the enantioselectivities obtained in the reduction of dimethyl itaconate.

A polymer-supported version of binol ligand-type **24** has been developed to favor catalyst separation while maintaining high activities and enantioselectivities.[14] Chiral ionic imidazolium[15a] and quaternary ammonium[15b,c] binol-based monophosphite ligands have also been developed to be used in ionic liquids and immobilized by ionic interaction on an anionic support (ee's up to 99%).[15] Binol-based monophosphite ligands have also been applied in the asymmetric hydrogenation of dimethyl itaconate using $scCO_2$ as a "green solvent", at the cost of a slightly lower asymmetric induction.[16]

Other groups have also explored the use of monophosphite ligands for the asymmetric hydrogenation of carbon−carbon double bonds.[17] In particular, the groups of Dreisbach and Ojima have recently extended the study to enantiomerically pure biphenyl-based monophosphites **26** (Figure 12).[17c−e] They studied the effect of the substituents (R_1-R_4) of the biphenyl moiety in combination with a variation in the alcohol unit attached to the biphenol basic framework (R) and found excellent ligands for the rhodium-catalyzed asymmetric hydrogenation of several dehydroamino acid derivatives and itaconates (ee's up to 99.6%).

More recently, Reetz and co-workers developed a new concept in combinatorial asymmetric catalysis.[18] They discovered that

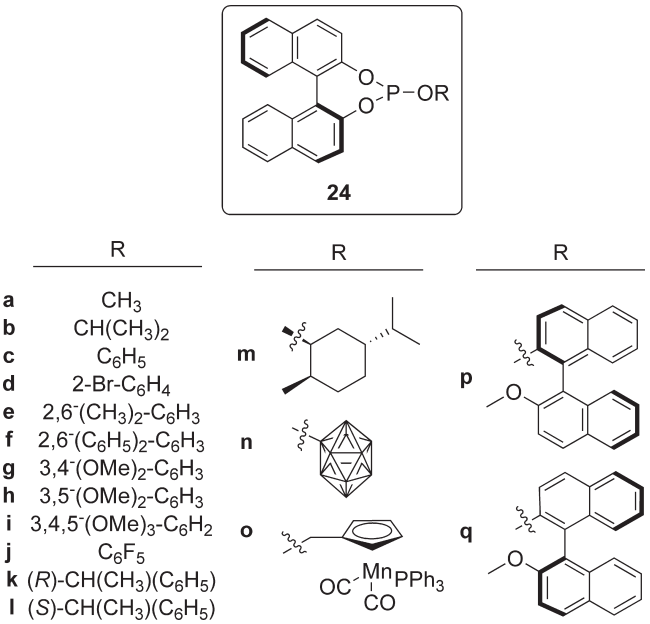

Figure 9. Representative binol-based monophosphite ligands **24**.

certain mixtures of different chiral monodentate ligands (in which two such ligands are bonded to rhodium) are much more active and enantioselective than either of the pure ligand systems (Scheme 2).[18a] This concept has also been applied by Gennari and co-workers.[12g,19] Reetz and co-workers also disclosed that high enantioselectivities can also be obtained by combining a chiral phosphite ligand with an achiral monodentate P-ligand as simple as PPh_3.[20]

Other work on the design of new monophosphite ligands has focused on the screening of carbohydrate-based ligands **27**−**34** for the Rh-catalyzed asymmetric hydrogenation of vinyl carboxylates, dehydroamino acids, and enamides (Figure 13).[21] In

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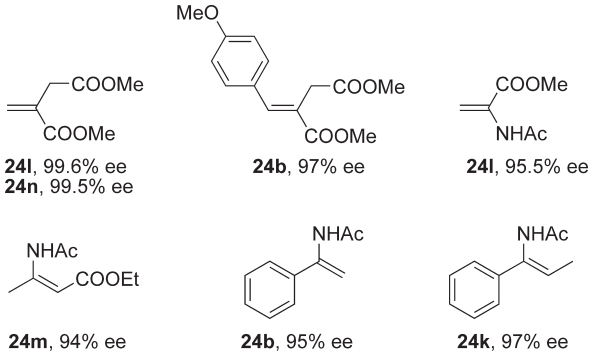
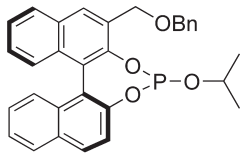
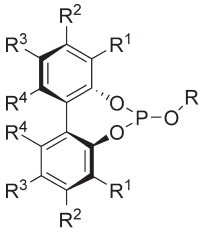


Figure 10. Summary of the best results obtained in the Rh-catalyzed hydrogenation of several substrates using ligands **24**.



25

Figure 11. Substituted binol-based monophosphite ligand **25**.

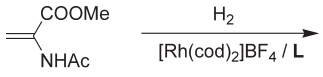


26

R^1= H, Me, ^{t}Bu
R^2= H, Me
R^3= R^4= Me, OMe
R= Ph, Cy, (+)-menthyl, (1*S*,2*R*)-2-Ph-Cy, ^{i}Pr, ...

Figure 12. General structure of configurationally stable chiral biphenyl monophosphite ligands **26** mainly developed by the groups of Dreisbach and Ojima.

Scheme 2. Comparison of the Traditional and the Combinatorial Approaches in the Rh-Catalyzed Asymmetric Hydrogenation of Dimethyl Itaconate



L	% ee
24a	76.6
24e	32.4
24a/24e	84.6

particular, Reetz and co-workers reported the use of ligands **27**−**29** in the Rh-catalyzed hydrogenation of vinyl carboxylates.[21a] The results show that there is a cooperative effect between the configuration of the binaphthyl moieties and the configuration of the sugar backbone. Therefore, enantioselectivities were best with phosphite **27b**, prepared from (*R*)-binol and a D-(+)-glucose derivative (ee's up to 94%).

Chen and co-workers have also successfully used ligands **27**−**28** and **31**−**33** in the Rh-catalyzed hydrogenation of dehydroamino acids (ee's up to 98.4%) and enamides (ee's up to 99.9%).[21b−21e] The hydrogenation results indicate that the enantiomeric excess depends strongly on the configuration of carbon atom C-3. In general, therefore, ligands **28** and **32** with an (*R*) configuration produced much higher enantioselectivity than ligands **29** and **33** with the opposite configuration. In this case, their results also suggest that there is a cooperative effect between the configuration of the binaphthyl moieties and the configuration of the carbohydrate backbone. The enantioselectivities (up to 99.6% ee) were therefore best with ligands **32b**. Ligands **33** and **34** were also highly efficient in the hydrogenation of dehydroamino acids and enamides, providing high enantioselectivities (ee's up to 99.9%) and activities (TON up to 5000).[21d]

In 2009, Reetz and co-workers again developed a new concept in chiral ligands. They synthesized C_3-symmetry monophosphite ligands **35** with a helical triskelion structure in which the sense of helicity does not interconvert (Figure 14).[22] The screwlike compound is derived from axially chiral (*R*)- or (*S*)-binol and sterically encumbered adamantane carboxylic acid. These ligands were applied to the Rh-catalyzed asymmetric hydrogenation of prochiral homoallylic alcohols, providing respectable enantioselectivities (78−98% ee).

Fan and co-workers recently developed supramolecular chiral dendritic monophosphite ligands **36** assembled by hydrogen bonding (Figure 15).[23] Their results in the asymmetric hydrogenation of enamides and dehydroamino acid derivatives are comparable to those obtained from the free monophosphite ligands (ee's up to 91%). The supramolecular catalysts could be easily recycled *via* solvent precipitation.

2.2. Phosphite−Heterodonor Ligands

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

2.2.1. Heterodonor P,P′ Ligands. In recent years, several phosphite−phosphine ligands have been applied in the Rh- and Ir-catalyzed hydrogenation reactions of several substrates.[24] Figure 16 shows the most representative examples of these ligands.

The first phosphite−phosphine ligands developed for asymmetric hydrogenation were based on a D-xylofuranoside backbone (ligands **37a**−, Figure 16). These ligands 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.[24a,b] The results also indicated that bulky substituents at both *ortho* and *para* positions of the biphenyl phosphite moiety are necessary to obtain excellent enantioselectivities. Enantioselectivity was therefore best using ligand **37b**. 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. ^{31}P-{^{1}H} NMR and kinetic studies on intermediates of the catalytic cycle show that the [Rh(**37**)(enamide)]BF_4 species are the resting state and that the rate dependence is first order in rhodium and hydrogen pressure and zero order in enamide concentration.[24b]

Following this pioneering work, several groups have developed new phosphite−phosphine ligands for this process. Chan and co-workers developed a ferrocenyl-based phosphite−phosphine ligand **38** (Figure 16) that provided an enantioselectivity of 99% in the Rh-catalyzed hydrogenation of methyl (*Z*)-(*N*)-acetylaminocinnamate.[24c]

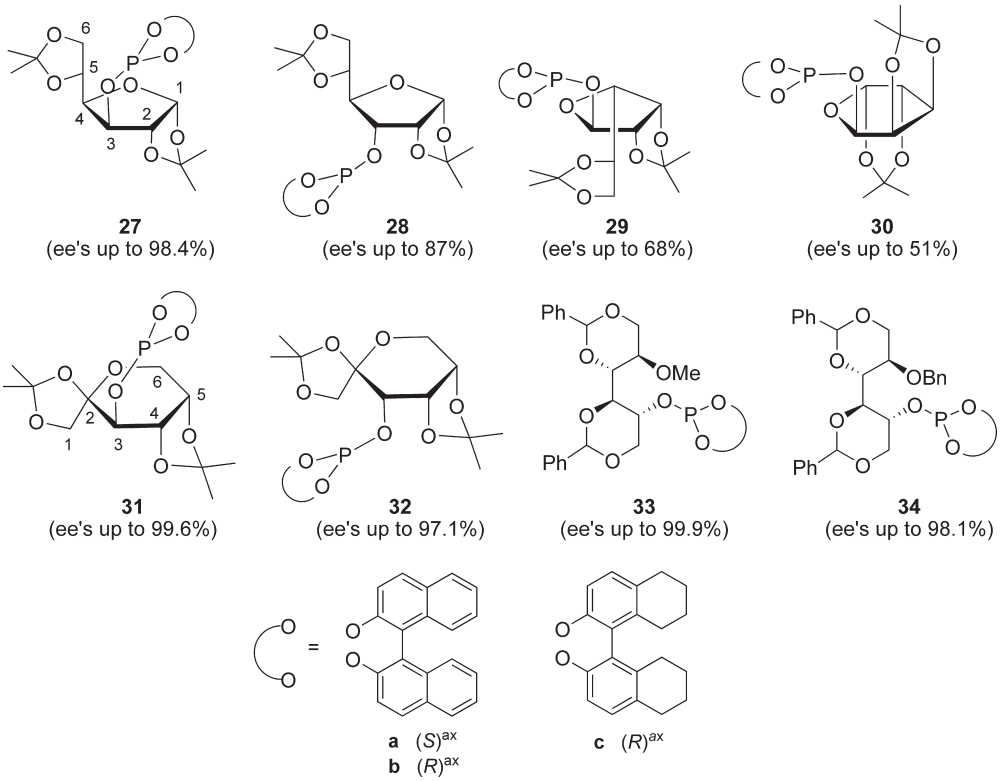


Figure 13. Sugar-derived monophosphite ligands **27**−**34**. The best enantioselectivities are shown in parentheses.

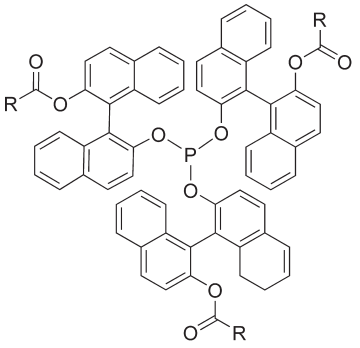


Figure 14. Chiral triskelion monophosphite ligands **35**.

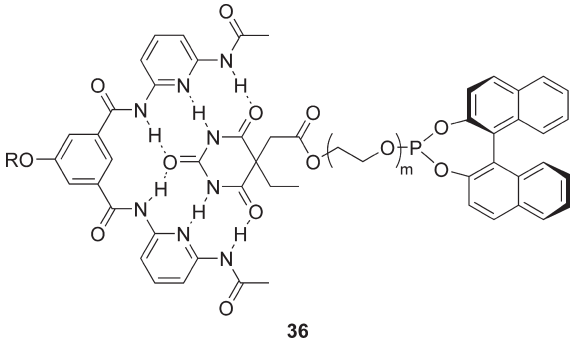


Figure 15. General structure of dendritic supramolecular monophosphites **36**.

We have also applied a series of modular phosphite−phosphine ligands (ligands **39** and **40**, Figure 16), containing a P-stereogenic center. Excellent enantioselectivities of up to 99% were obtained under mild conditions in the Rh-catalyzed hydrogenation of dehydroamino acid derivatives.[24d] Systematically varying the steric and electronic properties of the ligands showed that enantioselectivity is determined by the stereogenic carbon in the backbone. Although the phosphine moiety does not affect enantioselectivity, an electron-donating phosphine improves the reaction rate. Studies on the intermediates of the catalytic cycle again indicated that the [Rh(**39**)(enamide)]$^+$ species is the resting state. The alkene coordinates *trans* to the phosphine moiety, and it was proposed that the phosphite moiety determines the enantioselectivity of the reaction controlled by the substituent of the stereogenic carbon.

At the same time, Pizzano and co-workers developed new successful phosphite−phosphine ligands **41** and **42** (Figure 16) to be initially screened in the Rh-catalyzed hydrogenation of dehydroamino acids, itaconates, and enol phosphonates (ee's up to 99%).[24e−h] In connection with previous ligands **39** and **40**, ligands **41** and **42** are also highly modular (at both phosphine and phosphite moieties) and present a stereogenic phosphine moiety. They found that both functionalities need to be appropriately adjusted to obtain a high enantioselectivity. As previously observed when studying [Rh(**41**)(enamide)] cationic complexes, the coordination mode of the substrate is governed by the chiral ligand, directing the olefinic bond to a *cis* position with respect to the phosphite group. More recently, they extended this work to the Ir-catalyzed hydrogenation of *N*-arylamines, with excellent results (ee's up to 84%).[24i,j]

In 2004, Zhang and co-workers applied Binaphos-type phosphite−phosphine ligands **43** (Figure 16) in the asymmetric hydrogenation of several α-dehydroamino acid derivatives with

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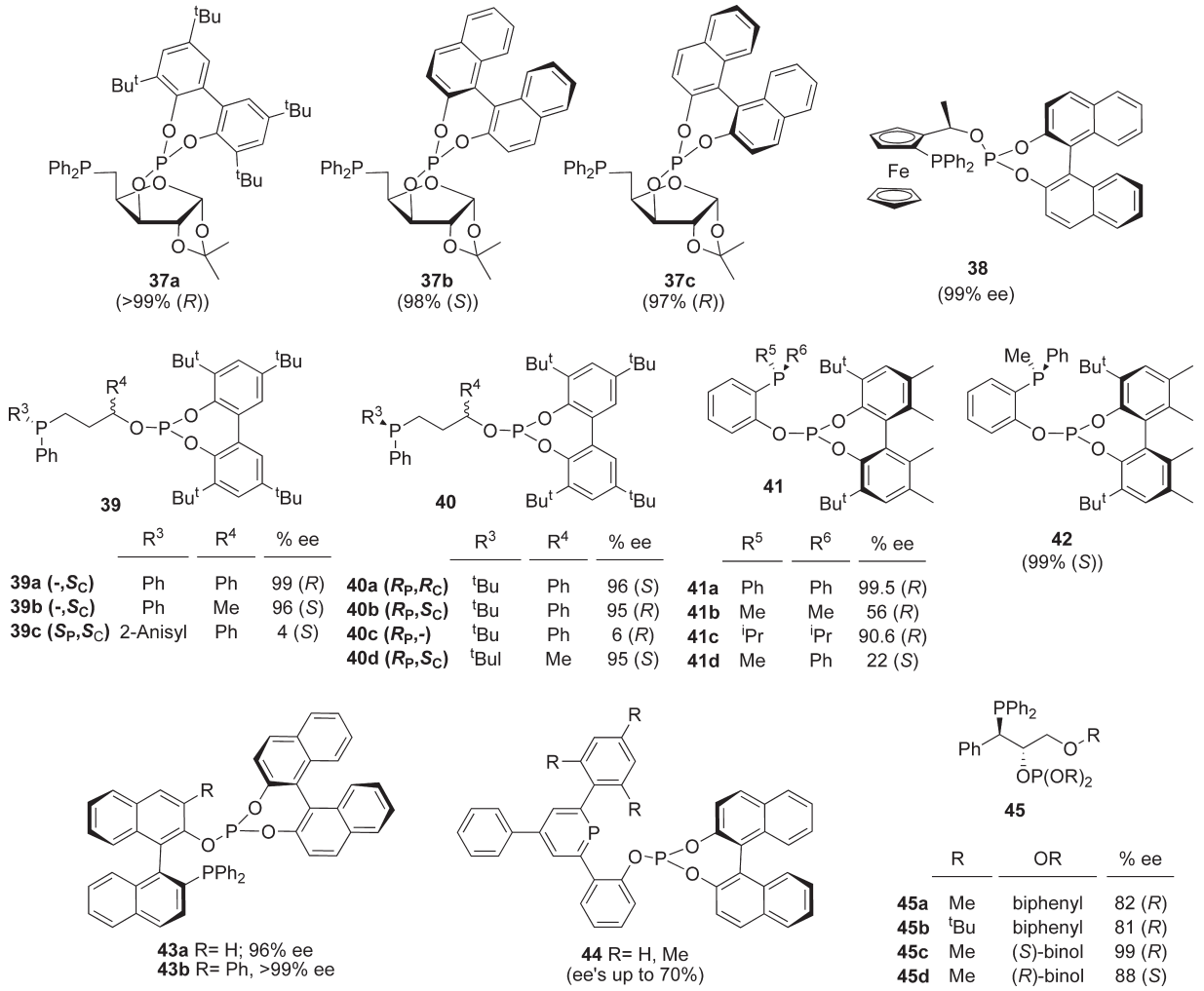

Figure 16. Representative phosphite−phosphine ligands **37**−**45** applied in asymmetric hydrogenation reactions. This figure also shows the best enantioselectivities obtained.

excellent enantioselectivities (up to >99%).[24k] Vogt and co-workers developed similar ligands by combining an (*S*)-binol phosphite moiety with several phosphabenzenes (ligand **44**, Figure 16) for the Rh-catalyzed hydrogenation of dehydroamino acid derivatives, albeit with low-to-moderate success (ee's up to 70%).[24l]

Recently, Vidal-Ferran and co-workers developed new phosphite-phosphine ligands **45** (Figure 16) for asymmetric Rh-catalyzed hydrogenation of several enamides, dehydroamino acids, and enol phosphonates.[24m,n] These ligands are highly modular and easy to obtain in two steps from enantiopure Sharpless epoxy ethers. Enantioselectivities were best (up to 99%) using ligand **45c**, which combines the optimal steric congestion around the CH_2OR chain and the matched combination between the configuration of the stereogenic centers at the ligand backbone and the binaphthyl moiety.

Other heterodonor ligands that have been successfully applied in hydrogenation are the phosphite−phosphoramidite ligands (Figure 17).[25] The first to be used were phosphite−phosphoramidite ligands **46**−**47**, derived from D-xylose and related to the diphosphite **2**−**3** and phosphite−phosphine **37** ligands (mentioned above).[25a] The introduction of a phosphoramidite moiety at C-5 of the ligand backbone is highly adventitious, leading to high enantioselectivities in the Rh-catalyzed hydrogenation of dehydroamino acids (ee's up to 99% using ligand **46b**).

In 2003, Cessaroti and co-workers developed phosphite−phosphoramidites **48** (Figure 17), derived from the proline, for the Rh-catalyzed asymmetric hydrogenation of dehydroamino acid derivatives (ee's up to 70%).[25b]

More recently, phosphite−phosphoramidites **49** (Figure 17), based on the tropane skeleton, were applied in the Rh-catalyzed asymmetric hydrogenation of dimethyl itaconate and methyl acetoamidocinnamate, with enantioselectivities up to 85% and 95%, respectively.[25c]

In 2008, a novel chiral phosphite−phosphoramidite ligand **50d** based on 2-anilinoethanol and (*R*)-binol moieties (Figure 17) had been synthesized for the asymmetric hydrogenation of several α- and β-dehydroamino acid derivatives and itaconates (ee's up to 61%).[25d]

Another class of heterodonor phosphite containing P,P′ is the phosphite−phosphinite **51** and phosphite−aminophosphine **52** ligands (Figure 18).[26] The former ligands **51** are related to **8**, in which a phosphite moiety is replaced by a phosphinite group. Ligand **51b** proved to be effective in the Ir-catalyzed hydrogenation of ketimines (ee's up to 73%).[26a] In 2008, Kamer and

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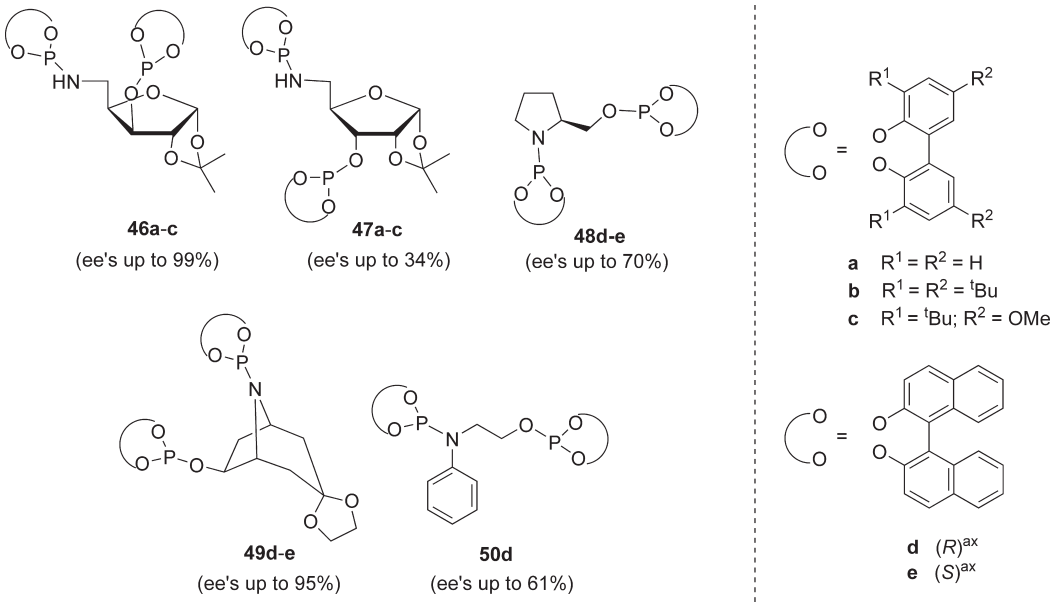

Figure 17. Representative phosphite−phosphoramidite ligands **46**−**50** applied in asymmetric hydrogenation reactions. The best enantioselectivities are shown in parentheses.

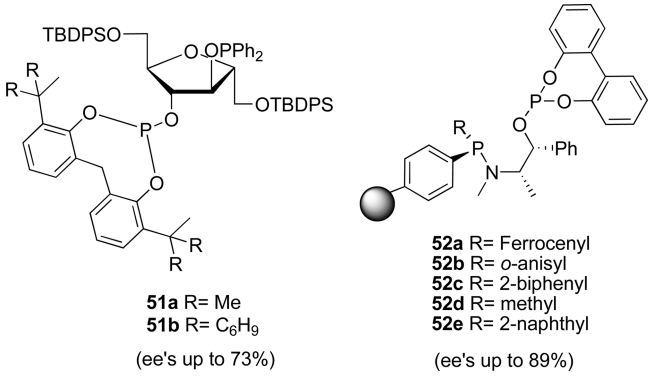

Figure 18. Representative phosphite−phosphinite **51** and phosphite−aminophosphine **52** ligands applied in asymmetric hydrogenation reactions. The best enantioselectivities are shown in parentheses.

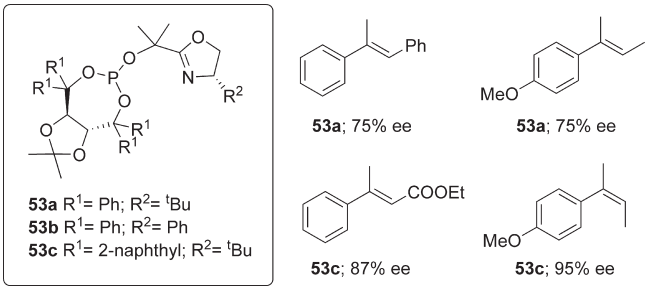

Figure 19. Taddol-based phosphite−oxazoline **53**. Summary of the best results obtained.

co-workers developed a parallel synthesis and screening of polymer-supported phosphite−aminophosphine ligands containing a stereogenic phosphorus (ligands **52**, Figure 18). These ligands form active hydrogenation Rh-catalysts, displaying moderate-to-good enantioselectivities (ee's up to 89%) in the reduction of benchmark dehydroamino acids.[26b]

2.2.2. Heterodonor P,N Ligands. Several phosphite−oxazoline ligands have recently been developed for the Ir-catalyzed hydrogenation of minimally functionalized olefins.[27] Taddol-based phosphite−oxazoline ligands **53**, developed by Pfaltz and co-workers, represented the first successful application of this type of ligands (Figure 19). These ligands provided enantioselectivities up to 95% in the hydrogenation of several *E*- and *Z*-trisubstituted alkenes (Figure 19).[27a]

More recently, two large libraries of phosphite−oxazoline ligands derived from hydroxyl-amino acid derivatives (ligands **54**−**69**)[27b,c] and D-glucosamine (ligands **70**−**73**)[27d] have been developed (Figure 20). These libraries are highly modular, and thus, several ligand parameters that are known to be important in catalytic performance can be studied. By carefully selecting the ligand components, high activities and enantioselectivities were obtained in the hydrogenation of several *E*- and *Z*-trisubstituted and 1,1-disubstituted olefins (Figure 21). It should be noted that the introduction of a bulky biaryl phosphite moiety in the ligand design is highly advantageous in the product outcome. Therefore, these ligands provided higher enantioselectivities than their Taddol-based phosphite-oxazoline **53** analogues.

Very recently, a library of readily available phosphite−oxazole/thiazole ligands (**74**−**80**, Figure 22) was applied in the Ir-catalyzed asymmetric hydrogenation of several largely unfunctionalized *E*-and *Z*-trisubstituted and 1,1-disubstituted terminal alkenes.[27e] This ligand library combines the advantages of the oxazole/thiazole moieties with those of the phosphite moiety. They are more stable than their oxazoline counterparts, less sensitive to air and other oxidizing agents than phosphines and phosphinites, and easy to synthesize from readily available alcohols. Diéguez and co-workers again found that the effectiveness at transferring the chiral information in the product can be tuned by choosing suitable ligand components, and in this way enantioselectivities can be maximized for each substrate as required. Enantioselectivities were therefore excellent (ee values

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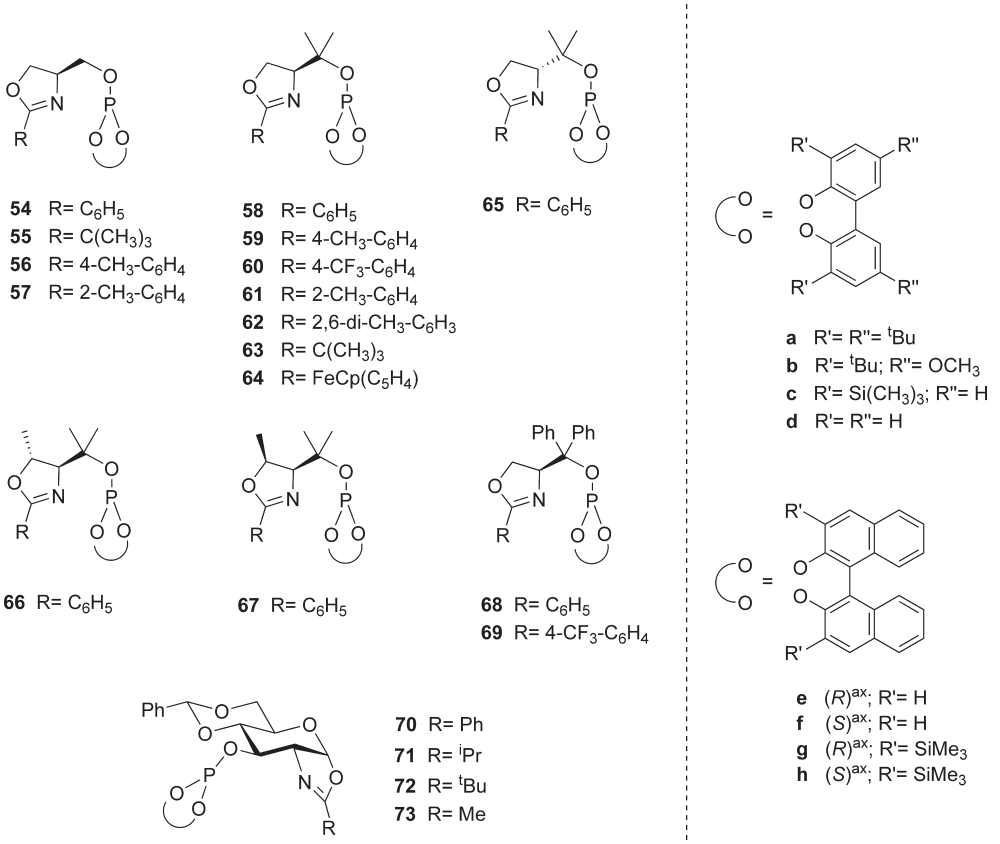

Figure 20. Phosphite-oxazoline ligand libraries derived from hydroxyl amino acid derivatives **54**−**69** and D-glucosamine **70**−**73**.

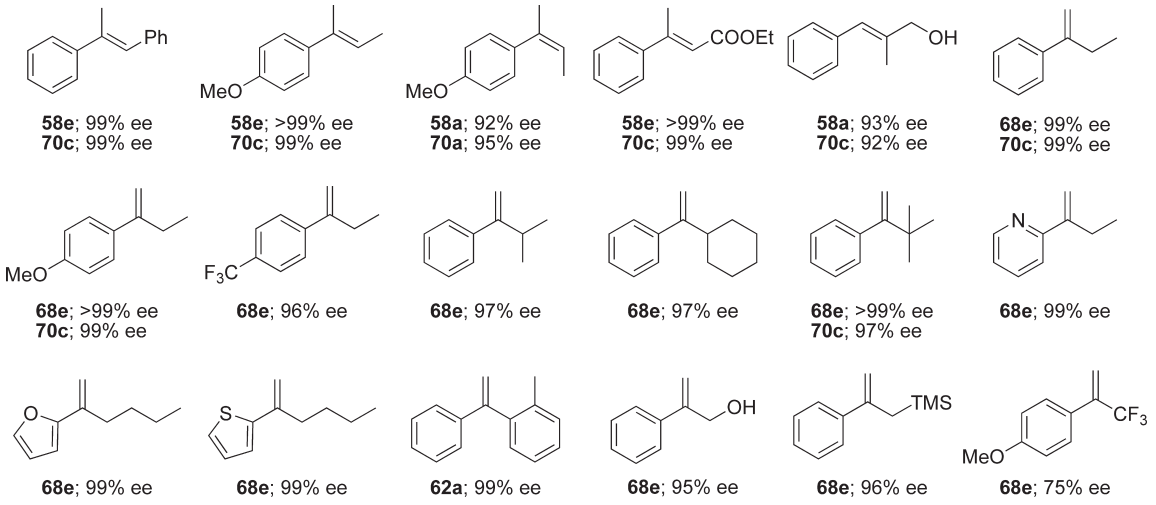

Figure 21. Summary of the best results obtained in the asymmetric hydrogenation of minimally functionalized alkenes using ligands **54**−**73**.

up to >99%) in a wide range of *E*- and *Z*-trisubstituted and 1,1-disubstituted terminal alkenes.[27e]

Other heterodonor phosphite-N ligands applied in asymmetric hydrogenation are the ferrocenyliminophosphites **81** (Figure 23). These ligands provided moderate-to-good enantioselectivities (up to 97%) in the Rh-catalyzed hydrogenation of α-dehydroamino acid derivatives[27f] and very poor ee's in the Pd-catalyzed reduction of α-ketophosphonates.[27g]

2.2.3. Other Heterodonor Ligands. In contrast to phosphinite−thioether,[28] phosphite−thioether ligands have been studied very little in hydrogenation. To the best of our knowledge, only one type of phosphite−thioether ligand has been applied to asymmetric hydrogenation,[29] viz. furanoside phosphite−thioether ligands **82** in the Rh- and Ir-catalyzed asymmetric hydrogenation of itaconic acid, with enantioselectivities up to 51% (Figure 24).

2.3. Key Ligand Parameters for High Selectivity

Mono- and diphosphite and heterodonor phosphite−phosphine/phosphoramidite ligands containing biaryl groups have been successfully applied in the Rh-catalyzed hydrogenation of

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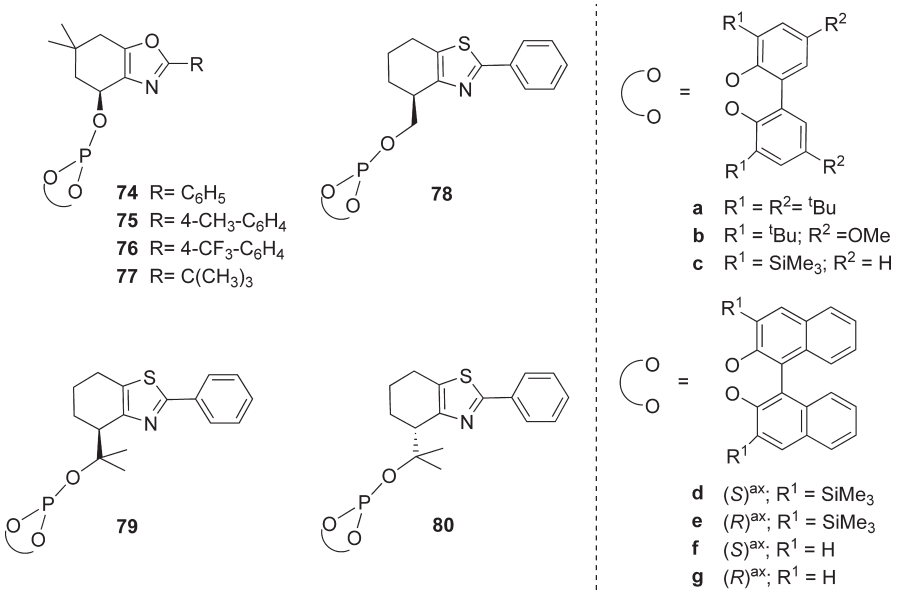

Figure 22. Phosphite−oxazole/thiazole ligand library.

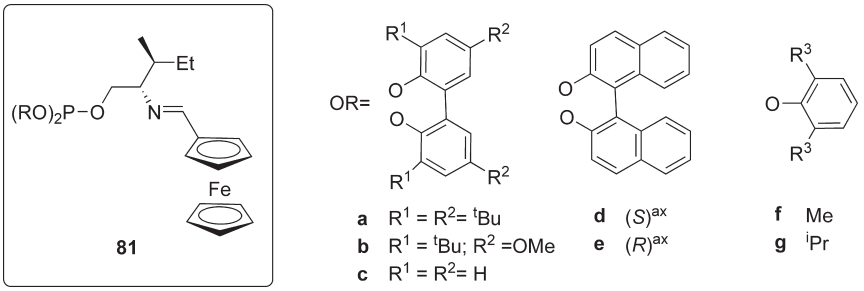

Figure 23. Ferrocenyliminophosphite ligands **81**.

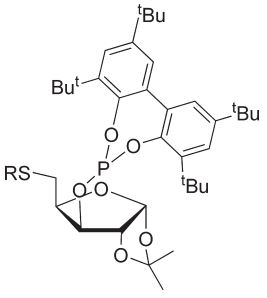

Figure 24. Phosphite−thioether ligands **82** applied in asymmetric hydrogenation.

functionalized alkenes. In general, the use of enantiopure atropoisomeric binaphthyl or biphenyl phosphite moieties is required for high enantioselectivities. However, often high enantioselectivities can also be achieved by using tropoisomeric, cheap, bulky biphenyl derivatives in combination with a suitable chiral ligand backbone that induces the preferential formation of one of the atropoisomers upon coordination to the metal center. There are ample examples showing that the presence of just one binaphthol (or Taddol) unit is sufficient to obtain efficient +enantioselective catalysts. While steric bulk is recognized as an important factor, steric variation in binaphthol moieties has been scarcely exploited. For the hydrogenation of minimally functionalized alkenes, Ir-complexes containing heterodonor phosphite−nitrogen ligands (phosphite−oxazoline/oxazole/thiazole) have been the most successful catalysts.

3. ASYMMETRIC HYDROFORMYLATION

Asymmetric hydroformylation has attracted much attention as a potential tool for preparing enantiomerically pure aldehydes.[30] Although complexes of Rh diphosphites and Rh−phosphine−phosphite (Binaphos) were for one decade the most efficient catalytic systems,[3,31] recently diphospholanes,[32] bis(diazaphospholodines),[33] and phosphine−phosphoramidites[34] have emerged as efficient alternative ligands. The hydroformylation of vinylarenes (Scheme 3) (R = aryl) is used as a model for the synthesis of 2-aryl propionaldehydes, which can be used as intermediates in the synthesis of 2-aryl propionic acids, the Profen class of nonsteroidal anti-inflammatory drugs, although as yet there are no commercial applications of this route. The Rh-catalyzed asymmetric hydroformylation of other substrates such as allyl cyanide, vinyl acetate, and cyclic and bicyclic olefins has been successfully carried out in recent years.[30−32]

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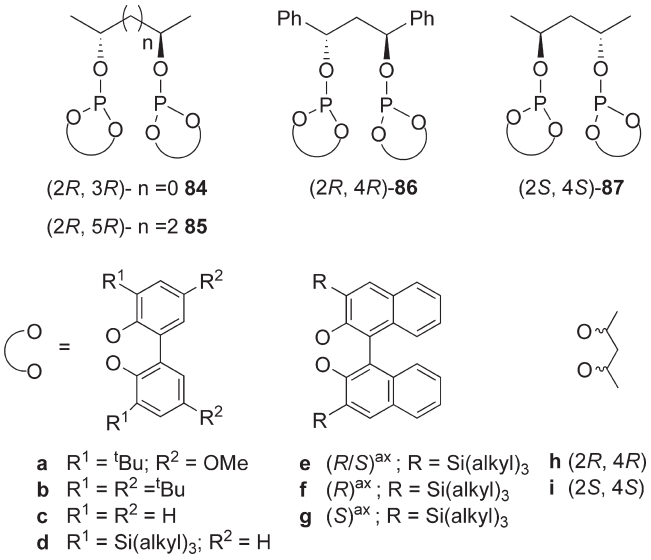
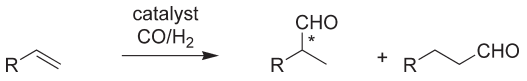


Figure 25. Diphosphite ligands **84**−**87**.

Scheme 3. Hydroformylation of Vinylarenes



3.1. Di- and Monophosphite Ligands

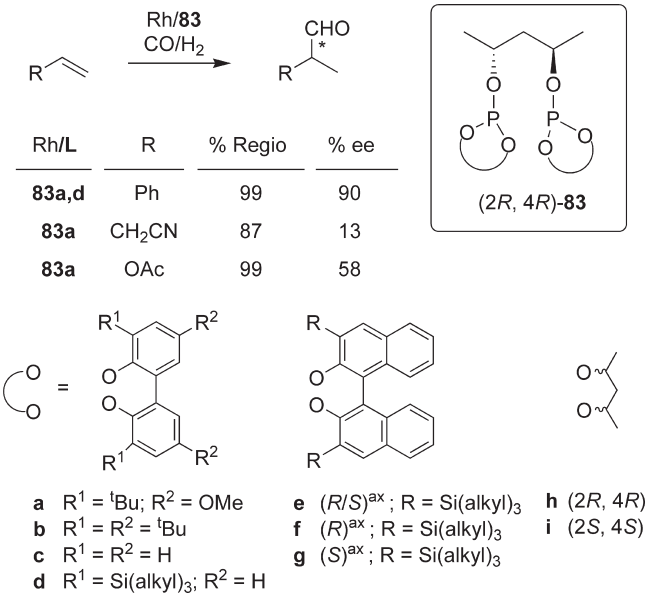
3.1.1. Diphosphite Ligands. The use of diphosphite ligands was intensively studied in this process as they provide high levels of selectivity mainly in the hydroformylation of vinylarenes.[3] The initial success started with the discovery of diphosphite ligands **83** based on (2*R*,4*R*)-pentane-2,4-diol (Scheme 4) by Union Carbide Corporation.[35] When the reaction was performed at room temperature, high regioselectivities and enantioselectivities (ee′s up to 90%) were obtained with (2*R*,4*R*)-pentane-2,4-diol diphosphite derivatives (**83a,d**). Diphosphites studied hitherto by van Leeuwen showed lower ee′s.[36a] A series of diphosphite ligands **84**−**87** were synthesized by van Leeuwen et al. in order to study the effect of several structural modifications on the Rh-catalyzed asymmetric hydroformylation of vinylarenes (Figure 25).[36,37]

The influence of the bite angle of these ligands was studied with diphosphite ligands (2*R*,4*R*)-pentane-2,4-diol (**83**), (2*R*,3*R*)-butane-2,4-diol (**84**), and (2*R*,5*R*)-hexane-2,4-diol (**85**).[35b] In general, ligand **83**, which contains a three-carbon-atom bridge, provided higher enantioselectivities than ligands **84** and **85**, which have a two- and four-carbon-atom bridge, respectively.

The effect of different phosphite moieties was studied with ligands **83a**−**g**.[35] In general, bulky phosphite moieties are necessary to achieve high enantioselectivities, but too large substituents gave poor ee's again.[36] The *ortho* and *para* substituents on the biphenyl and binaphthyl moieties also have a large effect on the asymmetric induction. The highest enantioselectivity (ee up to 90% at 20 bar of syngas and 25 °C) in the Rh-catalyzed asymmetric hydroformylation of styrene was obtained by using ligands **83a** and **83d**.

The influence of the backbone was studied by comparing the results obtained with ligands **83** and **86**.[35] Surprisingly, ligand **86**, which contains more sterically hindered phenyl groups, provided lower enantioselectivity than ligand **83**.

Scheme 4. Selected Results in the Rh-Catalyzed Asymmetric Hydroformylation Using Ligands 83



Rh/**L**	R	% Regio	% ee
83a,d	Ph	99	90
83a	CH_2CN	87	13
83a	OAc	99	58

A cooperative effect between the different chiral centers of the phosphite ligands **83f**−**i** and **87f**−**i** was demonstrated. Initially, van Leeuwen and co-workers studied the cooperative effect between the chiral ligand bridge and the axially chiral binaphthyl phosphite moieties by comparing ligands **83f,g** and **87f,g**. The hydroformylation results indicated a suitable combination for ligand **83g** (ee's up to 86%).[36c] Interestingly, the hydroformylation results obtained with ligands **83a** and **83d**, which are conformationally flexible and contain axially chiral biphenyl moieties, are similar to those obtained with ligand **83g**. This indicated that diphosphite ligands containing these biphenyl moieties predominantly exist as a single atropoisomer in the hydridorhodium complexes [$RhH(CO)_2$(diphosphite)] when bulky substituents are present in *ortho* positions.[36c] It is therefore not necessary to use expensive, conformationally rigid atropoisomeric binaphthyl moieties, as was shown in the matched−mismatched studies. Bakos and co-workers found a similar matched−mismatched effect between the chiral ligand bridge and the chiral phosphite moiety of ligands **83h,i** and **87h,i**.[37a]

To investigate whether a relationship exists between the solution structures of the [$RhH(CO)_2$(diphosphite)] species and catalytic performance, van Leeuwen and co-workers extensively studied the [$RhH(CO)_2$(diphosphite)] (diphosphite = **83**, **87**) species formed under hydroformylation conditions by high pressure NMR techniques (HP-NMR).[30e,31c] These trigonal bipyramidal (TBP) complexes can occur in two isomeric structures: one containing the diphosphite coordinated in a bis-equatorial (eq-eq) fashion and the other one containing the diphosphite in an equatorial-apical (eq-ax) coordination mode. The results indicated that the stability and catalytic performance of the [$RhH(CO)_2$(diphosphite)] (diphosphite = **83**, **87**) species strongly depended on the configuration of the pentane-2,4-diol ligand backbone and on the chiral biaryl phosphite moieties. Thus, ligands **83a**, **83d**, and **83g**, which form well-defined, stable

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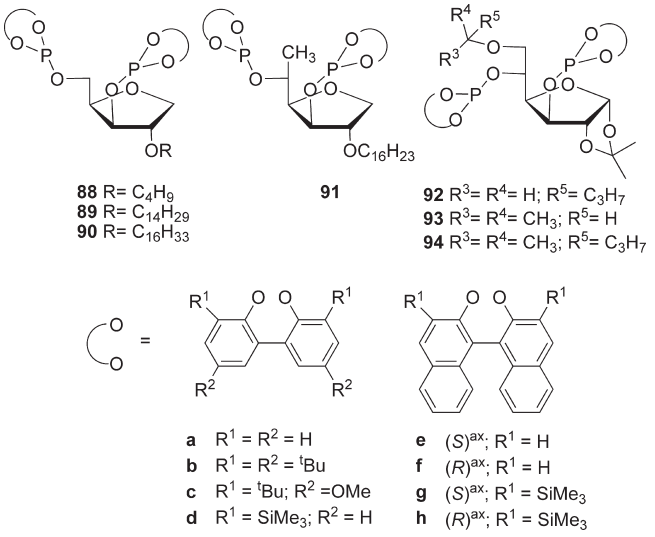


Figure 26. C_1-symmetric diphosphite ligands **88**−**94**.

bis-equatorial (eq-eq) complexes, led to high ee's. In contrast, ligands **83i** and **87g**, which form mixtures of complexes, led to low enantioselectivities.[36c,38] Ligand **83** was also evaluated in the Rh-catalyzed asymmetric hydroformylation of allyl cyanide and vinyl acetate, but low-to-moderate ee's (13 and 58%, respectively) were obtained for these substrates.[31b]

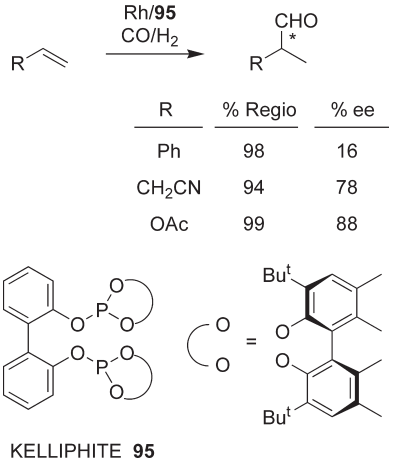
The previously mentioned sugar-based 1,3-diphosphite ligands derived from 1,2-*O*-isopropylidene-α-D-xylofuranose (Figure 3, ligands **2**−**3**) and 6-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose (Figure 3, ligands **4**−**7**) were applied in the Rh-catalyzed asymmetric hydroformylation of vinylarenes.[39] The use of diphosphite ligands **5c,d** and **6c,d** in the Rh-catalyzed asymmetric hydroformylation of styrene provided the (*S*)- and (*R*)-enantiomers of the product with high enantioselectivities (ee up to 93%) and excellent regioselectivity (regio's up to 99%).[39c,d] Ligand **5b** was also tested in the hydroformylation of vinyl acetate, giving excellent regioselectivity (99%) with an enantioselectivity of 73%.[40b]

Related C_1-symmetric diphosphite ligands, conformationally more flexible (**88**−**91**) or incorporating an increase in steric hindrance at the C-6 position (**92**−**94**), were synthesized (Figure 26).[40] These ligands were tested in the hydroformylation of styrene and vinyl acetate with good regio- and enantioselectivities (up to 81% and 68%, respectively). However, these selectivities resulted to be lower than those obtained with previous ligands **5c,d**. Therefore, both the bicyclic structure and the methyl substituent at the C-5 position seem to be required to achieve high enantioselectivity in the hydroformylation of styrene and vinyl acetate when using 1,3-diphosphites derived from carbohydrates.

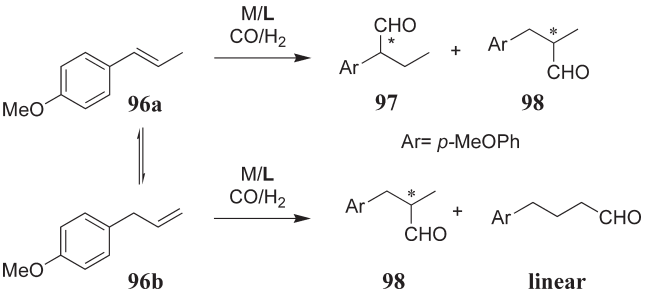
Interestingly, ligands **5** and **6**, for which only $[RhH(CO)_2(L)]$ species with eq-eq coordination were observed by HP-NMR and HP-IR techniques, provided higher enantioselectivity (ee's up to 93%) than the related ligands **4** and **7** (ee's up to 64%), for which an equilibrium between the isomeric eq-eq and eq-ap $[RhH(CO)_2(L)]$ species was observed. Therefore, the presence of a single coordination isomer, in this case the equatorial-equatorial (eq-eq) isomer, is needed to produce high levels of enantioselectivity in the Rh-catalyzed asymmetric hydroformylation of styrene, as previously mentioned.[39c,d,40]

In contrast with the previously mentioned diphosphites, KELLIPHITE ligand **95**, which was developed by Dow Chemical Company, contains the chirality in the bisphenol unit, while the backbone is achiral (Scheme 5). The catalytic system containing this ligand afforded very high enantioselectivity in the rhodium-catalyzed hydroformylation of vinyl acetate and allyl cyanide, although low selectivities were obtained in the hydroformylation of styrene.[41]

Scheme 5. Rh-Catalyzed Asymmetric Hydroformylation of Alkenes Using the Ligand KELLIPHITE (95)



Scheme 6. Isomerization Processes and Asymmetric Hydroformylation of *trans*-Anethole 96a and Estragole 96b

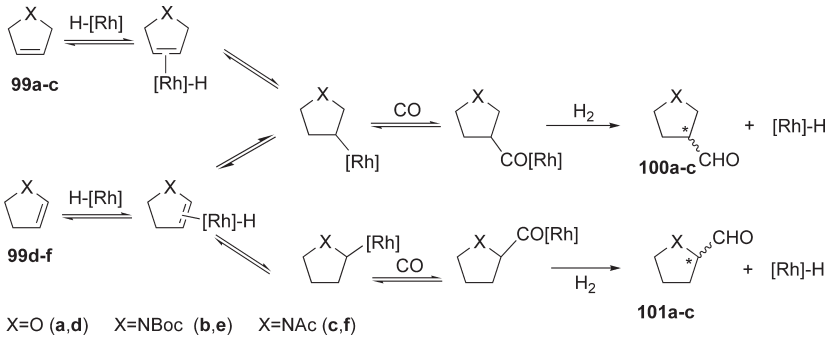


Over the years, new diphosphite ligands, containing several backbone types, have been developed for the Rh-catalyzed hydroformylation of vinylarenes with low-to-moderate success.[8,42]

Regarding the application of diphosphite ligands in the rhodium-catalyzed hydroformylation of other substrates, the asymmetric hydroformylation of propenylbenzenes was first studied by Kollár using $PtCl_2$(bdpp)/$SnCl_2$ as catalyst (bdpp = 1,3-bis(diphenylphosphino)propane).[43] The reaction was performed using *trans*-anethole **96a** and estragole **96b** as substrates in order to synthesize the branched chiral aldehydes **97** and **98** (Scheme 6). Unfortunately, the formation of the linear aldehyde was observed due to the isomerization of *trans*-anethole into the terminal, monosubstituted estragole; Pt catalysts are good isomerization catalysts and preferentially form linear aldehydes. Furthermore, moderate to low enantioselectivities were obtained (ee up to 27%). The Rh-catalyzed asymmetric hydroformylation of *trans*-anethole **96a** and estragole **96b** with 1,3-diphosphite ligands **2** (Scheme 6) gave also moderate to low enantioselectivities (ee's up to 15%).[44]

The asymmetric hydroformylation of heterocycles such as dihydrofurans and dihydropyrroles has been the object of several

Scheme 7. Isomerization Processes Observed during the Rh-Catalyzed Asymmetric Hydroformylation

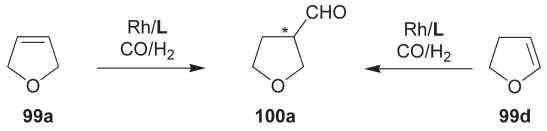


studies because of the interest in the corresponding aldehydes as building blocks in organic synthesis. The simultaneous control of the chemo-, regio-, and enantioselectivity is a key issue for these substrates, since isomerization takes place easily in the presence of a metal-hydride species. Previous studies using achiral ligands demonstrated that the reaction conditions highly affected the chemo- and regioselectivity of this reaction.[45] Indeed, allyl ethers were shown to isomerize rapidly into their vinyl analogues under hydroformylation conditions (Scheme 7).

This isomerization process is of critical importance, since it has a direct influence on the regioselectivity of the reaction but also on the enantioselectivity, since the opposite enantiomers of tetrahydro-3-carbaldehyde are formed from the allylic isomers **99a**−**c** and vinylic isomers **99d**−**f** of the substrate.[46] Therefore, isomerization should be prevented in order to obtain high selectivities. Diphosphites **2**−**7** (Figure 3) and **88**−**94** (Figure 26) derived from carbohydrates were applied in the Rh-catalyzed hydroformylation of these substrates.[47,40b] The results indicated that ligands **5** and **92**−**94**, which have a glucose configuration, are the most appropriate ones to obtain high enantioselectivity in the hydroformylation of these substrates (Scheme 8). In the case of 2,5-dihydrofuran **99a**, the highest enantioselectivity in aldehyde **100a** was obtained using ligand **92b** (88% S). Using this ligand, no isomerization was observed under hydroformylation conditions. Interestingly, the presence of bulky substituents at C-5, such as in ligands **93b**−**94b**, led to an increase of the degree of isomerization. When 2,3-dihydrofuran **99d** was used as the substrate, ee's up to 84% (*R*) for aldehyde **100a** were achieved using ligands **92b**−**94b**, together with a regioselectivity of 80%. 2,5-Dihydropyrrole was also tested with the Rh/**5b** system, giving 71% ee. These results are among the best that have been reported.[48,49] Only one Rh-based catalytic system containing a phosphine−phosphonite ligand related to Xantphos provided higher enantioselectivities (ee's up to 91%) in the hydroformylation of **99a** and **99d**.[49]

Although less studied, norbornene and its derivatives are also interesting substrates for carbonylation reactions. The first reports on the asymmetric Rh-catalyzed hydroformylation of norbornene afforded low enantiomeric induction with ee's below 25%.[50] In 2005, Bunel and co-workers reported the first highly enantioselective Rh-catalyzed hydroformylation of norbornene and derivatives to the exo aldehyde with ee's up to 92% using diphospholane ligands.[32b] More recently, hemispherical diphosphite ligand **102** (Figure 27), with a conical calixarene skeleton, was used in the asymmetric hydroformylation of norbornene, yielding enantioselectivities up to 61%, with the exo aldehyde being the major product.[32b]

Scheme 8. Selected Results for the Rh-Catalyzed Asymmetric Hydroformylation of Five-Membered Heterocyclic Alkenes



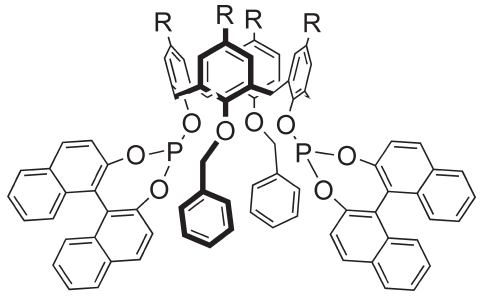
L	Product % Regio	100a % ee	L	Product % Regio	100a % ee
5b	99	75 (*S*)	**5b**	76	75 (*R*)
92b	99	88 (S)	**94b**	78	84 (*R*)

3.1.2. Monophosphite Ligands. Despite the successful use of monodentate ligands in many transition-metal-catalyzed processes, there are only a few reports concerning their use in asymmetric hydroformylation.[41a,b,51,52] The use of monodentate phosphorus donor ligands usually provides higher catalytic activity than their bidentate counterparts, but only moderate-to-good enantioselectivities were reported in asymmetric hydroformylation processes so far. For instance, ligand **26** (Figure 12, $R^1 = {}^tBu$, $R^2 = H$, $R^3 = R^4 = Me$, $R = 2\text{-}Ph{-}C_6H_3$) was tested in the Rh-catalyzed asymmetric hydroformylation of styrene and allyl cyanide and provided moderate enantioselectivities (ee's up to 38% and 43%, respectively). When vinyl acetate was the substrate, very poor ee's were obtained (ee's up to 8%).[41a,b] In 2004 Ojima and co-workers reported the use of phosphoramidite ligand **103** (Figure 28), related to monophosphite **26**, in the Rh-catalyzed asymmetric hydroformylation of allyl cyanide, and they achieved excellent regioselectivities (up to 96%) together with the highest enantiomeric excess (80%) ever reported for this reaction using a monodentate ligand.[51] These results are very promising, but as yet achieving high ee's using monodentate ligands remains a challenge.

3.2. Phosphite−Heterodonor Ligands

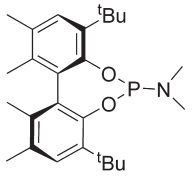
3.2.1. Phosphite−Phosphine Ligands. The discovery of the (*R,S*)-BINAPHOS (**104**) and (*S,R*)-BINAPHOS (**105**) ligands in 1993 by Takaya and Nozaki produced a real breakthrough in the Rh-catalyzed asymmetric hydroformylation reaction (Scheme 9),[53] as this attracted a lot more attention than the less accessible publications concerning diphosphites, the year before.[35a,36a]

dx.doi.org/10.1021/cr1002497 |*Chem. Rev.* 2011, 111, 2077–2118



102

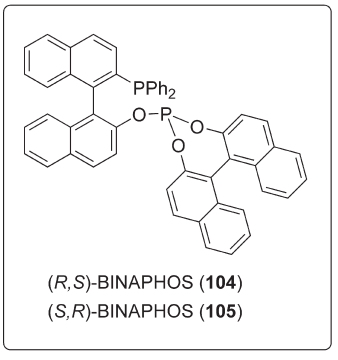
Figure 27. Hemispherical diphosphite ligand **102** with a conical calixarene skeleton.



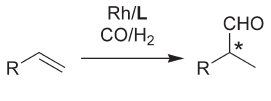
103

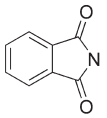
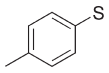
Figure 28. Phosphoramidite ligand **103**, related to monophosphite **26**, reported by Ojima and co-workers.

Scheme 9. Selected Results for the Rh-Catalyzed Hydroformylation of Several Substrate Types Using BINAPHOS Ligands 104 and 105



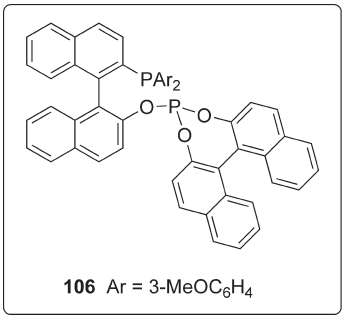
(*R*,*S*)-BINAPHOS (**104**)
(*S*,*R*)-BINAPHOS (**105**)



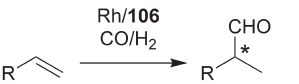
R	% Regio	% ee
Ph	90	94
C_6F_5	96	98
OAc	86	92
CH_2CN	72	66
CF_3	95	93
Ef	21	83
	89	85
	96	74

These ligands allowed extension of the scope of the asymmetric hydroformylation, since they provided high enantioselectivity in the Rh-catalyzed asymmetric hydroformylation of several classes of alkenes, such as vinyl arenes, 1-heteroatom-functionalized alkenes, and disubstituted 1,3-dienes (Scheme 9), and still BINAPHOS is a benchmark ligand in this area.[54] Excellent regio- and enantioselectivity were achieved with most of these substrates, although the formation of the branched product (21%) was disfavored when but-1-ene was the substrate. In 2003, De Vries and co-workers reported the first Rh-catalyzed asymmetric hydroformylation of allyl cyanide, and although moderate regioselectivity was obtained (72%), the highest enantioselectivity

Scheme 10. Selected Results for the Rh-Catalyzed Asymmetric Hydroformylation of Monosubstituted Alkenes Using Ligand 106



106 Ar = 3-$MeOC_6H_4$



R	% Regio	% ee
Ph	95	97
3-furan	92	99
2-thiophene	-	93

(66%) by far was achieved using ligand **104**.[55] As a general rule, the presence of electron-withdrawing substituents such as phenyl or heteroatoms in the alkene substrate leads to a control of the regioselectivity in favor of the branched product, independently of the ligand used.[31b]

It is noteworthy that (*R*,*S*)-BINAPHOS (**104**) or (*S*,*R*)-BINAPHOS (**105**) yield as products the opposite enantiomers, both with high enantioselectivity;[56] on the contrary, the diastereoisomers (*R*,*R*)- and (*S*,*S*)-BINAPHOS yielded much lower enantioselectivities, thus demonstrating the importance of the combination of opposite configurations for the binaphthyl bridge and the bis-naphthol phosphite group.

In contrast with the previously mentioned diphosphite ligands, which coordinate to the Rh center in an eq-eq fashion, BINAPHOS was found to coordinate to Rh in an equatorial-apical mode as a single isomer in the resting state $[RhH(CO)_2(L\text{-}L)]$, having the phosphite unexpectedly in the apical position.[56] Note, however, that the exchange between the two eq-ap isomers is extremely rapid and that the coupling constants found indicate that some of the isomer containing the phosphine in the apical position is also present.[57]

Related BINAPHOS-type ligands (Scheme 10) were developed by the introduction of 3-methoxy substituents on the aryl phosphine units (ligand **106**).[54b,c] Catalyst Rh/**106** increased the regio- and enantioselectivity in the asymmetric hydroformylation of styrene, vinylfurans, and vinylthiophenes (Scheme 10).

Several new phosphine−phosphite ligands with several backbones were developed, but the catalytic results using these ligands provided lower enantioselectivity (from 20 to 85%) than those with BINAPHOS.[58]

Nozaki and co-workers reported the Rh-catalyzed asymmetric hydroformylation of *trans*-anethole **96a** into **97a** (Scheme 6) using BINAPHOS **104** with a regioselectivity of 98% and an enantioselectivity of 80% ee.[59] In the Rh-catalyzed asymmetric hydroformylation of 1,2-alkyl-disubstituted alkenes (Scheme 11) as substrates, **104** provided the highest ee's.[59] Interestingly, the *E*-isomers *trans*-2-butene and *trans*-3-hexene yielded lower enantioselectivity than their *Z*-counterparts *cis*-2-butene and *cis*-3-hexene. In the reaction sequence envisaged, for the *Z*-isomers, the ee is determined in the migratory insertion step, as each carbon will lead to opposite enantiomers, while, for the *E*-isomers, the coordination of alkene to Rh determines the ee, as the C_2 symmetry of the substrate makes that hydride migration to either carbon give the same enantiomer.

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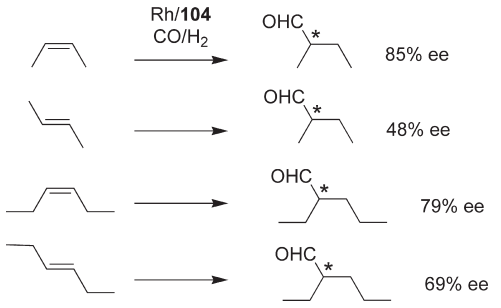
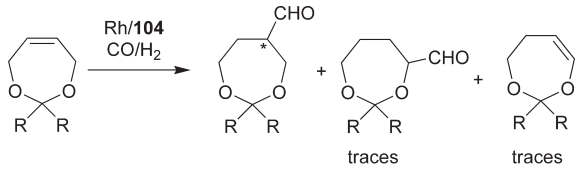
Scheme 11. Rh-Catalyzed Hydroformylation of 1,2-Alkyl-Disubstituted Alkenes Using Ligand 104



Scheme 12. Rh-Catalyzed Asymmetric Hydroformylation of Several Dioxepines



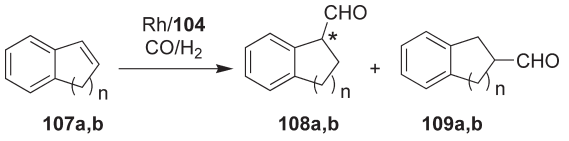
R	% Regio	% ee
H	99	76 (-)
Me	99	70 (*R*)

The use of BINAPHOS **104** in the Rh-catalyzed asymmetric hydroformylation of 2,5-dihydrofuran (**99a**) yielded total regioselectivity to tetrahydro-3-carbaldehyde (**100a**) with 68% ee (*R*) (Scheme 7).[48] However, when 2,3-dihydrofuran (**99d**) was tested with the same catalyst, no regioselectivity was observed and the ee obtained for aldehyde **100a** decreased to 38% with *S* configuration. This catalytic system was thus suitable to avoid isomerization of **99a** into **99d** but was not selective for the hydroformylation of **99d**. Similar results were obtained in the hydroformylation of the amine analogues **99b,c** and **99e** using the same catalytic system. BINAPHOS **104** was also successfully applied in the Rh-catalyzed asymmetric hydroformylation of several dioxepines, providing total regioselectivity together with ee's up to 76% (Scheme 12).[48]

The Rh-catalyzed asymmetric hydroformylation of substrates **107a** and **107b** was reported by Nozaki and co-workers using ligand **104** (Scheme 13).[59] The results are really remarkable, in particular with substrate **107b**, for which compound **108b** was obtained with practically total regioselectivity and high enantioselectivity (Scheme 13). The corresponding products **108a** and **108b** are of interest, since aldehyde **108a** can be converted in a single step into the corresponding amine, which exhibits hypotensive activity, and product **108b** is an intermediate in the synthesis of tetrahydrozoline, a vasoconstrictor.[60]

3.2.2. Other Phosphite−Heterodonor Ligands. Other related BINAPHOS-type ligands were developed by replacement of the phosphite group by a phosphoramidite function, yielding YANPHOS ligand **110** (Scheme 14).[34] YANPHOS **110** provided higher enantioselectivity than BINAPHOS **104** without altering the regioselectivity in the Rh-catalyzed asymmetric hydroformylation of styrene and vinyl acetate (ee's up to 99 and 96%, respectively). Recently, the efficiency of ligand **110** was

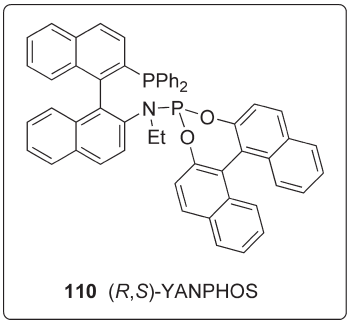
Scheme 13. Rh-Catalyzed Asymmetric Hydroformylation of Bicyclic Alkenes Using (*R,S*)-BINAPHOS (104)



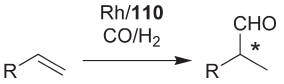
107a,b **108a,b** **109a,b**

Product	% Regio	% ee
108a n=1	92	88
108b n=2	96	97

Scheme 14. Selected Results for the Rh-Catalyzed Asymmetric Hydroformylation of Monosubstituted Alkenes Using Ligand 110



110 (*R,S*)-YANPHOS



R	% Regio	% ee
Ph	89	99
OAc	93	96
4-Me-C_6H_4	88	99
^{t}BuCOO	94	98

again demonstrated in the Rh-catalyzed hydroformylation of monosubstituted alkenes such as derivatives of styrene and vinyl acetate, giving ee's up to 99% and 98%, respectively (Scheme 14).[61]

Several other heterodonor ligands containing a phosphite moiety in combination with phosphite−thioether and phosphite−N ligands have also been tested in this reaction with low-to-moderate success.[25b,29,42i,62] This is not surprising, as *in situ* spectroscopic studies showed that the ligands function as monodentates toward Rh hydrido carbonyls in the presence of CO.[29,63]

3.3. Key Ligand Parameters for High Selectivity

As monodentates are clearly lagging behind, we will concentrate here on bidentate phosphite ligands and phosphine−phosphite ligands. Phosphite ligands contain, in general, aryl groups, and alkyl groups mostly occur as bridges (several diols and many sugar-based backbones). The reason is that alkyl phosphites are subject to the Arbuzov reaction, which may involve the metal as the electrophile, initiating the decomposition of a phosphite, while aryl phosphite ligands do not undergo this reaction due to the high energy of aryl cation intermediates. Rhodium under hydroformylation conditions rarely seems to initiate the Arbuzov reaction. The most common decomposition reaction of phosphites is a reaction with the aldehyde product giving phosphonic acids, which catalyze this very reaction, and an autocatalytic decomposition results.[64] Although the acids can be effectively removed by a bed containing a solid base, no industrial applications of the phosphites described here are known.

Diphosphites should coordinate in an eq-eq fashion, as was shown in an early stage by van Leeuwen, but this is not a

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guarantee for high ee![36,38,39a] 1,2-Diol bridges lead to mainly eq-ap coordination and low ee's. 1,3-Diols give eq-eq coordination, and high ee's may be achieved. 1,4-Diols also give eq-eq coordination modes, but no acceptable ee's were obtained, although steric variations were not attempted in view of the poor results of the simple (bis)phenol or (bis)naphthol substituents compared to the 1,3-diols. The same holds for 1,2-diols, and in view of the success of phosphine−phosphites that coordinate in an eq-ap fashion, perhaps more sterically hindered 1,2-diol-based diphosphites are also a viable option. Bisphenol derived backbones, containing constrained 1,4-diols, lead to eq-eq coordination modes and often to high ee's.

Tropos (bisphenol) substituents or backbones may constitute a useful entity replacing enantiopure bisnaphthyl units, as several examples show that other chiral elements may induce the optimal chirality in this fragment, turning it into an atropos constituent of the ligand.

Substituents in the hydrocarbyl groups of phosphites are farther away from the metal than those in phosphines, and as a result, substituents in aryl phosphites tend to be rather large in the most effective ligands (Ph, ^{t}Bu, $SiMe_3$). It was found that, in bisphenol diphosphites, $SiMe_3$ groups were optimal, as both $SiEt_3$ and $SiPh_3$ gave poor results.

In sugar-based diphosphites, all variants of "1,3"-diol diphosphites, the absolute configuration of the product is governed by the configuration at the stereogenic center C-3, although the level of enantioselectivity is influenced by the stereocenters at C-3 and C-5 to which the phosphorus atoms are attached. *Pseudo*-enantiomeric ligands afford the same level of enantioselectivity.

BINAPHOS ligands (having a 5 atom binaphthyl bridge) coordinate in an eq-ap fashion, with the phosphine group coordinating in the equatorial position, while electronically one would expect the reverse. Ligands having more flexible bridges coordinate equally well in both fashions or indeed with an equatorial phosphite group. Apparently, in this group of ligands, larger substituents in the aryl phosphites are needed. The reason for BINAPHOS's coordination mode must be steric, and this is not understood. The two bis-naphthyl moieties in BINAPHOS must have opposite absolute configurations, as, otherwise, ee's are lower.

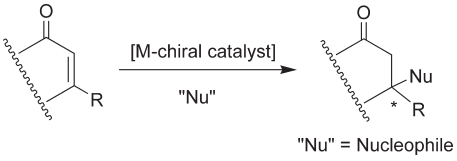
4. ASYMMETRIC CONJUGATE ADDITIONS

The catalytic asymmetric conjugate addition of nucleophiles to α,β-unsaturated compounds is one of the most powerful C−C and C−X bond-forming reactions in organic synthesis (Scheme 15).[4,65] The reaction is extremely useful for the construction of enantiopure, highly functionalized carbon skeletons for the total synthesis of numerous biologically active compounds. The scope of the reaction is broad, because of the availability of a large variety of donor and acceptor compounds. The high potential of this synthetic method is evident because multiple stereocenters can be built in a single synthetic operation, and many asymmetric catalytic systems exhibit high activity and enantioselectivity.[4,65i]

4.1. Copper-Catalyzed Conjugate Addition

The past decade has seen dramatic breakthroughs in the area of Cu-catalyzed asymmetric 1,4-addition of alkyl organometallic nucleophiles to enones. Most of the successful asymmetric versions of this chemistry have made use of organozinc reagents, especially $ZnEt_2$, a trend started by Alexakis.[66] The inherently

Scheme 15. Typical Asymmetric Conjugate Addition



low reactivity of organozinc reagents toward unsaturated carbonyl compounds has facilitated the development of a plethora of chiral phosphorus-based ligands capable of providing highly efficient ligand-accelerated catalysis with excellent regio- and enantioselectivities (>95% ee) to disubstituted cyclic and acyclic enones, lactones or lactams, nitro-olefins, amides, and malonates.[4] By far the most studied ligands are phosphites and phosphoramidites. Trialkylaluminum reagents have recently emerged as an interesting alternative to organozinc reagents, since they are also commercially available and can be prepared by additional hydro- and carboalumination.[67] Additionally, their higher reactivity allows Cu-catalyzed 1,4-addition to very challenging substrates (i.e., β-trisubstituted enones), which are inert to organozinc methodologies. Nowadays, very successful examples with cyclic and acyclic enones and nitro-olefins have been described.[4]

In this section we compile the catalytic data reported using phosphite-containing ligands in the Cu-catalyzed conjugate addition of nonstabilized nucleophiles to α,β-unsaturated compounds.

4.1.1. Mono- and Diphosphite Ligands

4.1.1.1. Monophosphite Ligands. Research into monophosphite ligands has focused on four main types: tartrate-based ligands, Taddol derivatives, binaphthol-based ligands, and biphenol-type ligands.

In tartrate-based ligands, the phosphorus atom is incorporated into a five-membered ring (Figure 29). Despite the variety of structures tested, only low-to-moderate ee values have been attained.[66,68] The best result was achieved with benzalacetone and the most hindered ligand **111c** (65% ee), bearing (1*R*)-endo-(+)-fenchol as the chiral exocyclic component. Unlike most ligands, it seems that the ester functionality of the tartrate part of the ligand also participates in the coordination of the organometallic species.

Taddol-based ligands **112**, which are readily accessible from tartaric acid, incorporate the phosphorus atom into a seven-membered ring (Figure 29). Many ligands of this type have been prepared and tested in the conjugate addition.[69] In the absence of exocyclic chirality, the Taddol part of the ligand induces low enantioselectivity on enones (up to 18% ee on cyclohexenone).[69a] When an exocyclic chiral alcohol is attached, however, enantioselectivities have been high. Thus, for instance, when the 2-phenylcyclohexanol derivative **112h** was used, a 96% ee was obtained in the diethylzinc addition to cyclohexenone,[69a,c] and when the 2-[2-naphthyl]cyclohexanol derivative **112j** was used in the diethylzinc addition to diethyl benzylidenepropanedioate, 73% ee was obtained.[69b] In contrast to tartrate-based ligands **111**, Taddol ligands with two chiral moieties (the Taddol part and the exocyclic part) show strong matched/mismatched character. For example, ligand **112h** affords a 96% ee with cyclohexenone, whereas its diastereomer **112g** affords a racemic product.[69a]

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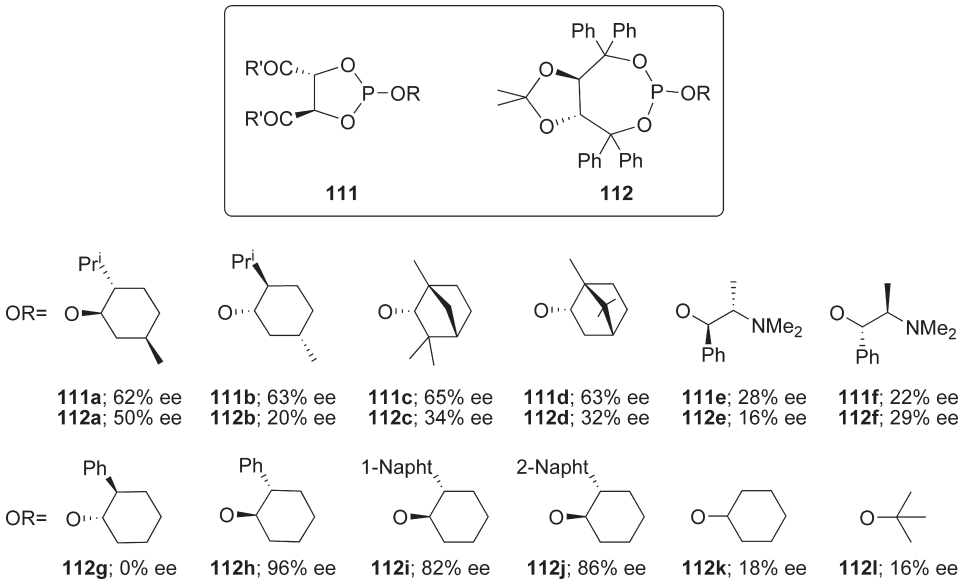


Figure 29. Representative tartrate-based **111** and Taddol-based **112** ligands. This figure also shows the best enantioselectivities obtained in asymmetric conjugate addition reactions.

Binaphthol-based ligands also incorporate the phosphorus atom into a seven-membered ring (Figure 30). Several modifications to the exocyclic alcohol have been made (**24q**−**v**, Figure 30).[66,70] The results indicated that (i) an appropriate exocyclic chiral alcohol needs to be incorporated for high enantioselectivities and (ii) there is a pronounced cooperative effect. The best enantioselectivity was therefore obtained using ligand **24t**, with (1*S*,2*R*)-2-phenylcyclohexanyloxy in the exocyclic position. The highest ee value was obtained in the addition to cyclopentadecenone (87% ee). This reaction has been used for the synthesis of (*R*)-muscone, a valuable fragrance.

More recently, biphenol-type ligands have appeared as alternatives to the related binaphthol-based ligands (Figure 31).[71] They have the advantage of being much less expensive. Unlike the binaphthol moiety, the biphenol unit presents tropoisomerism. However, the chirality of the exocyclic part induces the preferential formation of one of the atropoisomers, which in turn controls the enantioselectivity.[4] The matched/mismatched problem is therefore avoided. However, results were no better than the binaphthol-based ones. Thus, tropos deoxycholic acid-derived biphenylphosphites **113a**−**d** (Figure 31) were applied in the Cu-catalyzed addition of diethylzinc to linear enones with enantioselectivities up to 65%.[71a] In 2006, Hoppe et al. developed a novel type of tropos biphenyl-based ligands **114** (Figure 31), in which the chiral information is introduced in the 3,3′-positions as *N*-arenesulfonyl-1,3-oxazolidines.[71b] Ligand **114d** presents high diasteroselectivity of up to 98% on the chiral axis and provides enantioselectivities up to 83% and 50% in the diethylzinc addition to cyclohexenone and 2-carbamoyloxy-2-cycloxen-1-one, respectively.[71c]

The monophosphite ligands **27**−**32** (Figure 13) mentioned above, which combine a sugar backbone with biphenyl- and binaphthyl phosphite moieties, have also been applied in the Cu-catalyzed asymmetric conjugate addition or β-substituted (cyclic and linear) and β,β'-disubstituted cyclic enones using both diorganozinc and triorganoaluminum reagents.[72] In general, high activities but moderate enantioselectivities were obtained. By carefully selecting the ligand parameters, enantioselectivities of up to 57% for cyclic substrates (ligand **28a**, Figure 13) and 72% for linear substrates (ligand **27a**, Figure 13) were achieved.

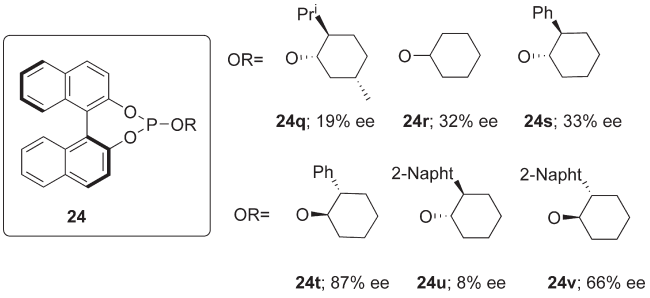
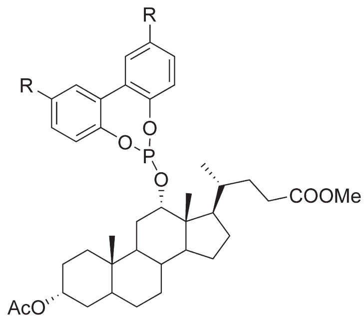


Figure 30. Representative monodentate binaphthol-based phosphite **24q**−**v**. This figure also shows the best enantioselectivities obtained in the asymmetric conjugate addition reactions.

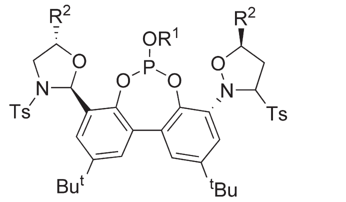
4.1.1.2. Diphosphite Ligands. Several diphosphite ligands have been developed for this process.[70b,73−75] Chan and coworkers developed diphosphite ligands **115** and **116** (Figure 32) with two binaphthyl phosphite moieties.[70b,73] These ligands were successfully applied to the diethylzinc conjugate addition of cyclic enones (ee's up to 98%) and lactones (ee's up to 92%). It should be noted that configurational stable binaphthol diphosphites **115** provided somewhat higher enantioselectivities than the biphenyl-based ones **116**. The same group also reported the synthesis and application of pyranoside diphosphite ligands **117**−**118**[74a] and diphosphite ligands **119**,[74b] derived from D-mannitol (Figure 32). Ligands **117**−**118** were applied in the Cu-catalyzed asymmetric conjugate addition of diethylzinc to cyclic enones. Results indicated that enantioselectivity depends on the absolute configuration of the C-4 stereogenic center of the ligand backbone, while the sense of enantioselectivity is controlled by the configuration of the binaphthyl phosphite moieties. Enantioselectivites up to 88% were obtained with ligand **117b**.[74a] Ligands **119** were also applied to the same process, albeit with lower enantioselectivities (up to 71%).[74b]

The furanoside phosphite ligands **2**−**7a**−**h** mentioned above (Figure 3) were also screened in the Cu-catalyzed conjugate addition of diethylzinc to cyclic enones.[75] The results indicated

dx.doi.org/10.1021/cr1002497 |*Chem. Rev.* 2011, 111, 2077–2118



	R	% ee
113a	H	43
113b	Br	45
113c	Ph	50
113d	^{i}Pr	65



	R^1	R^2	% ee
114a	Ph	Et	68
114b	Ph	^{i}Pr	78
114c	Ph	Bn	68
114d	^{i}Pr	Et	83
114e	CH(^{i}Pr)$_2$	Et	68

Figure 31. Representative monodentate biphenol-based phosphite ligands **113** and **114**. This figure also shows the best enantioselectivities obtained in the asymmetric conjugate addition reactions.

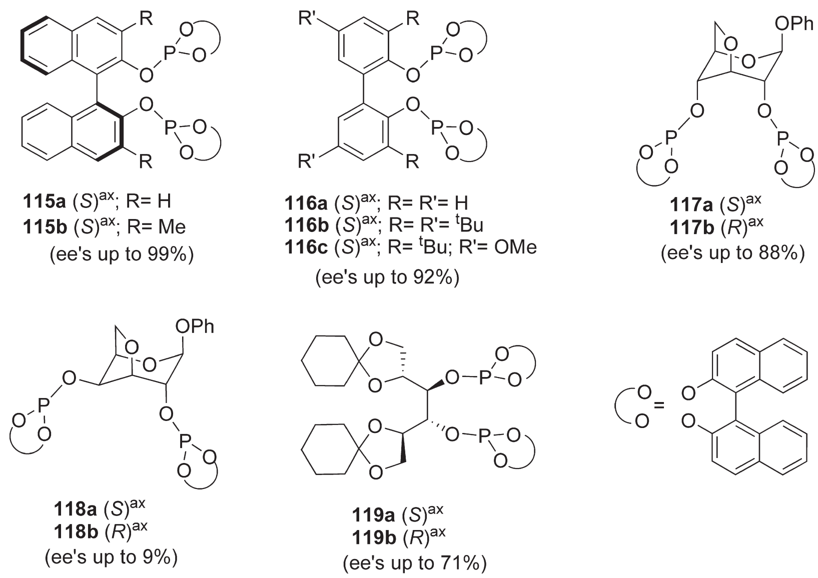


Figure 32. Diphosphite ligands **115**−**119** developed by Chan and co-workers. This figure also shows the best enantioselectivities obtained in the asymmetric conjugate addition reactions.

that enantioselectivity depends strongly on the absolute configuration of the C-3 stereogenic center, while the sense of enantiodiscrimination is predominantly controlled by the configuration of the biaryl groups of the phosphite moieties. Enantioselectivities were therefore best (up to 84%) using glucofuranoside ligand **4g**, which contains *ortho* disubsituted trimethylsilyl (*S*)-binaphthyl phosphite moieties.[75c]

4.1.2. Phosphite−Heterodonor Ligands.

Several heterodonor phosphite-containing ligands have been described and found to be very efficient in this enantioselective conjugate addition. The most successful ligands combine the phosphite moiety with a nitrogen donor group.

A review of the research into heterodonor phosphite−nitrogen ligands reveals three main types: phosphite−oxazoline,[71c,76] phosphite−pyridine,[77] and phosphite−amine[78] ligands.

Among the phosphite−oxazoline ligands, the family of ligands **120a**−**d** is of particular note (Figure 33).[76a,b] The results indicated that increasing the steric bulk in the *ortho* positions of the binaphthyl phosphite moiety has a positive effect on enantioselectivity. Thus, ligands **120a,c** provided high enantioselectivities for cyclic enones (ee's up to 96%) but not for disubstituted linear enones. The pyranoside ligands **70**−**73a**−**h** mentioned above (Figure 20) provided enantioselectivities up to 80% in the Cu-catalyzed conjugated addition of *trans*-5-methyl-3-hexen-2-one with trimethylaluminum.[76c] Very recently, biphenyl-based phosphite-oxazoline **121**, related to monophosphites **114** (Figure 31), was applied to the Cu-catalyzed conjugate addition of diethylzinc to several cyclic enones with poor-to-moderate success (ee's up to 37%).[71c]

Unlike phosphite−oxazolines, phosphite−pyridine ligands **122**−**124** (Figure 33) provided excellent results for several linear enones (ee's up to 98%) but only moderate enantioselectivities for cyclic enones.[77]

Finally, furanoside amino-phosphite ligands **125** (Figure 33) have also been applied with moderate success in the Cu-catalyzed conjugate addition of diethylzinc to cyclohexenone (ee's up to 63%; R = Ph).[78]

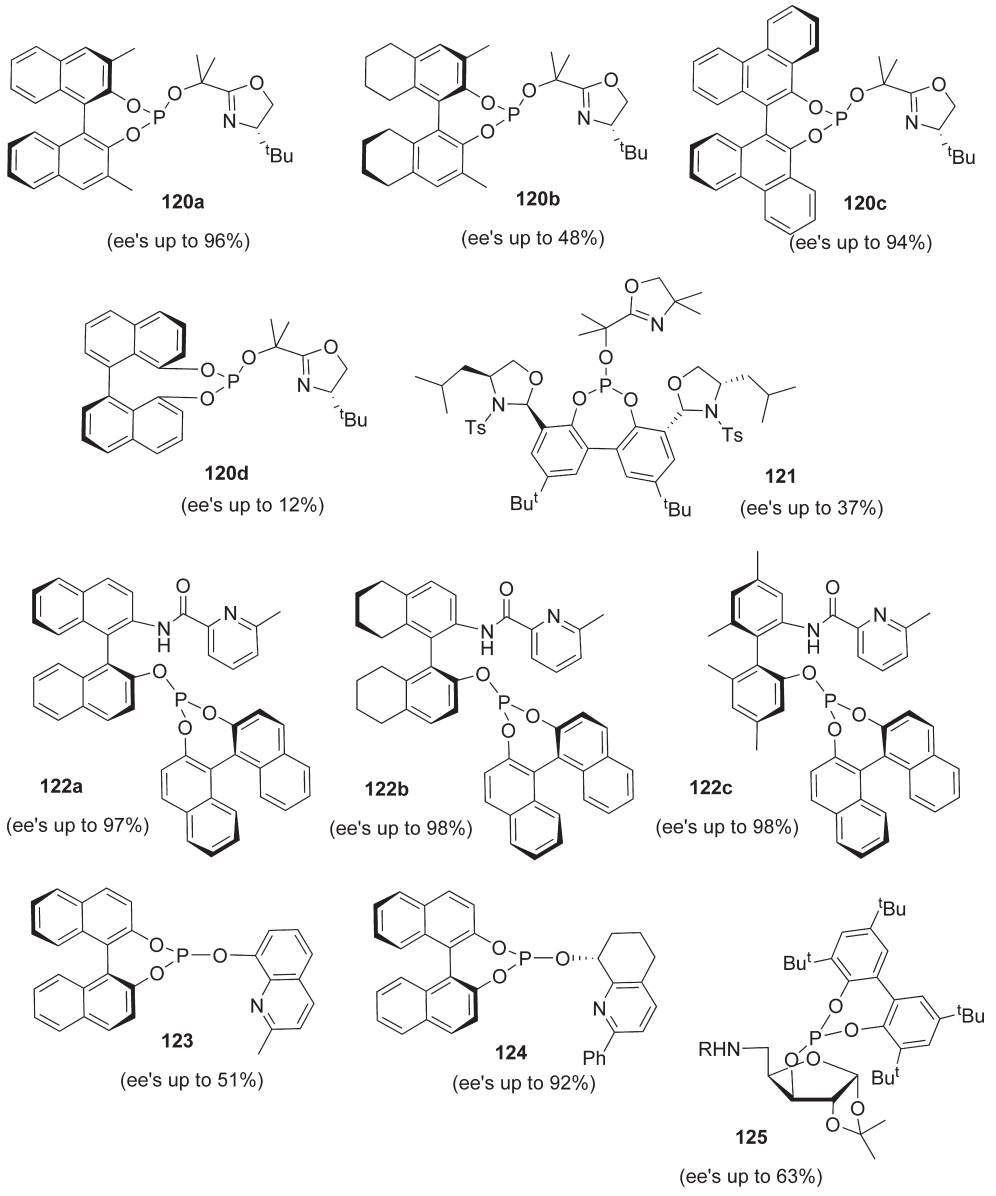


Figure 33. Heterodonor phosphite−nitrogen ligands **120**−**125**.

Heterodonor phosphite−phosphine[79] and phosphite−phosphoramidite[25c,80] ligands have also been applied to copper-catalyzed conjugate addition with different degrees of success. It should be noted that Taddol-based phosphite−phosphines **126** (Figure 34) are suitable ligands for the Cu-catalyzed conjugate addition of Grignard reagents to cyclohexenone.[79b] These readily available ligands proved to be compatible with an unsurpassed range of Grignard reagents to provide the addition products in high enantioselectivities (82−92% ee).

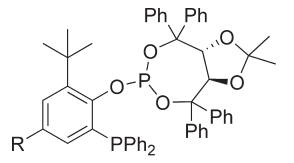


Figure 34. Taddol-based phosphite−phosphine ligands **126**.

4.2. Rhodium-Catalyzed Conjugate Addition

The asymmetric Rh-catalyzed conjugate addition of organoborane reagents to α,β-unsaturated substrates has become the method of choice for introducing an aryl or vinyl group in the β position.[65i] This approach therefore complements the Cu-catalyzed conjugate addition that usually provides the highest levels of enantioselectivity when alkyl groups are introduced.[4] Binaphthyl-based diphosphines, such as BINAP,[65i,81] and phosphoramidites[82] have been the ligands of choice for this asymmetric transformation. Nevertheless, Gennari and co-workers developed highly enantioselective Rh-catalyzed conjugate addition of phenylboronic acid to enones using a tropos biphenyl-based monodentate dynamic ligand library containing both phosphites and phosphoramidites (ligands **127**, Figure 35).[83] They found that the heterocombination of a biphenyl-based phosphite derived from (1*R*,2*S*)-2-(2-phenylpropan-2-yl)cyclohexanol and a biphenyl-based

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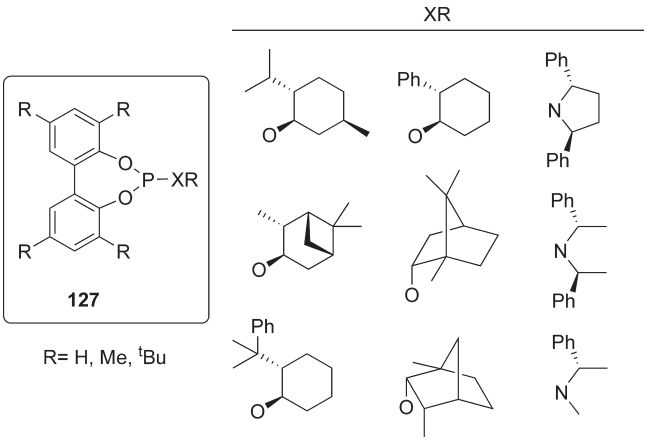


Figure 35. General structure of tropos monophosphite and monophosphoramidite ligands **127** used by Gennary and co-workers.

phosphoramidite derived from (2*R*,5*R*)-2,5-diphenylpyrrolidine gave the most enantioselective catalyst (ee's up to 99%).[83b]

More recently, the above-mentioned biphenyl-based tropos monophosphite ligands derived from deoxycholic acid (**113**, Figure 31) were also used in the Rh-catalyzed addition of arylboronic acids to cyclic enones, giving ee's up to 92%.[84]

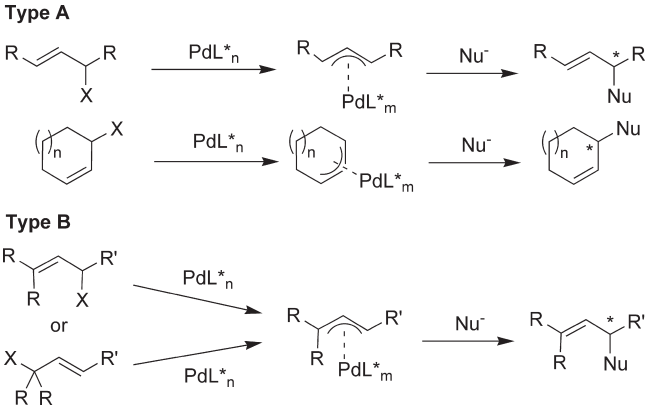
4.3. Key Ligand Parameters for High Selectivity

In contrast to the hydroformylation reaction, high enantioselectivities can be obtained using both mono- and diphosphite ligands as well as heterodonor phosphite−nitrogen containing ligands. Another major difference with previous reactions is that an appropriate choice of the reaction conditions (source of copper, alkylating reagent, solvent, etc.) is crucial for high enantioselectivities. Despite the fact that tartrate- and Taddol-based phosphite ligands were the first to be successfully explored, the use of biaryl-based phosphite ligands has proved to be superior, providing high enantioselectivities in a broader type of substrates, matching in some cases the best obtained using monophosphoramidite analogues.

5. ASYMMETRIC PD-ALLYLIC SUBSTITUTION

The palladium-catalyzed asymmetric allylic substitution—which allows the enantioselective formation of carbon−carbon and carbon−heteroatom bonds—is a powerful synthetic tool for preparing enantiomerically enriched compounds.[85] Scheme 16 shows two important classes of allylic substitutions that can be carried out enantioselectively with chiral catalysts. Type A reactions start from a racemic substrate (linear or cyclic) and proceed via symmetrical allylic systems. The enantioselectivity is determined by the ability of the chiral ligand to differentiate between the two allylic termini.[85,86] In type B reactions, racemic or prochiral substrates possessing two identical geminal substituents at one of the allylic termini react via a π-allyl intermediate which can isomerize via the $\pi-\sigma-\pi$ mechanism.[85] In this case, enantioselection can occur either in the ionization step, leading to the allyl intermediate, or in the nucleophilic addition step.[85] For these latter substrates, not only does the enantioselectivity of the process need to be controlled, but the regioselectivity is also a problem because a mixture of regioisomers may be obtained. Most Pd-catalysts developed to date favor the formation of an achiral linear product rather than the desired branched isomer.[85] In contrast to Pd-catalytic systems, Ir-, Ru-, W-, and Mo-catalysts provide very high selectivity for the attack at the nonterminal carbon to give the chiral product.[85,87]

Scheme 16. Two Classes of Asymmetric Allylic Substitution Reactions



Most of the successful ligands reported to date for this process have been designed using three main strategies. The first was a secondary interaction of the nucleophile with a side chain of the ligand to direct the approach of the nucleophile to one of the allylic terminal carbon atoms.[88] The second one, propagated by Trost, was the increase of the ligand's bite angle to create a chiral cavity in which the allyl system is perfectly embedded. This idea paved the way for the successful application of ligands with large bite angles for the allylic substitution of sterically undemanding substrates.[85,89] The third and final strategy was the use of heterodonor ligands that electronically discriminate between the two allylic terminal carbon atoms due to the different *trans* influences and *trans* effects of the donor groups.[85,90] This made it possible to successfully use a wide range of heterodonor ligands (mainly P,N-ligands) in allylic substitution reactions.[85] More recently, the use of biaryl-phosphites in the ligand design has emerged as a new strategy.[91] The benefits are as follows: (1) substrate specificity decreases because the chiral pocket created is flexible enough to enable the perfect coordination of hindered and unhindered substrates,[92] (2) reaction rates increase thanks to the larger π-acceptor ability of these moieties,[93] and (3) regioselectivity toward the desired branched isomer in monosubstituted linear substrates increases thanks to the π-acceptor ability of the phosphite moiety, which decreases the electron density of the most substituted allylic terminal carbon atom via the *trans*-influence, favoring the nucleophilic attack to this carbon atom.[94]

In this section we will discuss the application of diphosphite, phosphite-N ligands (N = oxazoline, oxazole, thiazole, and imine), and heterodonor phosphite-P′ ligands (P′ = phosphoramidite and phosphine) in the Pd-catalyzed asymmetric allylic substitution of several substrate types.

5.1. Di- and Monophosphite Ligands

5.1.1. Diphosphite Ligands. In recent years, several biaryl diphosphite ligands have been applied in the Pd-catalyzed allylic substitution reactions of several substrate types. Table 1 shows the results obtained with the most representative ligands applied to the Pd-catalyzed allylic substitution of 1,3-diphenylprop-2-enyl acetate.[93b,c,95] All the ligands except **24w** and **128**−**130** (Figure 36) have already been applied in the above-mentioned asymmetric catalytic processes. These ligands present systematic modifications in several ligand parameters, which are known to have an important effect on the process. The results indicated

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Table 1. Selected Results for the Pd-Catalyzed Allylic Substitution of 1,3-Diphenylprop-2-enyl Acetate Using Diphosphite Ligands[a]

entry	ligand	% conv (min)[b]	% ee[c]	entry	ligand	% conv (min)[b]	% ee[c]
1	**84b**	100 (30)	80 (*R*)	14	**7b**	100 (5)	29 (*R*)
2[d]	**8b**	100 (30)	98 (*S*)	15	**128**	93 (5)	73 (*R*)
3	**87b**	100 (5)	94 (*R*)	16	**2b**	21 (5)	97 (*S*)
4	**4b**	100 (5)	45 (*R*)	17	**3b**	18 (5)	13 (*R*)
5	**5a**	13 (5)	31 (*S*)	18	**85b**	100 (30)	10 (*S*)
6	**5c**	100 (5)	96 (*S*)	19	**129**	100 (30)	3 (*S*)
7[d,e]	**5b**	100 (5)	98 (*S*)	20	**130**	60 (30)	49 (*S*)
8	**5d**	74 (5)	98 (*S*)	21	**1b**	87 (30)	30 (*S*)
9	**5e**	13 (5)	16 (*R*)	22	**115a**	30 (30)	41 (*R*)
10	**5f**	14 (5)	21 (*S*)	23[f]	**15a**	70 (2880)	20 (*S*)
11	**5g**	72 (5)	97 (*S*)	24[f]	**24w**	54 (−)	83 (*R*)
12	**5h**	44 (5)	83 (*R*)	25[g]	**5b**	100 (45)	99 (*R*)
13	**6b**	100 (5)	15 (*R*)				

[a] Reactions carried out at 1 mol % Pd using dimethyl malonate as nucleophile in dichloromethane at room temperature. [b] Conversion measured by ^{1}H NMR. [c] Enantiomeric excess (ee) measured by chiral HPLC. [d] TON up to 10,000. [e] At 5 °C, it provides 100% conversion in 7 min and >99% ee. [f] Using pyrrolidine as nucleophile. [g] Using benzylamine as nucleophile.

that the ligand parameters did indeed have an important effect on the catalytic performance. It is worth noting that results were best with the ligands that contain a furanoside backbone (ligands **2**, **5**, and **8**, Figure 3) (ee's up to 99%, TOF's up to 22,000 mol·mol^{-1}·h^{-1}.

In general, ligands which have two and three carbon atoms in the bridge provided higher enantioselectivities than ligands with four carbon atoms (i.e., Table 1, entries 1, 3, and 19).

The influence of the ligand backbone indicates that increasing the rigidity of the ligand is beneficial. Thus, for 1,2-diphosphite ligands, the introduction of a more rigid furanoside backbone showed higher enantioselectivity (Table 1, entries 1 vs 2). Similar behavior was observed for the 1,3-diphosphites (entries 3 and 15 vs 7 and 16, respectively) and 1,4-diphosphite ligands (entries 18 and 19 vs 20 and 21). It should be noted that for 1,3-furanoside diphosphites (**4**−**7** and **2**−**3**) it was also found that catalytic performance was affected by the substituent at C-5 and the configurations of carbon atoms C-3 and C-5 of the furanoside backbone. Therefore, the best activities and enantioselectivities were obtained using glucofuranoside ligands **5**, which combine the presence of a methyl substituent at C-5 with an (*S*)-configuration at C-3 and an (*R*)-configuration at C-5.

As far as the effect of the substituents at the biaryl phosphite moiety was concerned, it was found that the best activities and enantioselectivities were obtained using *tert*-butyl groups at both *ortho* and *para* positions of the biphenyl phosphite moieties. Finally, with ligands **5g** and **5h**, which contain different bulky enantiomerically pure binaphthyl moieties, it was found that there is a cooperative effect between the configuration of the biaryl moiety and the configuration of the ligand backbone on enantioselectivity. This led to a matched combination for ligand **5g**, which contains (*S*)-binaphthyl moieties (entries 11 and 12). In addition, by comparing the results obtained using ligand **5d** with those of the related binaphthyl ligands **5g** and **5h** (entries 7 vs 11 and 12), it can also be concluded that the tropoisomeric biphenyl moieties in ligands **5b**−**d** adopt an (*S*)-configuration when coordinated to the Pd−π-allyl intermediate species.

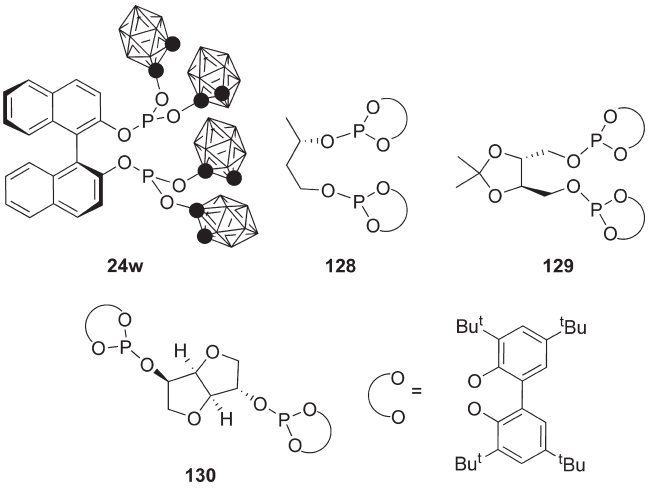


Figure 36. Diphosphite ligands **24w** and **128**−**130**.

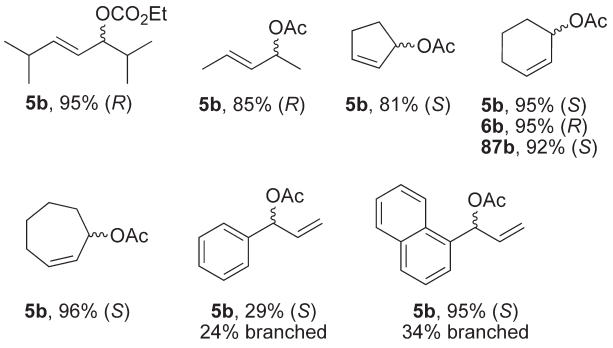


Figure 37. Summary of the best results for the Pd-catalyzed allylic substitution using diphosphite ligands.

Diphosphite ligands **2**−**7a**−**h** and **87a**−**h** were also tested in the allylic alkylation of more challenging disubstituted linear and cyclic substrates (Figure 37).[93b,95c] These substrates have different steric requirements. Therefore, if enantioselectivities need to be high, the ligand must be able to tune the size of the chiral pocket to enable the perfect coordination of hindered and unhindered substrates. The vast majority of the successful Pd-catalysts reported are unable to tune the chiral pocket as each substrate requires, and therefore, they can only provide high ee's for one type of substrate: hindered or unhindered.[85] The results using diphosphites **2**−**7a**−**h** and **87a**−**h** indicated that the ligand backbone and the flexibility of the biaryl phosphite moieties play an important role in controlling the size of the chiral pocket and achieving high versatility. Therefore, ligand **5b**, which combines the glucofuranoside backbone with tetra-*tert*-butyl-biphenyl phosphite moieties, emerged as a privileged structure, providing unprecedented enantioselectivities for both hindered (ee's up to >99%) and unhindered substrates (ee's up to 96%).[93b]

Finally, diphosphite ligands **2**−**7a**−**h** and **87a**−**h** were also applied to the asymmetric Pd-catalyzed allylic substitution of monosubstituted substrates (Figure 37). Again, ligand **5b** provided the best results.[93b,95c] Unfortunately, the regioselectivity for the branched products was not high. However, high enantioselectivities can be obtained by increasing the size of the substrate substituent. Therefore, enantioselectivities increased from 29% to 95% when the phenyl substituent was replaced with a

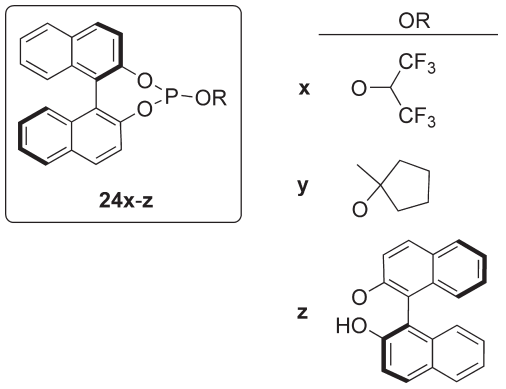


Figure 38. Binol-based monophosphite ligands **24x−z**.

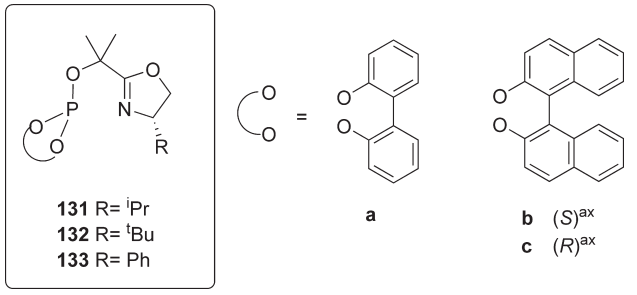
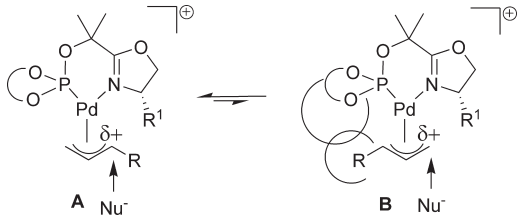


Figure 39. Phosphite-oxazoline ligands **131−133a−c**.

Scheme 17. Key Pd−Allyl Intermediates Containing Monosubstituted Substrates



2-naphthyl group using ligand **5b**. Also of particular note are the high activities (TOF's up to >600 mol·mol^{-1}·h^{-1} observed for these substrates.[93b]

5.1.2. Monophosphite Ligands. Much less attention has been paid to catalysts containing monodentate ligands in this process. However, in 2000, the groups of RajanBabu and Zhang obtained an enantioselectivity of 94% with catalyst precursors containing monophospholane ligands in the Pd-catalyzed allylic alkylation to *rac*-1,3-diphenyl-3-acetoxyprop-1-ene.[96] Despite this success, few monophosphorus ligands have been applied in Pd-catalyzed asymmetric allylic substitution. The above-mentioned tartrate-based **111a,b,g,h**[97] (Figure 29) and binol-based **24p**, **24q**, and **24x−z** (Figures 9 and 38)[12f,15a,98] monophosphite ligands have been applied to this process. In general, the allylic alkylation of 1,3-diphenyl-3-acetoxyprop-1-ene using dimethyl malonate proceeds with moderate-to-high enantioselectivities, and the most successful ligands are the tartrate-based monophosphite **L2a** (ee's up 79%) and binol-based **24z** ligand (ee's up to 95%). Binol-based ligands **24x−y** also provided enantioselectivities up to 83% and 74% in the allylic sulfonylation and amination of 1,3-diphenyl-3-acetoxyprop-1-ene, respectively.

5.2. Phosphite−Heterodonor Ligands

5.2.1. Phosphite−Oxazoline Ligands. In recent years, several phosphite−oxazoline ligands have been applied in the Pd-catalyzed allylic substitution reactions of several substrate types (Scheme 16).[27a,92a,b,94a,99−103]

Phosphite−oxazoline ligands (**131−133a−c**) were first successfully applied in this process by Pfaltz and co-workers (Figure 39).[94a] Ligands **131−133a−c** were designed to overcome the problem of regioselectivity in the allylic alkylation of monosubstituted linear substrates. Pfaltz et al. found that regio- and enantioselectivities were affected by substituents in the oxazoline moiety and by the substituents/configuration of the phosphite moiety. The best results were obtained with ligand **132b**, which provides an excellent combination of regioselectivities (up to 95%) in the desired branched isomer and enantioselectivities (up to 94%). These ligands were successful because of the combination of two ligand parameters that direct the nucleophilic attack to the most substituted allyl terminus (Scheme 17).[94a] The first of these parameters is the π-acceptor capacity of the phosphite moiety, which decreases the electron density of the most substituted allylic terminal carbon atom via the *trans*-influence, favoring the nucleophilic attack to this carbon atom. The second is the introduction of a bulky biaryl phosphite moiety, which shifts the equilibrium to the desired Pd−**A** allyl intermediate. Despite this success, these ligands produced moderate results for hindered and unhindered disubstituted substrates (ee's up to 60% for 1,3-diphenyl-3-acetoxyprop-1-ene and 70% for 3-acetoxycyclohexene, respectively).[94b]

Subsequently, the same group applied the above-mentioned Taddol-based phosphite-oxazoline ligands **53** (Figure 19) in the Pd-catalyzed allylic substitution of the standard substrate 1,3-diphenyl-3-acetoxyprop-1-ene and monosubstituted substrates 1-phenylallyl acetate and 1-phenyl-3-acetoxyprop-1-ene.[27a] Although high enantioselectivites were obtained for monosubstituted substrates (ee's up to 94%), the regioselectivities toward the desired branched product (up to 66%) were lower than those produced with the previous biaryl phosphite derivatives **132b**. Again, moderate enantioselectivity was obtained in the allylic alkylation of disubstituted substrate 1,3-diphenyl-3-acetoxyprop-1-ene (ee's up to 56%).

In order to find a more versatile phosphite-oxazoline ligand, we decided to take one of the most successful ligand families for this process, the phosphine−oxazoline PHOX ligands, and replace the phosphine group with a bulky diphenyl phosphite moiety (**134−139a−d**, Figure 40).[92a,99] The application of these ligands in the asymmetric Pd-catalyzed allylic substitution reactions was very successful. Therefore, excellent activities (TOF's > 2400 mol·mol^{-1}·h^{-1}, and regio- (up to 99%) and enantioselectivities (ee's up to >99%) were obtained for hindered and unhindered disubstituted and monosubstituted substrates (Figure 41). It is noteworthy that these ligands show higher versatility than their phosphine−oxazoline PHOX analogues. These excellent results are in line with the presence of a π-acceptor flexible bulky biphenyl phosphite moiety.

The results indicate that the enantioselectivity is affected by the substituents in the biphenyl phosphite and in the oxazoline moieties. The best enantioselectivities are obtained using a bulky tetra-*tert*-butyl-biphenyl phosphite moiety. It should be noted that the choice of the oxazoline substituent depends on the substrate. Thus, for hindered linear substrates, a phenyl

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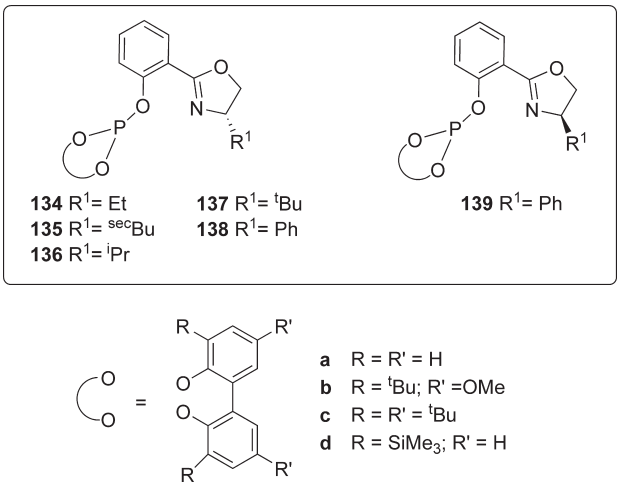

Figure 40. Phosphite−oxazoline ligands **134**−**139a**−**d**.

substituent is required, while for unhindered ones more sterically demanding substituents (^{t}Bu or ^{i}Pr) are needed. Interestingly, both enantiomers of the substitution products can be obtained by simply changing the configuration of the oxazoline substituent (i.e., ligands **138** and **139**).

After these significant contributions, new phosphite−oxazoline ligands were applied. The first of these were the chiral (*S*)-binaphthalene-core ligands **140a**−**b** (Figure 42), developed by Gladiali and co-workers and applied to the Pd-catalyzed asymmetric allylic substitution of 1,3-diphenyl-3-acetoxyprop-1-ene, albeit with moderate results (100% conv, ee's up to 43% in 7 h).[100]

The second group of ligands to be applied were the above-mentioned pyranoside phosphite−oxazoline ligand library **70**−**73a**−**h** (Figure 20) derived from D-glucosamine.[92b,101] The results indicate that activities and enantioselectivities are mainly affected by the substituents in both the oxazoline and the phosphite moieties and by the cooperative effect between stereocenters. However, the effect of these parameters depends on each substrate class. By carefully selecting the ligand components, high enantioselectivities (ee's up to 99%) and good activities (TON's up to 10,000[104]) have been achieved in a broad range of mono-, di-, and trisubstituted linear hindered and unhindered linear and cyclic substrates (Figure 43). In addition, the efficiency of this ligand design is corroborated by the fact that these Pd-phosphite-oxazoline catalysts provided higher enantioselectivity than their phosphinite−oxazoline analogues in several substrate types.[105] The study of the Pd-1,3-diphenyl, 1,3-dimethyl, and 1,3-cyclohexenyl allyl intermediates indicates that for enantioselectivities to be high, the substituents in the biaryl phosphite moiety and the electronic and steric properties at the oxazoline substituents need to be correctly combined in order to form predominantly the isomer that reacts fastest with the nucleophile and to avoid the formation of species with ligands coordinated in monodentate fashion. This study also indicates that the nucleophilic attack takes place predominantly at the allylic terminal carbon atom located *trans* to the phosphite moiety.[101]

In the third place, the above-mentioned phosphite−oxazoline ligand library **54**−**69a**−**h** was screened in the Pd-catalyzed allylic substitution reactions of several substrate types (Figure 20).[102] By selecting the ligand parameters, high regio- and enantioselectivities (ee's up to 99%) have been achieved in a broad range of

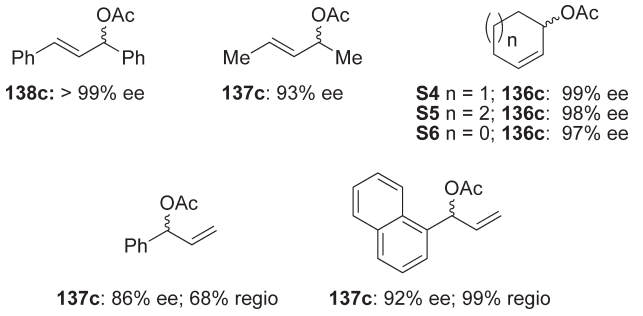

Figure 41. Summary of the best results obtained in the Pd-catalyzed allylic substitution using ligands **134**−**139a**−**d**.

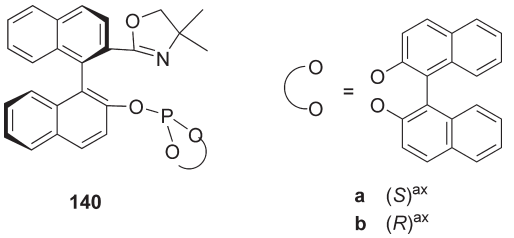

Figure 42. Binol-based phosphite−oxazoline ligands **140a**−**b**.

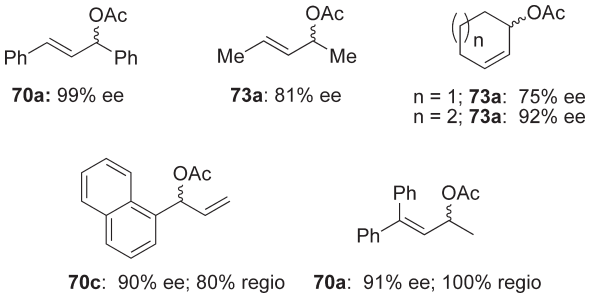

Figure 43. Summary of the best results obtained in the Pd-catalyzed allylic substitution using ligands **70**−**73a**−**h**.

mono- and disubstituted hindered and unhindered linear and cyclic substrates (Figure 44).[102b] In addition, for hindered disubstituted and monosubstituted substrates, both enantiomers of substitution products can be obtained with high enantioselectivities by simply changing either the absolute configuration of the alkyl backbone chain or the absolute configuration of the biaryl phosphite moiety.

Finally, Gavrilov and co-workers reported the synthesis of a phosphite−oxazoline ligand **141** (Figure 45), related to **134**−**139**. This ligand contained an acyclic phosphorus center with a [(1*S*)-endo]-(−)-borneol) fragment and a chiral oxazoline substituent. Ligand **141** was applied in the Pd-catalyzed amination of 1,3-diphenyl-3-acetoxyprop-1-ene, affording enantioselectivities up to 86%.[103]

5.2.2. Phosphite−Oxazole/Thiazole Ligands. The above-mentioned phosphite−oxazole/thiazole ligand library **74**−**80a**−**g** (Figure 22) was successfully applied in the Pd-catalyzed allylic substitution of several substrate types (Figure 46).[106] By carefully selecting the ligand components, high regio- and enantioselectivities (ee's up to 96%) and good activities were obtained in a broad range of mono-, di-, and trisubstituted linear hindered and unhindered substrates and

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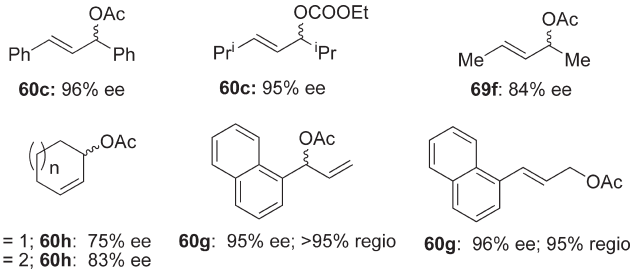

Figure 44. Summary of the best results obtained in the Pd-catalyzed allylic substitution using ligands **54**−**69a**−**h**.

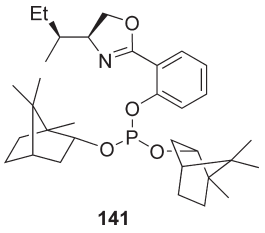

Figure 45. Phosphite-oxazoline ligand **141**.

cyclic substrates. Of particular note were the high regio- and enantioselectivities (up to 96% ee) combined with high activities obtained for the mono- and trisubstituted substrates. In addition, for all substrates, both enantiomers of the substitution products were obtained with high enantioselectivities.

5.2.3. Phosphite−Imino Ligands. In 2005, chiral *P*,*P*,*N*,*N*-tetradentate ferrocene-derived iminophosphites **142** (Figure 47) were synthesized and applied in the Pd-catalyzed allylic substitution of 1,3-diphenyl-3-acetoxyprop-1-ene with dimethyl malonate (up to 86% ee) and pyrrolidine (up to 15% ee).[107]

Subsequently, the same authors developed P,N-bidentate ferrocene- and cymantrene-based iminoarylphosphites **143** (Figure 47) for the Pd-catalyzed allylic substitution of 1,3-diphenyl-3-acetoxyprop-1-ene with dimethyl malonate (ee's up to 97%) and sodium diformylamide (ee's up to 96%).[108]

In 2007, the above-mentioned ferrocenyliminophosphite ligands **81** (Figure 23) were applied in the Pd-catalyzed allylic substitution of 1,3-diphenyl-3-acetoxyprop-1-ene with several nucleophiles (ee's up to 60%). The Pd/**81f** catalytic system provided good enantioselectivities (up to 80%), albeit with moderate regioselectivity (41% in favor of the branched product) in the allylic substitution of monosubstituted substrate 1-(4-chlorophenyl)allyl methyl carbonate.[27f,109]

5.2.4. Phosphite−Phosphoramidite Ligands. Despite the successful use of phosphite and phosphoramidite ligands in asymmetric catalysis,[2] phosphite−phosphoramidite ligands, which combine the advantages of both ligand types, have been used very little. To the best of our knowledge, there are only three families of phosphite−phosphoramidite ligands applied to this process.[110]

The ligand family **144**−**153** (Figure 48) was created in an attempt to solve the two main problems observed using the previous diphosphite ligands **84** (Figure 25): (a) the low regioselectivity obtained for monosubstituted substrates; and (b) the low substrate versatility.[95c] This phosphite−phosphoramidite ligand design therefore makes electronic differentiation possible while maintaining a similar spatial disposition around the metal center. Moreover, the high activities obtained with diphosphite

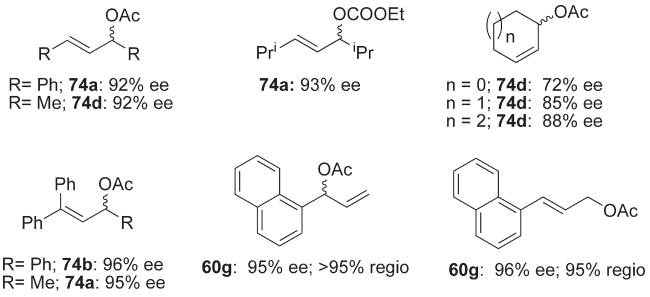

Figure 46. Summary of the best results obtained in the Pd-catalyzed allylic substitution using ligands **74**−**80a**−**g**.

ligands are expected to be maintained in these phosphite−phosphoramidite ligands because the phosphoramidite moiety is also a good π-acceptor group. Therefore, higher enantioselectivities (ee's up to 99%) than for related 1,2-diphosphite **84** and similar high activities (TOF's up to >800 mol·mol^{-1}·h^{-1}) were achieved in a wider range of substrates by selecting the substituents/configurations in the aminoalcohol backbone (C-1 and C-2), the amino group, and the biaryl phosphite moiety (Figure 49).[110c,d] It should be noted that both enantiomers of the product can be obtained with high ee's simply by changing either the absolute configuration of the biaryl moieties or the absolute configuration of the aminoalcohol unit. It is also worth noting that these ligands can be prepared in one step from readily available chiral 1,2-aminoalcohols.

The second family is the furanoside phosphite−phosphoramidite ligands **46**−**47** (Figure 17) and **154**−**155** (Figure 50). By correctly combining the ligand parameters (position of the phosphoramidite group, configuration of C-3 of the furanoside backbone, and substituents/configurations in the biaryl phosphite/phosphoramidite moieties), high regio- and enantioselectivities (ee's up to 98%) and good activities (TOF's > 2000 mol·mol^{-1}·h^{-1}) were achieved in a broad range of mono- and disubstituted hindered and unhindered substrates (Figure 51).[110a,110b] It should be noted that for unhindered linear and cyclic substrates, both enantiomers of substitution products can be obtained with high enantioselectivities by simply changing either the absolute configuration of C-3 or the position of the phosphoramidite group. In addition, the efficiency of this ligand design is also corroborated by the fact that these Pd−phosphite−phosphoramidite catalysts provided higher enantioselectivity than their diphosphite analogues in several substrate types and overcame the drawback of low regioselectivities in Pd allylic substitution of monosubstituted substrates using diphosphite analogues and the previous phosphite−phosphoramidite **144**−**153a**−**h** ligands.

Study of the Pd−allyl intermediates in both families indicated that the nucleophilic attack takes place predominantly at the allylic terminal carbon atom located *trans* to the phosphoramidite moiety.[110b,110d] It also showed that, for enantioselectivities to be high, the ligand parameters need to be correctly combined in order to increase the differentiation between the most electrophilic allylic terminus carbon atoms of the isomers formed and/or to predominantly form the isomer that reacts fastest with the nucleophile.

Pyranoside ligands **156** (Figure 52) were also applied in the Pd-catalyzed allylic substitution reactions of several substrates with different steric and electronic properties. Enantiomeric excesses of up to 89% with high activities were obtained for 1,3-diphenyl-3-acetoxyprop-1-ene, (*E*)-ethyl-2,5-dimethyl-3-hex-4-enylcarbonate, and 3-acetoxycycloheptene.[110e]

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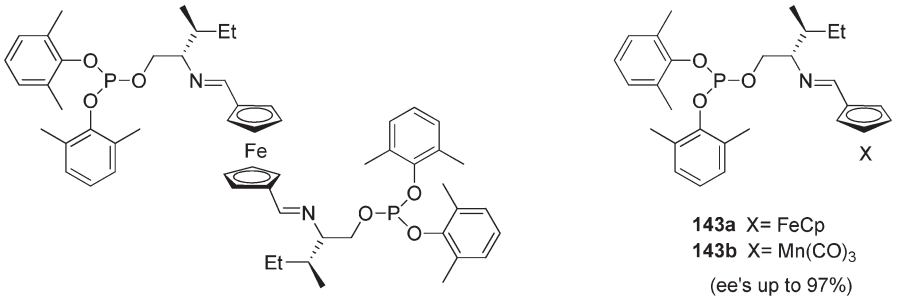

Figure 47. Iminophosphite ligands **142**−**143**.

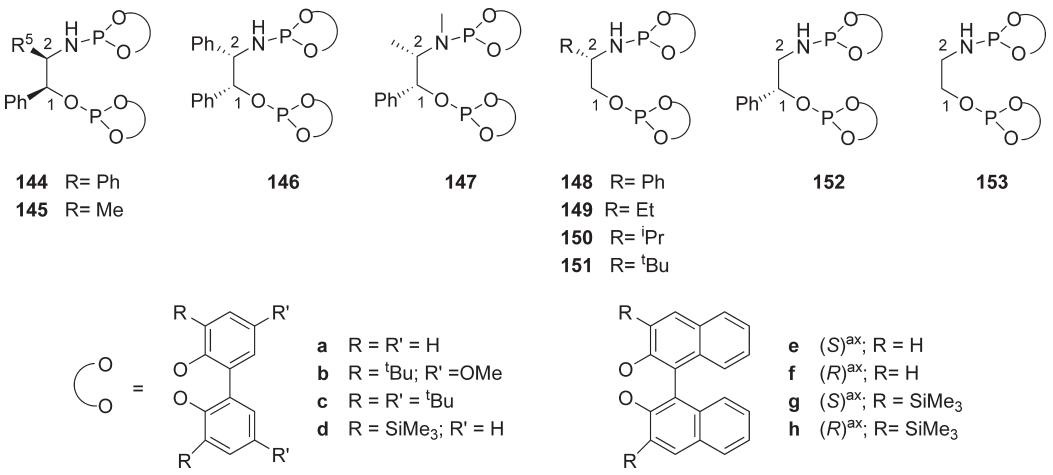

Figure 48. Phosphite−phosphoramidite ligands **144**−**153a**−**h**.

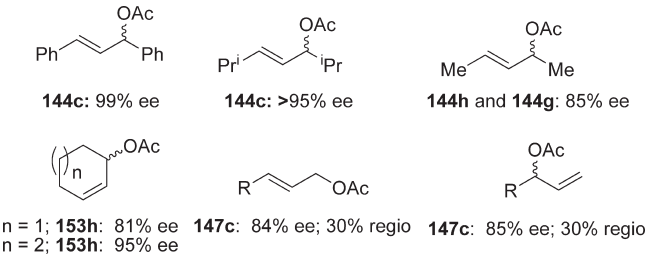

Figure 49. Summary of the best results obtained in Pd-catalyzed allylic substitution using ligands **144**−**153a**−**h**.

Heterodonor phosphite−phosphine ligands have also been used in this process, although to a lesser extent than other heterodonor ligands. To our knowledge, there are only two reports on this topic. The first describes the application of the above-mentioned phosphite−phosphine ligands **39**−**41** (Figure 16), which contain a stereogenic P atom, in the Pd-catalyzed allylic alkylation of 1,3-diphenyl-3-acetoxyprop-1-ene with dimethyl malonate.[111] The X-ray crystal structure of the allylpalladium complex revealed a longer palladium−carbon bond distance *trans* to the phosphine moiety, indicating that the attack of the nucleophile takes place at the carbon *trans* to the phosphine moiety. This was confirmed by the fact that the phosphine moiety did not affect the enantioselectivity directly. The biaryl moiety induces the enantioselectivity controlled by the stereogenic center next to the phosphite moiety. Experiments with ligands that have different bridge lengths show that a larger bite angle improves the enantioselectivity. Therefore, the best enantioselectivities (ee's up to 83%) were obtained using ligand **39a**.

The second report describes the application of the above-mentioned furanoside ligands **37** (Figure 16) in the Pd-catalyzed allylic alkylation of 1,3-diphenyl-3-acetoxyprop-1-ene with little success (ee's up to 42% with ligand **37a**).[95b]

5.3. Other Metal-Catalyzed Allylic Substitution Reactions

Although Pd-catalyzed allylic alkylation is by far the most popular version, the poor regioselectivity observed with non-symmetrical allylic substrates is a serious limitation of this protocol. In this respect, the Ir- and Cu-catalyzed processes are an interesting alternative and have led to a considerable amount of research during recent years. Copper is also attractive because it tolerates a wide range of nonstabilized nucleophiles such as organometallics.

In the Ir-catalyzed allylic alkylation using phosphite ligands, the successful application of bidentate phosphite−thioether ligand **157** (Figure 53) is noteworthy.[112] This ligand provided high regio- (up to 89%) and enantioselectivities (up to 97%) in the Ir-catalyzed allylic substitution of cinnamyl phosphonate-type substrates with diphenylimino glycinate.

Binol-based monophosphite ligands **24** (Figure 9) have also been used in the Ir-catalyzed allylic alkylation of cinnamyl-type substrates with dimethyl malonate using diethylzinc as base. Ir/**24c** provided the enantioselectivities (up to 77%) with a

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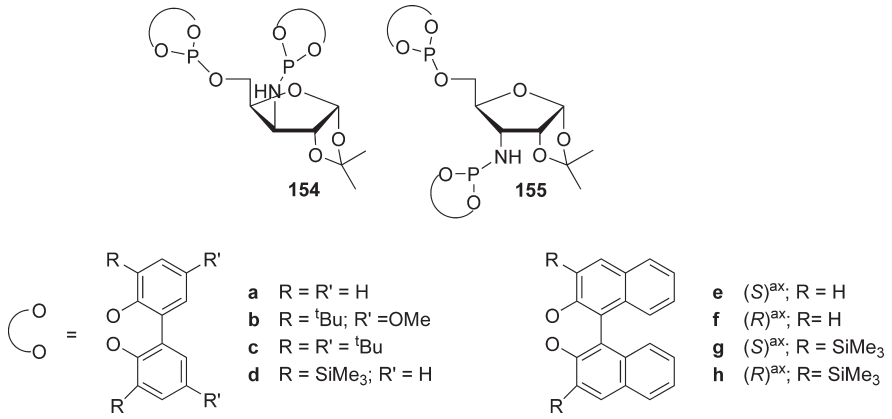

Figure 50. Furanoside phosphite−phosphoramidite ligands **154**−**155a**−**h**.

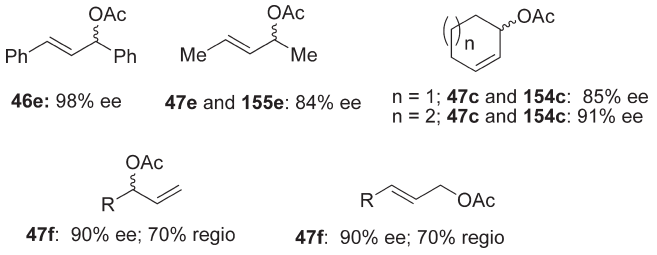

Figure 51. Summary of the best results obtained in Pd-catalyzed allylic substitution using ligands **154**−**155a**−**h**.

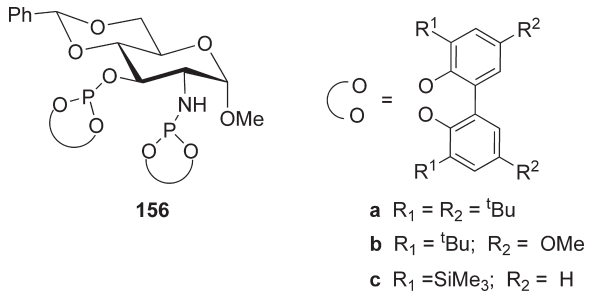

Figure 52. Pyranoside phosphite−phosphoramidite ligands **156**.

regioselectivity of 92%.[113] Binol-based monophosphites have also been used in the Ir-catalyzed allylic substitution of cinnamyl phosphonate-type substrates with diphenylimino glycinate, albeit with little success.[112]

More recently, the above-mentioned diphosphite ligand **15** (Figure 5) has been successfully applied to the Ir-catalyzed allylic amination of 1,3-diphenyl-3-acetoxyprop-1-ene with pyrrolidine (ee's up to 90%).[101]

To the best of our knowledge, only two papers have been published on the use of phosphite ligands in Cu-catalyzed allylic alkylation.[114] They reported the successful application of the above-mentioned Taddol-based phosphite **111e** (Figure 29) in the Cu-catalyzed addition of EtMgBr to cinnamyl chloride with regio- and enantioslectivities up to 96% and 82%, respectively.

5.4. Key Ligand Parameters for High Selectivity

The presence of biaryl groups in the phosphite moieties seems to be crucial to achieve high levels of enantioselectivity for a wide range of substrate types in the Pd-catalyzed allylic substitution reactions. The benefit of incorporating these biaryl groups is that

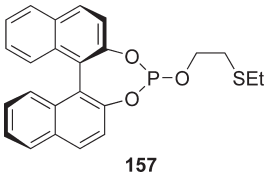

Figure 53. Phosphite−thioether ligand **157**.

the substrate specificity decreases because the chiral pocket created is sufficiently flexible to enable the necessary enbracement of both hindered and unhindered substrates. Moreover, the π-acceptor capacity of the phosphite groups has two main advantages in this reaction: (i) reaction rates increase and (ii) the regioselectivity toward the desired branched isomer in monosubstituted linear substrates increases, since the electron density of the most substituted allylic terminal carbon atom decreases via the *trans*-influence, favoring the nucleophilic attack to this carbon atom.

For diphosphite ligands, high activities and enantioselectivities can be obtained for several disubstituted hindered and unhindered substrates by combining the biaryl phosphite groups with an appropriate ligand backbone; ligands with two and three carbon atoms in the backbone's bridge provided higher enantioselectivity than ligands with four. However, the regioselectivity in monosubstituted substrates remains a major challenge.

Heterodonor phosphite-containing ligands have emerged as suitable ligands that overcome the limitation of the diphosphite ligands for monosubstituted substrates, while maintaining the excellent results for disubstituted substrates. For example, several phosphite−oxazoline, phosphite−oxazole/thiazole, and phosphite−phosphoramidite ligands have therefore been applied with high success.

6. ASYMMETRIC NI-CATALYZED HYDROCYANATION OF ALKENES

Hydrocyanation of alkenes, the introduction of HCN across a double bond, is an efficient C−C bond forming reaction and a very useful reaction for the functionalization of organic substrates (Scheme 18). For substrates other than ethene, the regioselectivity to the Markovnikov or *anti*-Markovnikov products becomes an important issue. The nitrile products can be easily converted to a plethora of valuable intermediates in fine chemical synthesis, such as amides, esters, carboxylic esters, aldehydes,

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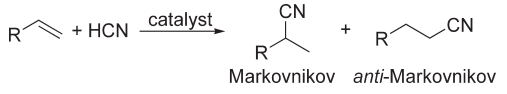
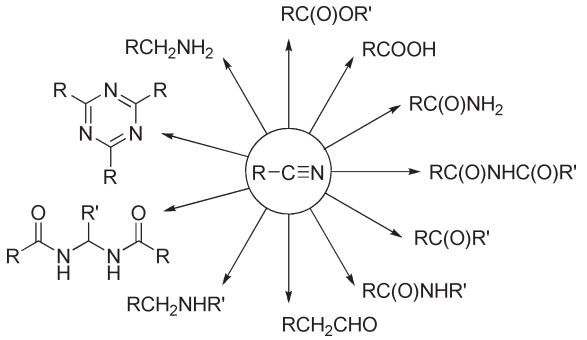
Scheme 18. Hydrocyanation of Alkenes



Scheme 19. Examples of Functional Groups Derived from Nitriles



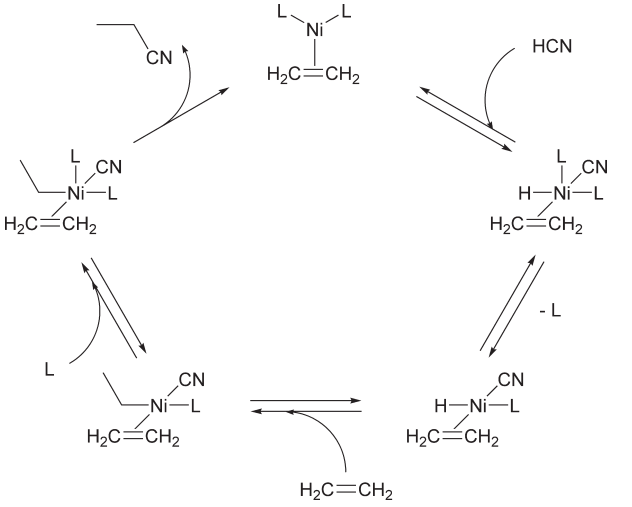
imines (see Scheme 19).[115] Although the toxicity of HCN requires a special experimental setup, the 100% atom economy and the inexpensive feedstocks of the reaction are great advantages. The initial reports on Ni/PPh_3 giving poor conversion and cobalt-catalyzed hydrocyanation of alkenes[116] were followed by the development of more efficient nickel phosphite catalysts.[117]

The reaction has tremendous industrial impact, mainly because of the adiponitrile production by DuPont via hydrocyanation of butadiene using aryl phosphite modified nickel catalysts.[118] The industrial process is among the early success stories of homogeneous catalysis, which shows a practical application accompanied by and probably the result of thorough understanding acquired by in-depth mechanistic studies. The actual catalyst is a Ni(0) complex which contains tris-*o*-tolylphosphite as stabilizing ligands and Lewis acids added as promotor.[119] The superior catalyst performance of the ligand tris-*o*-tolylphosphite is most likely the result of an advantageous combination of a relatively large cone angle of 141° and the strong π-acidity, as illustrated by the high χ value.[120] More recently, bidentate phosphites have also been reported to show good performance in the hydrocyanation reaction.[121]

The mechanism for the nickel-catalyzed hydrocyanation has been intensively studied by McKinney and Roe,[122] and a simplified mechanism is shown in Scheme 20. The catalytic cycle starts with an oxidative addition of HCN to a three coordinate Ni(0) species accompanied by ligand dissociation. The resulting square planar Ni(II) π-olefin complex is prone to hydride migration, assisted by alkene coordination, providing the σ-alkyl complex. Subsequent reductive elimination of RCN by an associative process yields the alkyl nitrile and the tetrahedral Ni(0) species.

The kinetic studies of McKinney and Roe clearly showed that rate-determining reductive elimination of RCN yielding the alkyl nitrile is assisted by phosphite addition.[122] This product forming step results also in the restoration of the tetrahedral Ni(0) complex out of a square planar Ni(II) compound (Scheme 20). This explains that phosphite ligands perform better

Scheme 20. Mechanism of Ni-Catalyzed Hydrocyanation[122]



than comparable phosphine analogues, as the reductive elimination is facilitated by electron-withdrawing ligands.[117,123] As a consequence, many phosphites have proven to be versatile ligands in the hydrocyanation reaction, whereas phosphine ligands lead to catalysts with hardly any activity.[117b,123−126]

The reaction is strongly promoted by the addition of Lewis acids, resulting in both higher activity and better catalyst stability.[127] Also, the regioselectivity of the reaction to the linear Markovnikov product can be improved in this way. The Lewis acids are most likely coordinating to the nitrile ligand, thereby rendering the Ni center more electron deficient and sterically encumbered, which promotes both the rate of reductive elimination and a preference for the linear Ni−alkyl complex.

The major catalyst decomposition pathway proceeds via reaction of a second HCN molecule with the intermediate square planar Ni(II) hydride or alkyl complex (Scheme 21). A molecule of dihydrogen is lost, and an inactive square planar biscyano Ni (II) species is generated. As the reaction has a second order rate dependency on the HCN concentration, this deactivation pathway can be minimized by slow addition of HCN, keeping the concentration low at all times.[128,129]

As reductive elimination is the rate-limiting step, both space-time yields and catalyst stability can be improved by promoting this elementary step of the catalytic cycle.[122,130−132] The rate-limiting reductive elimination is faster when more electron-withdrawing phosphites or phosphinites are being used (Scheme 20).

In the case of bidentate ligands, wide bite angles can destabilize the square planar Ni(II) species and stabilize the tetrahedral Ni(0) complexes, thus enhancing the reductive elimination and the overall catalysis.[133] In addition, the catalyst derailment reaction leading to insoluble Ni(II) dicyanide complexes is disfavored (Scheme 21). Indeed, an experimental study of Marcone and Moloy showed that reductive elimination of nitriles from nickeldiphosphine complexes was strongly enhanced by ligands that induce large bite angles.[134] This phenomenon had already been successfully exploited for the rational design of bidentate phosphine ligands for nickel-catalyzed hydrocyanation of styrene.[135] Up to that point application of phosphines as ligands had been unsuccessful and the catalytic performance

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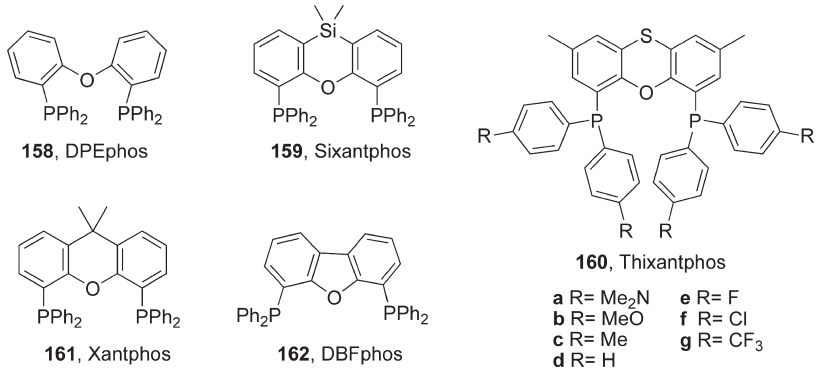
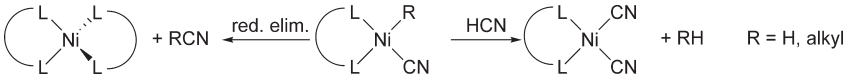
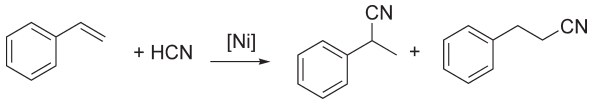


Figure 54. Diphosphine ligands **158**−**162**.

Scheme 21. Catalyst Decomposition Pathway



Scheme 22. Nickel-Catalyzed Hydrocyanation of Styrene



could not compete with structurally related phosphites. Diphosphines with an appropriate bite angle were expected to destabilize Ni(II) square planar and stabilize Ni(0) tetrahedral complexes. This should lead to a faster rate-limiting reductive elimination step, and consequently, the overall catalytic reaction should be enhanced.

The nickel-catalyzed hydrocyanation of styrene using ligands enforcing large bite angles **158**−**162** (Figure 54) resulted in remarkable yields and selectivity compared to monophosphines and traditional diphosphines (Scheme 22).[135] Using DPEphos **158** with a calculated bite angle of 101° induced a yield of 35−41% based on HCN. This is still a modest yield but a significant improvement compared to PPh_3 or small bite angle chelating diphosphines. The effect becomes more pronounced when the bite angle increases further using ligands **159** and **160**, which results in better stabilization of tetrahedral coordination; the yields increased up to 95%. These results were strikingly better than with several well-known common diphosphines, which gave yields of 0−11% (based on HCN) accompanied by the formation of large amounts of nickel dicyanides.[135] These results show clearly that enforcing large bite angles can enhance the reductive elimination step by stabilizing a tetrahedral geometry, resulting in effective nickel−phosphine-catalyzed hydrocyanation. The systematic change of the natural bite angle[136] proved to be a powerful tool to optimize catalyst performance, resulting in a sharp optimum in yield and regioselectivity at wide bite angles around 106°, a huge improvement compared to the cases of other diphosphines in the hydrocyanation of styrene.[135]

6.1. Phosphite Ligands

Already in the early 1990s, attempts to stabilize the nickel complex and reduce nickeldicyanide complex formation, a disadvantage of the DuPont system, were pursued by employing bidentate phosphite ligands. Pringle and co-workers synthesized a series of new chiral diphosphite ligands based upon binaphthol backbones (ligand **24**, R = 4-OMe-C_6H_4, Figure 9, and ligand **163**, Figure 55).[137,121e]

Although the 2,2′-bisphenol diphosphite ligand showed lower selectivity than the DuPont system for hydrocyanation of butadiene, the turnover numbers were increased 4-fold compared to the *ortho*-tolylphosphite system, indicating a strongly enhanced stability.[121e] Also, the diphosphite complex-based binaphthol **163** showed greater stability than the monodentate analogue **24** (R = 4-OMe-C_6H_4) and bidentate phosphines, and the reported yields reached up to 70%. The enhanced stability might be due to a favorable combination of electronic properties and the wide bite angle and chelating character of the ligand. More importantly, enantioselectivities of up to 38% were obtained for the hydrocyanation of norbornene using the Ni−**163** complexes with BPh_3 added as Lewis acid promotor.[137] At that time, these values were higher than those of both the Ni−DIOP[126] and Ni−monophosphite catalyst **24** (R = 4-OMe-C_6H_4).

The same ligand **163** was used by Babin and Whiteker for the hydrocyanation of styrene, for which they reported 56% regioselectivity for the desired *anti*-Markovnikov product with 13% ee.[35a] They also applied a related ligand based on (2*R*,4*R*)-pentanediol **83a** (Scheme 4) for the asymmetric hydrocyanation of norbornene with 50% enantioselectivity. This ligand was also successfully applied in asymmetric hydroformylation of styrene[35a] and was later shown to coordinate exclusively in a bisequatorial coordination mode in the trigonal bipyramidal rhodium complexes.[36b,38,138] This indicated that (2*R*,4*R*)-Chiraphite (**83a**) has a preference for wide bite angles, which probably promotes the hydrocyanation reaction in addition to the electronic effect.

Detailed studies on the influence of the steric properties of the binaphthol-based ligand **163**, originally developed by Pringle et al.,[121e] were reported by the groups of Vogt[139] and Chan.[140] Vogt et al. systematically changed the degree of steric hindrance of the binaphthol-based ligands **164a**−**e** (Figure 56). It was

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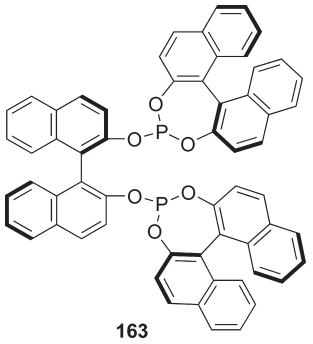

Figure 55. Diphosphite ligand **163**.

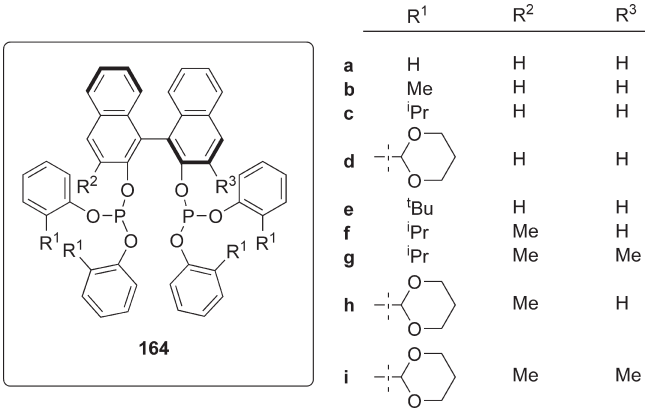

Figure 56. Diphosphite ligands **164a**−**i**.

found that ligands **164c** and **164d** gave the highest activities and best enantioselectivities up to 43% in the nickel-catalyzed hydrocyanation of styrene.[139] Ligand **164d** gave quantitative conversion to the branched nitrile with a small amount of polystyrene as side product. The steric effects proved to be very subtle, with both smaller (**164a**, **164b**) and larger (**164e**) substituents giving extremely low conversions. The good performance of ligand **164d** was attributed to an optimal steric bulk of the ligand leading to both reduced formation of inactive bischelate complexes[129] and an enhanced reductive elimination.[130a]

Next to styrene, ligand **164d** was also tested with other substrates, such as 4-methylstyrene and 1,3-cyclohexadiene, which all gave moderate enantioselectivities. Further optimization of the catalyst performance was achieved by introduction of additional substituents at the 3 and 3′ positions of the binaphthol backbone (**164f**−**i**, Figure 56). The best ligand turned out to be **164h**, leading to very good conversions for all tested substrates. It not only gave an excellent regioselectivity of 99% for the formation of α-ethylbenzyl nitrile for the hydrocyanation of *β*-methylstyrene, but it also gave high selectivity for the formation of 2-cyclohexene-1-carbonitrile with 86% ee when 1,3-cyclohexadiene was the substrate.[139]

In a related study, Chan et al. used the previously mentioned diphosphite ligands derived from binaphthol (**115a**,**b** and **116b**, Figure 32) for the nickel-catalyzed hydrocyanation of styrene.[140] The relatively small ligand **115a**, the opposite enantiomer of Pringle's ligand **163**, gave 23% ee in the asymmetric hydrocyanation of styrene. Remarkably, the enantioselectivity and catalyst were lower after introduction of steric bulk at the bridging (**115b**, 12% ee) binaphthol moiety. The best results were obtained by introduction of a very bulky bisphenol bridge (**116b**), providing 65% ee when the reaction was performed at 20 °C. Unfortunately, the cooperative effect which could be expected by inverting the configuration of either bridging or terminal bisaryl moieties, as has been reported for asymmetric hydroformylation of alkenes,[36c] was not investigated. Therefore, it is not possible to decide if the beneficial effect of the bulky bisphenol bridge is due to steric effects or formation of the opposite enantiomer of the bridge. The best ligand **116b** was also tested with other substrates, with a good enantioselectivity of 73% in the hydrocyanation of vinyl acetate as the most promising result.

It is noteworthy that an extensive series of derivatives of the chiraphite ligand **83a** and biaryl-based ligands **163** and **116b** has been studied by Dupont in the nickel-catalyzed hydrocyanation of butadiene and intermediates of the adiponitrile production.[121,141] The wide range of substrates and ligands which have been tested are illustrative of the power of phosphite ligands in nickel-catalyzed hydrocyanation.

Nevertheless, most successful ligands in asymmetric hydrocyanation are the diphosphinites **165** (Figure 57) based on carbohydrate backbones which have been developed by Casalnuovo and Rajanbabu.[130,142] These ligands proved to be very successful in the asymmetric hydrocyanation of vinylarenes.[142a−c] Using strongly electron-withdrawing CF_3 substituents (**165a**), a very high enanatioselectivity of 91% could be obtained in the nickel-catalyzed hydrocyanation of 6-methoxyvinylnaphthalene (MVE). The high enantioselectivity was merely attributed to an electronic and not a steric ligand effect, as ligand **165d** gave lower ee than ligand **165c**.[130a,142a−c] The electron-withdrawing ligands gave high enantioselectivities for a wide range of vinylarenes[130a] and several dienes.[142d]

6.2. Phosphite−Heterodonor Ligands

The first indication that introduction of electronic dissimilarities in bidentate ligands could lead to enhanced enantioselectivities was also reported by Rajanbabu and Casalnuovo.[130b] They prepared a series of unsymmetrical α-D-fructofuranoside diphosphinite ligands **166a**−**f** (Figure 58) with varying electronic properties. They studied this ligand series with fairly constant steric effects in the asymmetric nickel-catalyzed hydrocyanation of MVE. As expected, electron-donating ligands such as **166a** gave the lowest ee (25%) whereas electron-withdrawing ligands gave much higher enantioselectivities (56% for **166c**).[130b] Remarkably, the highest enantioselectivity was obtained when the substituent at C-3 is relatively electron donating and the substituent at C-4 is electron withdrawing, as in **166d**, which gave excellent enantioselectivities of up to 95% at 0 °C. This trend was confirmed by a series of structural derivatives within this series of ligands.

Nozaki et al. corroborated the promising approach of electronically dissimilar donor ligands by applying their famous Binaphos ligand **104** (Scheme 9) in the hydrocyanation of norbornene.[143] They obtained 40% ee by employing a Ni Binaphos ligand, which is an improvement compared to the case of the solely binol-based ligand **163** of Pringle et al.[137] The enantioselectivity could be increased to 48% by switching to palladium as catalyst using the same Binaphos ligand.[143]

6.3. Key Ligand Parameters for High Selectivity

The generally accepted mechanism for alkene hydrocyanation is depicted in Scheme 20. This mechanism is also applicable to vinylarenes and dienes, but the order of alkene addition and oxidative addition of HCN might be reversed. There is general consensus that the rate-determining step is the reductive elimination

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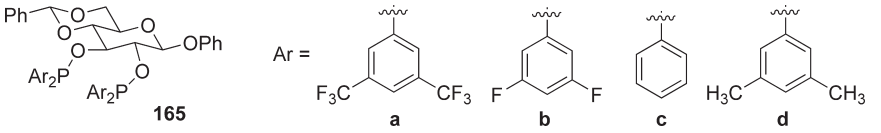
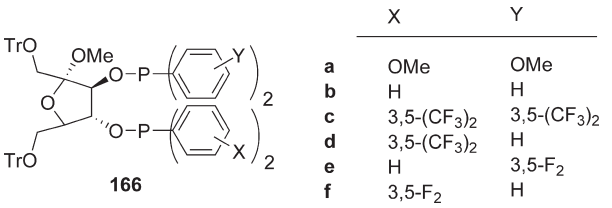


Figure 57. Diphosphinite ligands **165a−d**.



	X	Y
a	OMe	OMe
b	H	H
c	3,5-$(CF_3)_2$	3,5-$(CF_3)_2$
d	3,5-$(CF_3)_2$	H
e	H	3,5-F_2
f	3,5-F_2	H

Figure 58. Diphosphinite ligands **166a−f**.

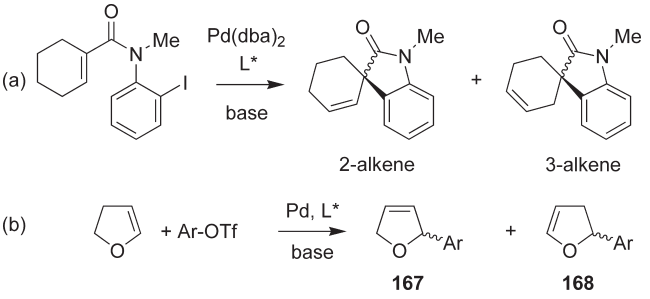
of the nitrile product.[122,144] This provides a rather straightforward explanation why phosphite and phosphinite ligands perform so well compared to phosphines. Product-forming reductive elimination from square planar Ni(II) complexes to electron rich Ni(0) is facilitated by strong π-accepting less-donating ligands, such as phosphites.[145] Next to these electronic effects, steric constraints also play an important role. Ni(II) complexes with strong ligands such as CN-, phosphines, and phosphites, are in general square planar, whereas Ni(0) complexes tend to be tetrahedral. Therefore, bidentate ligands with flexible bridges, which can support wide bite angles or more profoundly enforce such coordination, such as xantphos ligands, will promote reductive elimination.[133] By applying these principles, it was even possible to obtain good results with diphosphines, such as xantphos, where otherwise phosphine ligands tend to be unproductive.[129]

Whereas the relation between catalyst activity and ligand structure is relatively well understood, the ligand effects on enantioselectivity are more difficult to understand. Therefore, the design of a suitable ligand structure for efficient asymmetric hydrocyanation is still a tedious procedure. Casalnuovo and Rajanbabu investigated the enantioselective step by kinetic studies and deuterium labeling experiments.[130a] They concluded that the enantioselectivity of the reaction is determined either in the migratory insertion of the Ni-hydride to the substrate or in the reductive elimination step. They suggested that the observed improved enantioselectivity induced by electron-withdrawing substituents is caused by the promotion of this reductive elimination step.[130,142a−c]

Vogt et al. performed a very elegant deuterium labeling study which allowed them to investigate the intimate mechanism of the asymmetric hydrocyanation of 1,3-cyclohexadiene.[146] They unambiguously showed that for these systems the reductive elimination of the substrate is the rate-determining step. This implies that the insertion step may not be the enantioselectivity determining step.

Although the mechanistic insights have continuously been growing, the development of efficient catalysts for asymmetric hydrocyanation is still a process of delicate ligand fine-tuning. Several ligand parameters can be roughly predicted to be of importance. Strongly electron-withdrawing ligands promote reductive elimination, and experimentally, this is found to have a beneficial effect on enantioselectivity also. Steric constraints can be employed to prevent undesired formation of inactive bischelates and additionally promote reductive elimination also, but the effect on enantioselectivity is still not very clear. Wide bite angle ligands also strongly promote reductive elimination and also tend to result in good enantioselectivities. Nevertheless, the ultimate rational design of efficient catalysts is still beyond reach, and exploration of new ligand structures and tedious fine-tuning is still required.

Scheme 23. Representative Examples of (a) Intra- and (b) Intermolecular Heck Reaction



7. OTHER PROCESSES (HECK REACTION, NI-CATALYZED 1,2-ADDITIONS, HYDROVINYLATION, ETC.)

7.1. Asymmetric Heck Reaction

The palladium-catalyzed arylation or alkenylation of alkenes, better known as the Heck−Mizoroki reaction, has emerged as an extremely powerful tool for the formation of new carbon−carbon bonds.[147] The asymmetric Heck reaction is a versatile method for carbon−carbon bond formation in an enantioselective way and with large functional group tolerance.[148] The first reported successes concerned the intramolecular Heck coupling, which has been employed successfully in the construction of chiral trisubstituted and even tetrasubstituted olefins (Scheme 23a).[149] Since then the palladium-catalyzed intramolecular Heck reaction has been applied in many asymmetric total syntheses of different natural products.[150] The intermolecular Heck reaction proved to be more troublesome, mainly owing to complicated regioselectivity, but in recent years major advances have been achieved, mainly using dihydrofurans and dihydropyrans as substrates (Scheme 23b).[151] The initial Heck product **167** can isomerize to produce the major side product **168**.

The intermolecular Heck reaction has mainly been developed using diphosphine ligands[148b,152] or P−N ligands,[148c,e,153] and impressive enantioselectivities have been obtained. Still the general applicability of these catalyst systems is limited because the reaction rates are quite low, which requires long reaction times, high palladium loadings, and increased reaction temperatures. Obviously there is still a demand for catalyst improvement to obtain high enantioselectivities combined with high activities under mild reaction conditions.

The reaction rates of the Heck reaction could be tremendously improved by employing bulky monodentate ligands; both the palladacycle derived from *ortho*-tolylphosphine **169**[154] and

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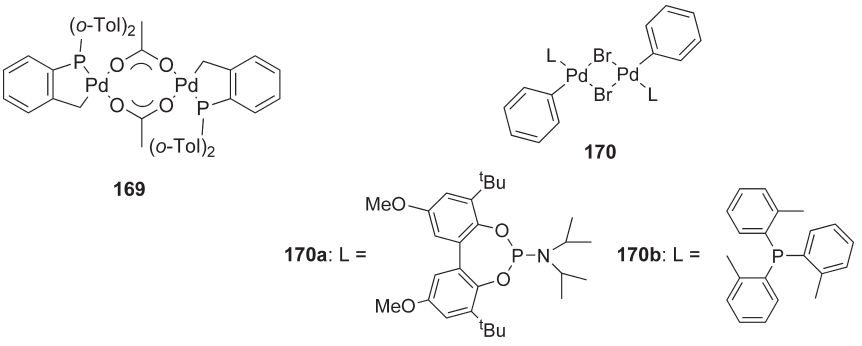
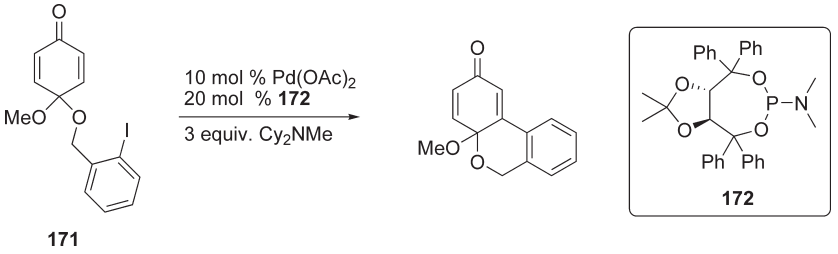


Figure 59. Dimeric palladium complexes **169** and **170**.

Scheme 24. Intramolecular Asymmetric Heck Reaction of 171 Using Ligand 172



dimeric palladium complexes of bulky phosphoramidite **170**[93a,155] gave extremely fast conversions in the Pd-catalyzed arylations of acylic esters and styrene (Figure 59).

The formation of monoligated mononuclear complexes proved to be responsible for the high reaction rates.[93a,155] The resting state of the catalytic cycle was shown to be the dimeric product of the oxidative addition reaction, which was in fast equilibrium with the highly reactive monomeric palladium complex as minor species.[93a,155,156] The kinetics of the reaction showed clearly that the oxidative addition is not the rate-determining step,[93a,155,156] which explains that good electron acceptors such as phosphoramidites and phosphites give such high reaction rates. More detailed studies using aryl and styrene substrates bearing electron-withdrawing and -donating substituents suggested that the migratory insertion is the rate-determining step.[155]

Feringa et al. realized that this might provide a solution for the low reaction rates for the intramolecular asymmetric Heck reactions developed by Overman and Hayashi,[150] which remained a disadvantage despite the wide applicability of this reaction in natural product synthesis.[150] They obtained 96% ee and good conversions in the intramolecular asymmetric Heck reaction of **171** using Taddol-based monodentate ligand **172** (Scheme 24).[157] Takemoto et al. applied the Feringa system successfully in the enantioselective intramolecular Heck reaction for the synthesis of 3,3-disubstituted piperidones.[158]

A major breakthrough in the asymmetric intermolecular Heck reaction was obtained by Pfaltz et al., who applied their phosphine−oxazoline (PHOX) ligands in the arylation of dihydrofuran and related substrates.[159] The obtained enantioselectivities were very high up to 98%, but the required reaction times were still quite long, typically about 3 days. The major advantage was that the isomerization reaction to 2,3-dihydrofuran prod ucts, which was a severe problem in the original BINAP (BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl) system of Hayashi,[152] was not observed. The successful application of PHOX ligands in the enantioselective intermolecular Heck reaction has triggered the development of a plethora of related phosphine−ozazoline ligands, including indene fused oxazolines,[160] 1,1′-binaphthyl-based ligands,[161] proline derivatives,[162] bicyclic phosphine-based ligands,[163] and planar chiral ferrocenyl-based ligands.[164] Furthermore, introduction of rigid cyclopropyl[165] or methylene[166] linkers in the PHOX ligands resulted also in effective catalysts for the arylation of dihydrofuran with enantioselectivities up to 99 and 95%, respectively.

Several studies have been dedicated to the introduction of alternative nitrogen donors instead of oxazolines, with varying success. Chiral pyridyl-phosphines resulted in very high enantioselectivity, up to 99%, with similar activity as the PHOX ligands.[167] Other heterocyclic imine donors, such as oxazines,[168] thiazoles,[169] and imidazoles,[169b] were equally successful, with enantioselectivities up to 98%. In contrast, tertiary amine donors proved to be less successful, as reported by Guiry et al., who prepared a series of phosphine−pyrrolidine ligands which provided moderate enantioselectivities and conversions in both asymmetric Heck arylation and olefination.[170]

An alternative approach is modification of the phosphine donor into better π-acceptors. Already in 1983, Spencer reported the use of triphenyl phosphite as ligand in the Heck reaction.[171] Uemura et al. prepared phosphinite−oxazoline ligands **173** based on D-glucosamine (Figure 60), which gave 96% ee in the arylation of 2,3-dihydrofuran.[172]

Diéguez and Pàmies et al. performed a systematic study toward the application of phosphite−oxazoline ligands in asymmetric Heck reactions.[173] They employed the previously mentioned phosphite analogues **70**−**73** (Figure 20) of Uemura's phosphinite ligand **173** and obtained excellent enantioselectivities up to 99% and, more importantly, great activities; full

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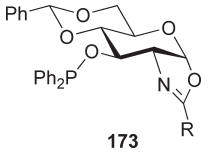


173

Figure 60. Phosphinite−oxazoline ligands **173** based on D-glucosamine.

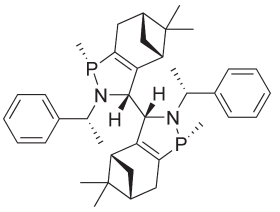
conversion could be obtained in 24 h at 50 °C for the arylation of 2,3-dihydrofuran.[173a,b] Remarkably, bulky substituents had a deleterious effect on both regio- and enantioselectivity as well as the activities: Ph ≫ Me > ^{i}Pr > ^{t}Bu.

Extensive exploration of a phosphite−oxazoline ligand library **54**−**69** (Figure 20) resulted in optimal performance for a range of alkene substrates and aryl triflates. Typically by changing to microwave heating, more than 99% regio- and enantioselectivity could be obtained in 10 min at 70 °C.[173c]

7.2. Asymmetric Hydrovinylation

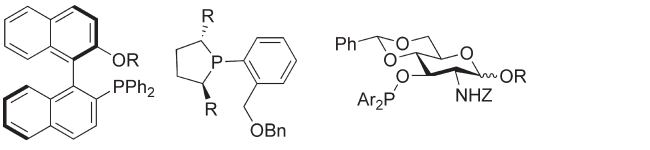
The catalytic asymmetric coupling of ethene with other alkene substrates is a powerful and 100% atom economic carbon−carbon bond forming reaction.[174] The discovery of the Wilke catalyst has triggered many applications of this powerful reaction,[175] including the Ni-catalyzed enantioselective hydrovinylation, which was already reported in the 1970s.[176] For example, chiral menthyl-based monophosphines were successfully employed in the asymmetric cyclization of 1,6-heptadiene and diallyl ether as well as the dimerization of styrene.[176] Wilke et al. revealed already in 1988 that asymmetric hydrovinylation is a powerful synthetic tool. Using an azaphospholene ligand **174** derived from myrtenal (Figure 61), they obtained 95% ee in the codimerization of ethene and styrene.[177]

In general, the nickel halide precursors were activated by addition of Lewis acids to create cationic nickel with weakly coordinating counterions. Muller et al. showed that excellent activities and selectivities could be obtained by using cationic Ni phosphine complexes with BF_4 as noncoordinating anion.[178] In subsequent studies they also showed that similar complexes derived from P-stereogenic phosphine ligands resulted in moderate to good enantioselectivities in palladium-catalyzed hydrovinylation.[179] Vogt et al. obtained similar results in the palladium-catalyzed hydrovinylation of styrene using planar chiral chromiumtricarbonyl-based phosphines.[180] Rajanbabu et al. explored the application of phosphine ligands carrying hemilabile groups.[181] They used a series of derivatives of Hayashi's MOP ligand,[182] and by fine-tuning the structure of the alkoxy substituent of **175** (Figure 62), they were able to optimize the enantioselectivity up to 80% for the Ni-catalyzed hydrovinylation of 6-methoxy-2-vinylnaphthalene using R = benzyl. Good results were also obtained by employing hemilabile 1-aryl-2,5-dialkylphospholanes in the hydrovinylation of styrene.[183] Vogt et al. already showed that monodentate phosphonites and phosphinites could be successfully applied in the asymmetric palladium-catalyzed hydrovinylation of styrene, reaching enantioselectivities up to 87%.[184] Rajanbabu et al. tested a series of hemilabile sugar phosphinites **177** (Figure 62) in the nickel-catalyzed hydrovinylation of styrene.[185] The advantage of these ligands is the modular structure, which gives rapid access to a large library of structural derivatives. Screening of many structural derivatives led to 89% selectivity for the formation of the desired 3-phenyl-1-butane in 81% ee.[185] Moreover, with 4-bromostyrene as



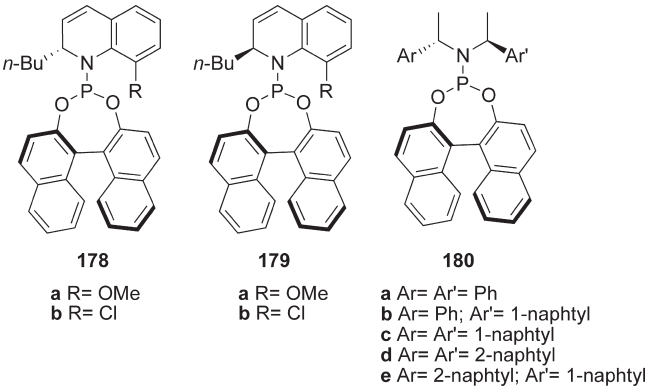
174

Figure 61. Azaphospholene ligand **174** derived from myrtenal.



175 **176**: R= Me, Et **177**: R= Me, Bn; Z= Ac, CF_3CO, PhCO

Figure 62. P-ligands **175**−**177**.



178 **179** **180**

a R= OMe
b R= Cl

a R= OMe
b R= Cl

a Ar= Ar'= Ph
b Ar= Ph; Ar'= 1-naphtyl
c Ar= Ar'= 1-naphtyl
d Ar= Ar'= 2-naphtyl
e Ar= 2-naphtyl; Ar'= 1-naphtyl

Figure 63. Monophosphoramidite ligands **178**−**180**.

substrate, an isolated yield of 98% could be obtained, with 99% selectivity for the desired product and an enantioselectivity of 89%.

The initial report[186] of Leitner et al. that chiral phosphoramidites **178**−**180** (Figure 63) gave very high enantio- and chemoselectivity in the nickel-catalyzed hydrovinylation of styrenes triggered a wider exploration of the use of phosphoramidites in this elegant reaction.[187] Further optimization of the ligand structures to **180b**−**e** resulted in astounding selectivities of 93−99% with enantioselectivities of 90−95% and with great activities in the hydrovinylation of vinylarenes.[188]

The impressive success of phosphoramidite ligands in the nickel-catalyzed asymmetric hydrovinylation has also initiated some exploration of phosphite ligands. Rajanbabu et al. studied the application of phosphoramidite and phosphite derivatives **181**−**183** (Figure 64) of their sugar-based ligands in the asymmetric hydrovinylation of vinylarenes and norbornene.[189] Moderate ee of 62% of the (*S*)-product in the hydrovinylation of styrene was obtained using ligand **181a**. Remarkably, a cooperative effect between the glucose backbone and the binol moitey was observed, as the enantioselectivity was reduced to 2% for the (*R*)-product when changing to the (*S*)-binol in ligand **181b**. Still the phosphite ligands did not meet the performance of their phosphinite analogues.

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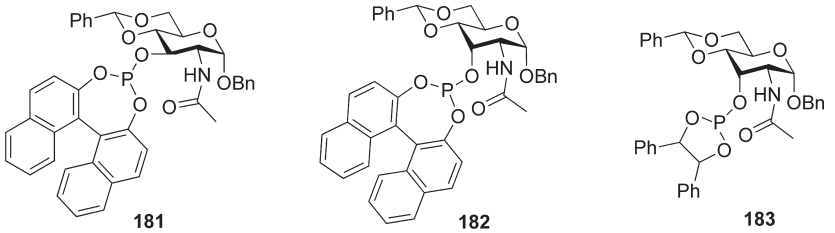

Figure 64. Phosphite ligands **181**−**183**.

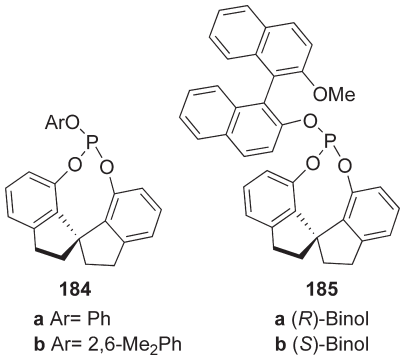

Figure 65. Spiro phosphite ligands **184**−**185**.

Zhou et al. applied monodentate spiro phosphite ligands **184**−**185** (Figure 65) in the palladium-catalyzed hydrovinylation of vinylarenes.[187c,190] In line with the results of Rajanbabu et al.,[189] they found that phosphites gave only moderate enantioselectivities, and the best results were obtained using the corresponding spiro phosphoramidite ligands.

7.3. Miscellaneous 1,2-Additions

Transition metal-catalyzed functionalization of unsaturated bonds is an efficient way to improve and/or invert the selectivity of stoichiometric additions and to achieve great rate accelerations of unactivated reagents.[145] Catalytic asymmetric hydrosilylation is an important reaction which finds many applications in organic synthesis.[191] The application of phosphites in the rhodium-catalyzed hydrosilylation of ketones was reported by Seebach, who applied the TADDOL-based phosphites **112m** and **n** (Figure 66), but the enantioselectivities were quite low.[192] Pastor and Shum applied a chiral trisphosphite ligand (*S*,*S*,*S*)-TRISPHOS (**186**) (Figure 66) in the Rh-catalyzed hydrosilylation of acetophenone. Good enantioselectivities up to 81% were obtained.[193]

Pizzano et al. tried to exploit the source of chirality of carbohydrates by synthesizing a series of ligands **27d**−**g** and **187a** and **b** (Figure 67) based on diacetone-D-glucofuranose.[194] They reported moderate enatioselectivities up to 58% for the asymmetric hydrosilylation of acetophenone. Diéguez et al. tested a wide range of diphosphite ligands **2**−**7** based on D-(+)-xylose and D-(+)-glucose (Figure 3), in which the stereocenters were systematically varied, but this did not result in higher enantioselectivities in the rhodium-catalyzed hydrosilylation of acetophenones.[195] Changing to phosphite−oxazoline ligands **134**−**139** (Figure 40) by the same authors did not lead to much improvement; the highest ee obtained was 62%.[196]

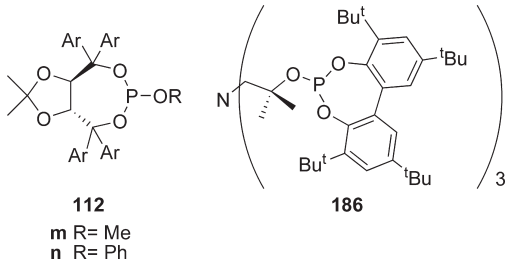

Figure 66. Phosphite ligands **112m**−**n** and **186**.

The regio- and enantioselectivities of the addition of boranes to alkenes can be altered by applying transition metal complexes.[197] Brown et al. applied phosphite−nitrogen ligands **188** based on binol and 1-(isoquinolyl)-2-naphthol in the asymmetric hydroboration of alkenes (Figure 68).[198] Especially in the case of electron-poor styrenes, they obtained good enantioselectivities up to 84%. A low temperature study revealed that a binuclear rhodium complex was present when catecholborane was the substrate.

Takacs et al. applied a series of derivatives biphenol **24** (Figure 9), binol **26** (Figure 12), and Taddol **112** (Figure 29) derived phosphites in the rhodium-catalyzed hydroboration of styrene with pinacolborane as reagent.[199] They obtained excellent enantioselectivities exceeding 90% with TADDOL-based phosphite **112h** (R = 1*R*,2*S*-Ph-cyclohexyl). The method proved also to be very efficient in the asymmetric hydroboration of β,γ-unsaturated amides, providing β-hydroxycarbonyl compounds with high enantioselectivity.[200]

Takacs et al. modified the TADDOL-based phosphite with a bisoxazoline moiety which formed chelating diphosphite **189** by an efficient self-assembly process in the presence of zinc(II) salts (Figure 69).[201] Remarkably, the self-assembly process resulted in the exclusive formation of a (*SS*,*RR*) self-assembled ligand combination. Variation of substituents on the rings of the biphenyl linkers provided a small ligand library, allowing for fast optimization of the enantioselectivity of the catalytic asymmetric hydroboration of *ortho*-substituted styrenes. Regioselectivities of 92−99% with high enantioselectivities of 91−96% ee could be obtained.

The nickel-catalyzed 1,2-addition to aldehydes using trialkylaluminium as nucleophile is a powerful method for the production of chiral alcohols.[202] The previously mentioned phosphoramidites **180** (Figure 63) proved to be versatile ligands, giving high enantioselectivities for a wide range of aliphatic and aromatic aldehydes. Diéguez and Pamies explored a modular sugar-based phosphite ligand library in this catalytic reaction.[203] Systematic screening of different sugar backbones and

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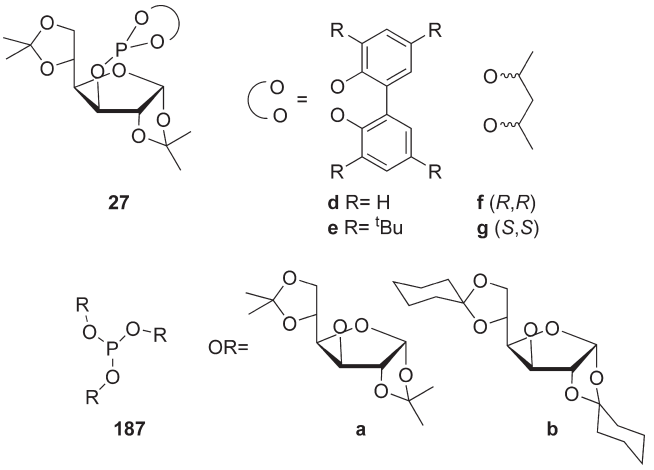

Figure 67. Phosphite ligands **27d**−**g** and **187a** and **b**.

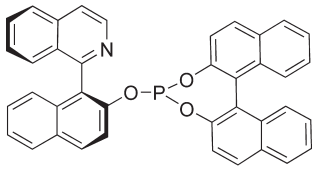

Figure 68. Phosphite−nitrogen ligands **188**.

substituents on the aryl phosphites provided an efficient ligand **27e** (Figure 67), which gave high enantioselectivities up to 94% in the Ni-catalyzed trialkylaluminium addition to several aryl aldehydes. In a subsequent study, they explored the combination of phosphite−phosphoramidite **46**−**47**, **154**−**155**, and **156** (Figures 17, 50, and 52, respectively) and phosphite−oxazoline **70**−**73** (Figure 20) donors in similar sugar-based bidentate ligands, but this did not result in improvement of the enantioselectivity.[204]

8. CONCLUDING REMARKS AND PERSPECTIVES

In the early 1990s, phosphites emerged as suitable ligands for asymmetric Rh-catalyzed hydroformylation and Cu-catalyzed 1,4-additions. In recent years, their use has been successfully extended to other catalytic reactions. As shown in this review, important breakthroughs have been achieved using phosphite-containing ligands in the asymmetric hydrogenation of functionalized and unfunctionalized olefins, asymmetric allylic substitution, and Heck reactions, among others. As we have seen in this review, the structural diversity of phosphites and the high density of ligand types (mono- and diphosphites and heterodonor phosphite-containing ligands) offer a wide variety of opportunities for derivatization and tailoring of synthetic tools in the search for the right ligand for each particular reaction. Another advantage of phosphite ligands is that they are less sensitive to air and other oxidizing agents than phosphines and they are amenable to parallel synthesis. On the other hand, phosphites are prone to decomposition reactions such as hydrolysis, alcoholysis, and the Arbuzov reaction. These side reactions can be suppressed, however, when bulky aryl phosphites are used. Therefore,

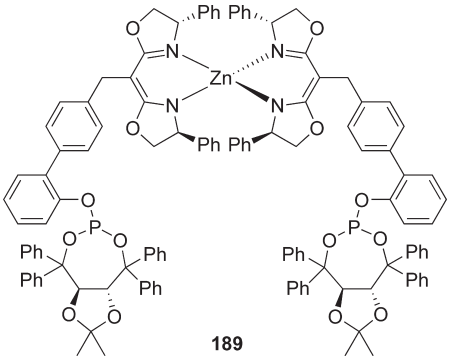

Figure 69. TADDOL-based diphosphite **189**.

biaryl-phosphite-containing ligands have undoubtedly become some of the most versatile ligands for enantioselective metal-catalyzed reactions. The excellent results obtained together with their facile synthesis are expected to lead to new designs of phosphite ligands for these processes and to expand the range of substrates to be studied. This will also lead to many other applications in forthcoming years.

BIOGRAPHIES

Piet van Leeuwen has been Group Leader at the ICIQ in Tarragona since April 2004. He chaired and directed many activities in the field of catalysis in The Netherlands. He worked with Shell Amsterdam for 26 years. Since 1989, part-time, and since 1994, full time, he initiated and led the homogeneous catalysis group at the University of Amsterdam. He held the chair of Industrial Homogeneous Catalysis at the Technical University of Eindhoven from 2001 until 2006, where he was also director of the National Research School on Catalysis. His interests range from fundamental aspects to applied catalysis, utilizing mainly late transition metals. New concepts to which he has contributed include host−guest catalysis, dendrimer catalysis, effects of wide bite-angles, and in situ spectroscopy. His main research areas are ligand effects in carbonylation reactions, carbon−carbon bond formation reactions, microflow reactor systems for homogeneous catalysis, and e-learning. In 2005 he was honored with the Holleman Prize by the Royal Netherlands Academy of Arts and Sciences. From 2006 to 2009 he held a Marie Curie Chair of Excellence in the ICIQ. In 2009 he received a doctorate honoris causa from the University

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Paul Kamer obtained a degree in biochemistry at the University of Amsterdam and his Ph.D. in organic chemistry at the University of Utrecht under the supervision of professors Wiendelt Drenth and Roeland J. M. Nolte. As a postdoctoral fellow of the Dutch Cancer Society (KWF), he did postdoctoral research at the California Institute of Technology with Peter B. Dervan and at the University of Leiden with professor Jacques H. van Boom in the field of DNA chemistry. He was appointed Lecturer at the University of Amsterdam and Full Professor of homogeneous catalysis in 2005. In 2005 he received a Marie Curie Excellence Grant and moved to the University of St. Andrews. His current research interests are ligand design, phosphorus chemistry, (asymmetric) homogeneous catalysis, organometallic chemistry, combinatorial synthesis, and artificial metalloenzymes.

Carmen Claver is Professor of Inorganic Chemistry at the University Rovira i Virgili (URV) in Tarragona (Spain), a position she has held since 1991. She received her Ph.D. in 1978 from the University of Zaragoza (Spain) in the field of organometallic chemistry and homogeneous catalysis. Her research aims at the development of new catalysts, covering the synthesis of ligands and complexes, and the characterization of intermediates, focusing mainly in enantioselective catalysis. In the last few years her research has been extended to the field of nanocatalysis. She has coauthored scientific contributions in this field, and she has participated in the edition and publication of several books. She has received several scientific awards, being recognized in 2003 as distinguished researcher by the Catalan Government and "Chaire Pierre de Fermat" in France in 2009.

Oscar Pàmies obtained his Ph.D. in Prof. Carmen Claver's group in 1999 at the Rovira i Virgili University. After 3 years of postdoctoral work in the group of Prof. J.-E. Bäckvall at the Department of Organic Chemistry at Stockholm University, he returned to Tarragona in 2002. He is currently working as Associate Professor at the Rovira i Virgili University. He received the Grant for Research Intensification from URV in 2008. His research interests are asymmetric catalysis, organometallic chemistry, and combinatorial synthesis.

Montserrat Diéguez studied chemistry at the Rovira i Virgili University in Tarragona (Spain), where she received her Ph.D. in 1997, working in the group of Prof. C. Claver. After a year as a postdoctoral fellow with Prof. R. H. Crabtree at Yale University, in New Haven, CT, she returned to Tarragona in 1999. She is currently working as Associate Professor at the Rovira i Virgili University. She obtained the Distinction from the Generalitat de Catalunya for the promotion of University Research in 2004 and the Grant for Research Intensification from URV in 2008. Recently she has been awarded the ICREA Academia Prize 2009 from the Catalan Institution for Research and Advanced Studies. Her present research is focused on organometallic chemistry, mainly the synthesis of chiral ligands and asymmetric catalysis using a combinatorial approach.

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