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# Rhodium-Catalysed Hydrogenations Using Monodentate Ligands

**Mattia Cettolin, Pim Puylaert, and Johannes G. de Vries**

**Abstract** The use of monodentate phosphorus ligands, such as phosphonites, phosphites and phosphoramidites, in the rhodium-catalysed asymmetric hydrogenation of a range of mostly alkene type substrates was reported for the first time in 2000. Not only are these ligands cheap and easy to prepare in one or two steps, their use has also created new opportunities, such as their robotic parallel synthesis and the use of complexes containing two different monodentate ligands, which tremendously increases the available diversity. This review covers the period between 2006 and 2016. Many new ligands have been made during this time; not only new variants on the three ligand types that were earlier reported, but also monodentate phosphines and secondary phosphine oxides. These were mostly tested on the usual *N*-acetyl-dehydroamino acids, itaconic esters and enamide type substrates. Other more novel substrates were *N*-formyl-dehydroamino acids, all the variants of the beta-dehydroamino acid family, enol esters, 2-methylidene-1,2,3,4-tetrahydro-β-carbolines, alkenes containing phosphonate or thioether substituents, several substituted acrylic acids as well as substituted cinnamic acids. The mechanism of the rhodium-catalysed hydrogenation with phosphites, phosphonites, phosphoramidites as well as phosphepines has been reported. A common theme in these mechanisms is the formation of a dimeric bimetallic complex after subjecting the $[RhL_2(cod)]X$ or $[RhL_2(nbd)]X$ ($X = BF_4, PF_6, SbF_6$) complexes to hydrogen. Since these hydrogenations are usually carried out in non-polar solvents,

M. Cettolin
Dipartimento di Chimica, Università degli Studi di Milano, via C. Golgi 19, 20133 Milan, Italy
Leibniz Institut für Katalyse e. V., Albert-Einstein-Strasse 29a, 18059 Rostock, Germany

P. Puylaert
Leibniz Institut für Katalyse e. V., Albert-Einstein-Strasse 29a, 18059 Rostock, Germany

J.G. de Vries (✉)
Leibniz Institut für Katalyse e. V., Albert-Einstein-Strasse 29a, 18059 Rostock, Germany
Stratingh Institute for Chemistry, Nijenborgh 4, 9747 AG, Groningen, The Netherlands
e-mail: Johannes.deVries@catalysis.de

the formation of the expected $RhL_2(Solvent)_2$ complexes does not occur after the removal of the diene and instead each rhodium atom in these dimeric complexes coordinates not only to two monodentate ligands, but also in $\eta^6$ fashion to an aromatic ring of one of the ligands that is bound to the other rhodium atom. These complexes can react with the substrate to form the substrate complex that is hydrogenated. Other studies also found that it is possible to form rhodium hydride complexes first, which react with the substrate to form product. There is one well-described industrial application on large scale in which a substituted 2-isopropyl-cinnamic acid is hydrogenated using a rhodium complex with a mixture of 2 eq. of 3,3'-dimethyl-PipPhos and 1 eq. of triphenylphosphine. The addition of the non-chiral triarylphosphine not only accelerated the reaction 50-fold, also the enantioselectivity was much improved. The product was used as a building block for Aliskiren™, a blood-pressure lowering agent.

**Keywords** Asymmetric hydrogenation • Homogeneous catalysis • Mechanism • Monodentate ligands • Phosphines • Phosphites • Phosphonites • Phosphoramidites • Production • Secondary phospineoxides • Supramolecular catalysis

**Contents**



## 1 Introduction

After the invention of the use of $RhCl(PPh_3)_3$ as hydrogenation catalyst by Wilkinson, Knowles [1, 2] and Horner [3] independently arrived at the idea of using chiral versions of triphenylphosphine in such a complex, to allow the hydrogenation reaction of prochiral substrates to take place with enantioselection. Initial attempts using chiral at phosphorus ligand **1** (Fig. 1) were successful, but enantioselectivity was rather low. Horner retired after his first attempts, but Knowles continued, initially guided by the desire to develop a catalyst that would enable the production of L-phenylalanine (for the production of the sweetener aspartame) via asymmetric hydrogenation of the dehydroderivative **6b** (Scheme 1, **1**). The ligand PAMP (**2**) already was much better than **1** in this reaction as the product was obtained in 55% ee. Knowles reasoned that the many degrees of freedom in the rhodium

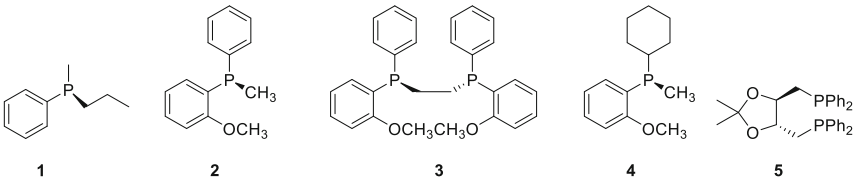
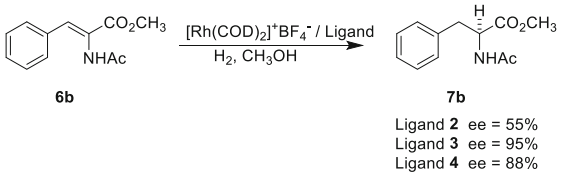



**Fig. 1** Early chiral monodentate and bidentate phosphorus ligands




**Scheme 1** Asymmetric hydrogenation of methyl 2-acetamido-cinnamate using PAMP, di-PAMP and CAMP as ligand

complex made from **2** were detrimental for the stereoinduction and based on this designed the bidentate analogue di-PAMP (**3**). Indeed, the use of this ligand led to formation of the product **7** in 95% ee [4]. These ligands took a rather large number of steps to make, but later Kagan invented DIOP (**5**) which has chirality in the backbone instead of on phosphorus [5, 6]. These types of ligands were much easier to synthesise starting from a rather large pool of commercially available chiral starting materials and thus started the highly successful era of the bidentate phosphine ligands. The complexes could be prepared in situ, simply by adding the bisphosphine to [Rh $(COD)_2]BF_4$ (COD = 1,5-cyclooctadiene). The bidentate ligand displaces one of the dienes and the other diene would be hydrogenated off, whereas methanol (the usual solvent) would occupy the remaining two vacant positions to give [Rh(PP) $(MeOH)_2]BF_4$. In spite of the fact that Knowles later showed that the monodentate ligand CAMP (**4**) induced 88% ee in the asymmetric hydrogenation of **6** [7], no more research was reported on the use of monodentate ligands in asymmetric hydrogenation for the next 30 years.

In the year 2000, suddenly three papers appeared that reported that BINOL-based monodentate phosphonites [8, 9], phosphites [10] and phosphoramidites [11, 12] were actually excellent ligands in the rhodium-catalysed asymmetric hydrogenation of substituted alkenes (Fig. 2). Enantioselectivities and reaction rates obtained in the hydrogenation of *N*-acetyl-dehydroamino acids and esters and a range of other alkene substrates were actually comparable to those obtained with bidentate phosphines. Not only that, but these ligands were easily obtained from cheap enantiopure BINOL (1,1′-Bi-2-naphthol) in just one or two synthetic steps, without the need for a further resolution. This also makes them at least an order of magnitude cheaper than the bidentate bisphoshines.

The advent of the monodentate ligands created more opportunities that would have been impossible to achieve with the bidentate bisphosphines. Since the active

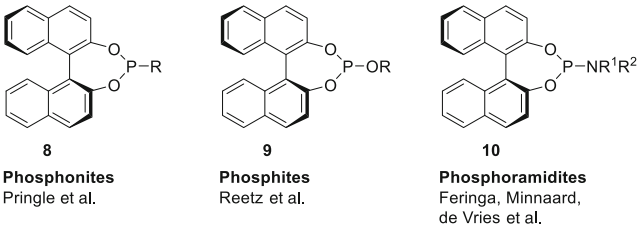



**Fig. 2** Monodentate BINOL-based ligands for asymmetric hydrogenation

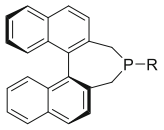
$$[RhL^1L^2]^+ \rightleftharpoons [RhL^1L^1]^+ + [RhL^2L^2]^+$$

**Scheme 2** Equilibrium mixture of rhodium complexes based on two different monodentate ligands

hydrogenation complex usually contains two monodentate ligands, it is possible in principle to create complexes based on two different ligands [13–18]. In practice, this is somewhat more problematic as ligand exchange tends to be fast in these complexes, so in the end a statistical mixture of three complexes is obtained, the ratio of which is determined by thermodynamics (Scheme 2). Nevertheless, the concept could work if the mixed complex is thermodynamically much more stable than the two homo-complexes or if it is kinetically superior.

In addition, it is possible to influence the ratio of complexes by varying the ratio of the two monodentate ligands. For instance, by using an $L^1/L^2$ ratio of 2, formation of $[RhL^2L^2]^+$ would be largely suppressed [16]. In screening large libraries of these combinations, it is usually found that the majority of combinations lead to worse results; however, there are always a few combinations that lead to better results, and hence, this is an attractive way to further increase the available diversity.

The easy synthesis of the monodentate ligands offers another opportunity: robotised parallel ligand synthesis. Methodology was developed by Lefort and co-workers at DSM in the Netherlands for the fully automated parallel synthesis of monodentate phosphoramidites (and phosphites) [19]. This was based on the fact that reaction between the BINOL-based phosphochloridate, which can be prepared in quantitative yield by refluxing the (substituted) BINOL with $PCl_3$ and stored indefinitely, and the amine (or alcohol) gives the phosphoramidites (phosphites) in between 90 and 98% purity based on the phosphorus NMR. However, it is very important that the $Et_3NHCl$ salt formed in this reaction is quantitatively removed, as chloride not only inhibits the hydrogenation, but it also reduces the enantioselectivity. This was accomplished by performing the reaction in toluene, which leads to full precipitation of the salt. Using a simple liquid-dispensing robot and a 96-well oleophobic titre well plate, 96 ligands could be prepared in a few hours, and after filtration of the salts, the slightly impure ligands were combined with the metal precursor and the substrate in a vial and subjected to a parallel hydrogenation reaction overnight. Although the enantioselectivity of these reactions is slightly

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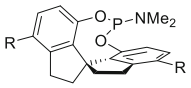


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Zhou


13

Minnaard, Feringa, de Vries

**Fig. 3** Non-BINOL-based monodentate ligands

reduced, the relative order of the enantioselectivity induced by the impure ligands is the same as those from the pure ligands [19]. This has remarkably reduced the time necessary to find a ligand that induces high enantioselectivity in combination with a high enough reaction rate.

The development of the BINOL-based monodentate ligands also spurred the development of other new non-BINOL-based monodentate ligands. The reader is referred to the earlier reviews for a detailed overview. Three ligand classes will be mentioned, in view of the many publications documenting their use. These are the 1,1′-binaphthyl-based phosphepines (**11**) [20–24]; the spirobiindane diol (SPINOL)-based ligands, such as SIPHOS (**12**) [25–27]; and the secondary phosphine oxides (**13**) [28, 29] (Fig. 3).

The first 5 years of these developments from 2000 to 2005 have been well documented in several reviews [12, 23, 24, 30–32]. In this review we will paint the new developments of the period 2006–2016.

## 2 New Monodentate Ligands

### *2.1 Phosphonites, Phosphites, Phosphoramidites*

Bondarev and Goddard reacted (*S*)-α,α-diphenylprolinol first with $PCl_3$ and next with aliphatic alcohols or phenols [33]. The bicyclic phosphoramidites **14** (Fig. 4) thus obtained were tested in the rhodium-catalysed enantioselective hydrogenation of **6b**, **27b** and **29b** in $CH_2Cl_2$ (Scheme 3). Depending on the chosen substituents, enantioselectivities between 22 and 95% were obtained. In a similar vein, (*S*)-α,α-diphenylprolinol was reacted with $RPCl_2$ in which R were aliphatic groups or phenyl to give the bicyclic aminophosphonates **15a**. The aliphatic analogues performed poorly and conversion was incomplete after overnight reaction, but the phenyl derivative performed well with ee's between 62 and 81%. Reaction of (*S*)-α,α-diphenylprolinol with $P(NMe_2)_3$ or $P(NEt_2)_3$ led to formation of the bicyclic diaminophosphites **15b**. The use of the dimethyl analogue led to full conversion and ee's between 61 and 91%. Armspach, Matt and co-workers synthesised four novel phosphoramidites **16** in which not only the diol but also the diamine contains a chiral 1,1′-binaphthyl structure [34]. These ligands were used for the rhodium-catalysed hydrogenation of substituted and unsubstituted methyl 2-acetamidocinnamates. The products were obtained quantitatively with ee's between 79 and

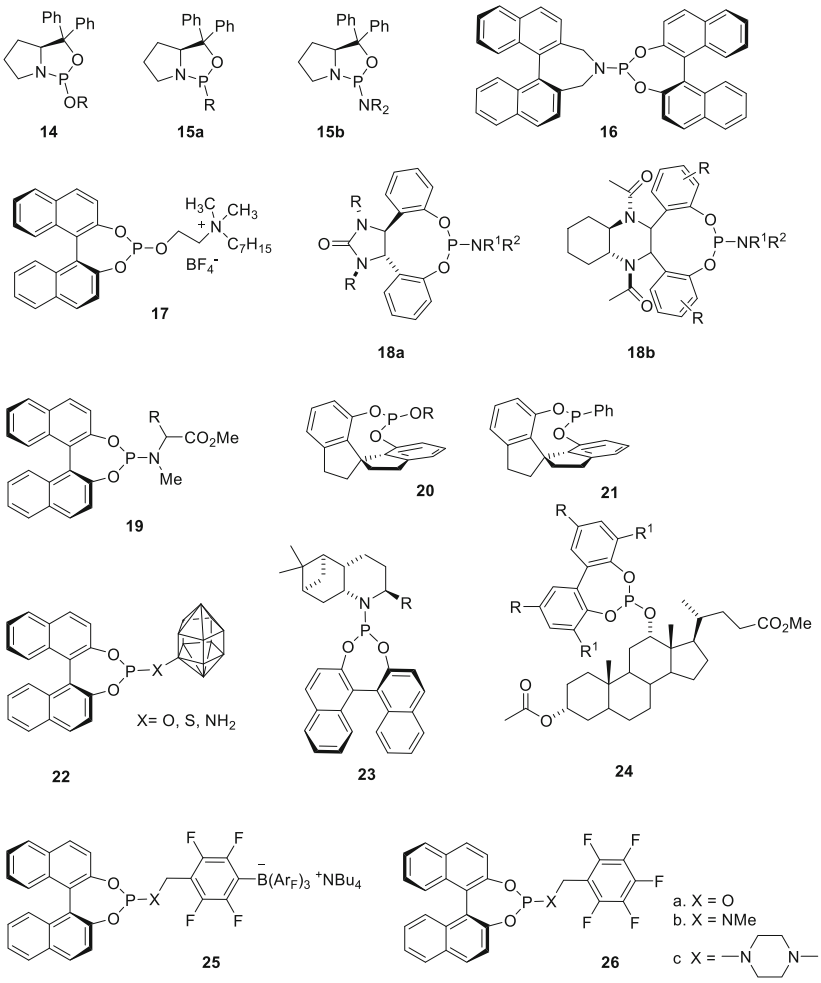
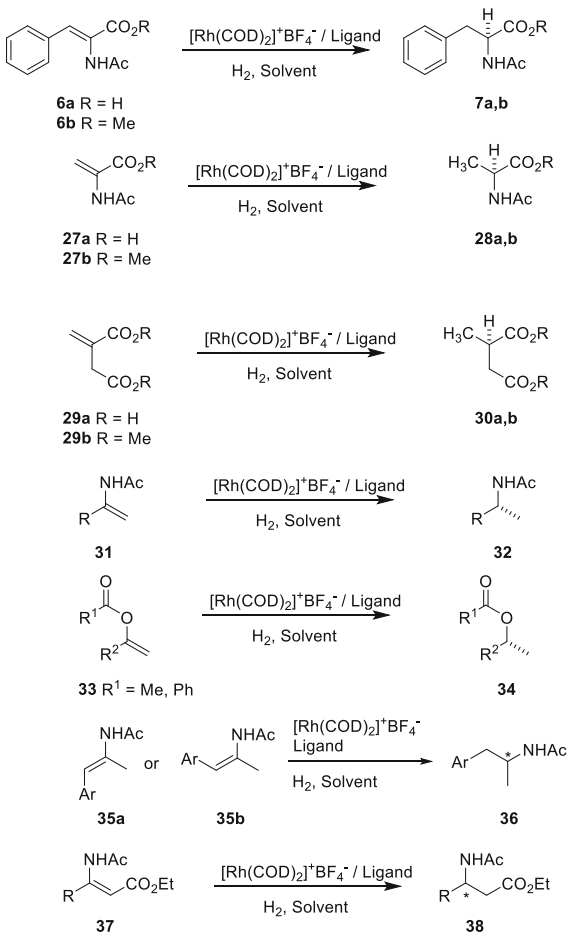



**Fig. 4** Monodentate phosphonites, phosphites and phosphoramidites

99%. The *R*,*S*- and the *S*,*R*-ligands induced much higher enantioselectivity than the *R*,*R*- and the *S*,*S*-ligands.

Bondarev synthesised BINOL-based phosphite **17** containing a quaternary ammonium salt in the side chain (Fig. 4) [35]. This creates opportunities for attachment to solid supports or for using ionic liquids in two-phase hydrogenations. The resulting rhodium catalyst carries three positive charges that were compensated by three eq. of $BF_4^-$. The catalyst was used for the hydrogenation of **6b** and **29b** in $CH_2Cl_2$. The products were obtained in excellent yields with ee's of 92 and 99%, respectively. Ding and co-workers created a new class of phosphoramidite ligands based on a chiral bisphenol, backbone [36, 37]. The backbone of these ligands, DpenPhos **18a** and CydamPhos **18b**, was prepared in three steps from the chiral

**Scheme 3** Rhodium-catalysed hydrogenation reactions with monodentate ligands




diamine, and the resulting bisphenols were reacted with $P(NMe_2)_3$ or $P(NEt_2)_3$ to form the ligands. Both ligands were used for the rhodium-catalysed enantioselective hydrogenation of **6b** and **31** (Scheme 3).

Full conversion was obtained at S/C 100 with very high enantioselectivities, between 96 and 99.9%. DpenPhos was also used in the rhodium-catalysed hydrogenation of terminal enol carboxylates **33** [38]. Several aliphatic enol benzoates were reduced quantitatively with ee's between 87 and 90%, whereas aromatic ($R^2$ = aryl) enol acetates were reduced with ee's between 88 and 95%. Many groups have reported on BINOL-based phosphoramidite ligands in which the effect of the substituents on nitrogen was investigated. The area has been reviewed by Armspach, Matt and co-workers [39]. They have reported themselves on BINOL-based phosphoramidites **19** in which the nitrogen atom was part of an *N*-methyl-amino acid ester in which the amino acid was either alanine or phenylalanine [40]. These ligands were examined in the rhodium-catalysed enantioselective

hydrogenation of a **6b** and a number of analogues that carried halide substituents on the aromatic ring. The products were obtained in varying yield with ee's ranging from 67 to 92%. Zhou and co-workers continued their work on the spirobiindane diol-based monodentate ligands and introduced the phosphites **20** and the phosphonate **21** [41]. These ligands were applied in the asymmetric hydrogenation of *E*- and *Z*-aromatic enamides (**35a**, **b**). They were able to find ligands for the hydrogenation of both substrates with ee's up to 94–95%. Lyubimow and co-workers have tried to increase the size of the substituent in the BINOL-based phosphites and phosphoramidites by using *ortho*- and *meta-closo*-dodecacarboranes carrying a hydroxyl, a thiol or an amino-substituent in the 9-position (**22**) [42–45]. Substrates **6**, **27**, **29**, several substituted 2-acetamido-cinammic esters and β-dehydroamino acid esters **37** (Scheme 3) were subjected to rhodium-catalysed hydrogenation with these ligands. Most substrates could be hydrogenated with ee's between 80 and 98%; however, the β-dehydroamino acid esters were more stubborn substrates. They needed the use of hexafluoro-2-propanol as solvent which raised the ee to 69–85% for the aliphatic substrates, but the phenyl-substituted substrate was reduced with 46% ee only.

The idea to introduce extra chirality into the side chain of these ligands has fascinated many groups.

Franciò and co-workers converted enantiopure pinene into a decahydrobenzoquinoline, which was used as the amine in the synthesis of a BINOL-based phosphoramidite (**23** R = H, Me. Cy) [46]. A range of substituted alkenes was hydrogenated using these ligands with ee's varying from 49 to 99%. Iuliano and co-workers synthesised a *tropos* phosphite ligand **24** based on a 3,3′- or 5,5′-disubstituted biphenyl and methyl 3-acetyldeoxy-cholate [47]. Here the bisphenol is free to rotate, but either one of the two diastereomeric conformations is formed preferentially in the catalyst, or one of the diastereomers forms a much faster catalyst than the other. This principle was earlier developed by Reetz and co-workers [48], and by Gennari and Piarulli and co-workers [49]. In the rhodium-catalysed hydrogenation of **29b**, the product was obtained quantitatively with 52–94% ee.

Pfaltz and co-workers developed phosphoramidites **25** containing an anionic group in the side chain (Fig. 4). They compared the efficacy of these ligands with the analogous non-ionic ligands **26** in the rhodium-catalysed hydrogenation of **6b** [50]. There was no general trend: sometimes the anionic ligands gave better results and sometimes the neutral ligands. Interestingly, these ligands perform very well in a mixture with neutral ligands. Since the homocatalyst with two anionic ligands is energetically less favourable because of charge repulsion, the equilibrium is shifted strongly towards the heterocatalyst. This effect was further amplified when a phosphoric acid diester was used as the neutral ligand as here a hydrogen bond may form between the phosphoramidite and the proton of the phosphoric acid diester.

## 2.2 *Phosphines and Secondary Phosphine Oxides*

Breit and Fuchs reported the synthesis of chiral phosphabarrelenes **39** in which $R^1$ and $R^2$ are two different aryl groups [51]. The racemic ligands were separated by chiral chromatography. In the rhodium-catalysed hydrogenation of **6b** and **29b** using these ligands, the products were obtained with ee's between 14 and 31% ee. Kokan and Kirin synthesised a series of triphenylphosphines **40** in which one of the phenyl groups is decorated in the 3- and 5-positions with chiral amides, amino acid esters or dipeptide esters (Fig. 5) [52]. These ligands were used in the enantioselective rhodium-catalysed hydrogenation of **6b** (37–77% ee) and **27b** (12–80% ee) In addition, the latter substrate was hydrogenated using binary mixtures of these ligands (12–78% ee). Pringle and co-workers extensively investigated the use of the phosphaadamantane motiv originally developed by Epstein and Buckler in the design of several classes of ligands. They were able to obtain phosphine **41** in enantiopure form via a resolution [53]. The ligands were used in the asymmetric hydrogenation of **6b** (60% ee) and **27b** (54% ee). Enantiopure phospholanes obtained notoriety in their bidentate variety as DuPhos. Fiaud, Toffano and co-workers synthesised enantiopure monodentate phospholane **42** and used it in the asymmetric hydrogenation of **6a**, **6b**, **27a**, **29a**, **29b** and a number of other enamides and enol ethers [54]. The products were obtained quantitatively in most cases with ee's between 8 and 82%. Toffano and co-workers have synthesised the monodentate alkylated and arylated phospholanes **43** [55]. These ligands were tested in the rhodium-catalysed enantioselective hydrogenation of **6b**. The alkylated ligand performed disappointingly with ee's between 34 and 62%. However, the arylated phospholanes gave much better results, and enantioselectivities up to 93% (R = Ph) were obtained. The same group also synthesised the phospholane-based secondary phosphine oxide **44** [54]. This ligand was tested

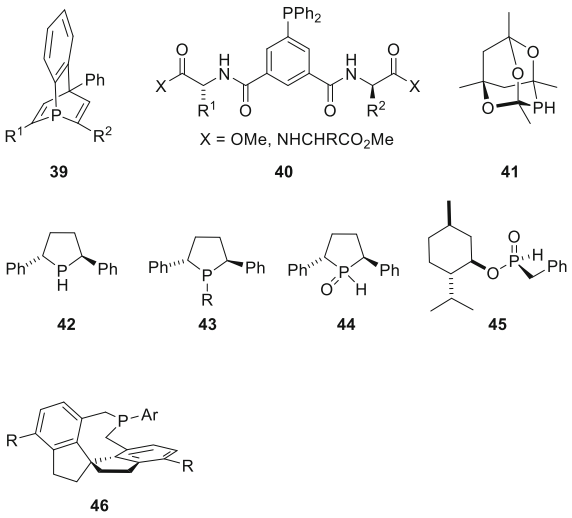



**Fig. 5** Monodentate phosphines and secondary phosphine oxides

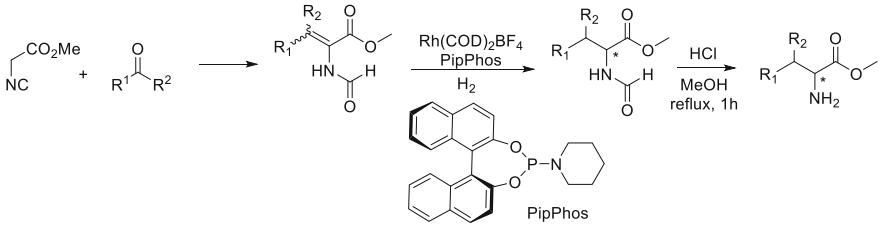
in the rhodium-catalysed asymmetric hydrogenation of **6b**. The enantioselectivity was highly solvent dependent. Whereas with most monodentate ligands, best results are obtained in non-protic solvents, such as $CH_2Cl_2$; in this case the result obtained in methanol (82% ee) was much better than that in $CH_2Cl_2$ (24%).

Han and co-workers synthesised a series of (*R*)-menthol-based H-phosphinates of which the benzyl derivative **45** performed best [56]. Asymmetric hydrogenation of **6b** and a number of ring-substituted analogues proceeded with excellent ee's between 93 and 99%. Hydrogenation of **29b** proceeded in 53% ee. Zhou and co-workers synthesised the SPINOL-based phosphines **46** (Ar = Ph, 4-$CF_3C_6H_4$, 4-$MeOC_6H_4$, 3,5-$Me_2$-4-$MeOC_6H_4$, 3,5-*t*Bu-4-$MeOC_6H_4$). These ligands were applied successfully in the rhodium-catalysed hydrogenation of **35a**. Best results (ee = 81–97%) were obtained with the ligand in which Ar = 3,5-*t*Bu-4-$MeOC_6H_4$.

## 3 New Hydrogenation Reactions

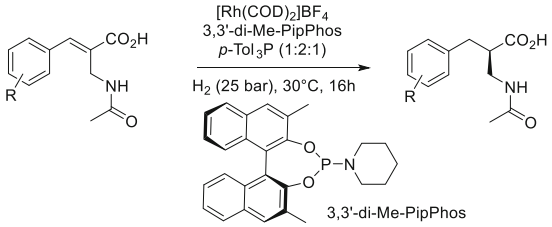
Most of the initial applications of the monodentate ligands concentrated on the hydrogenation of the *N*-acetyl dehydroamino acids and esters. In most applications the amino acid is needed without the protecting group on nitrogen. In practice it is not so easy to remove the *N*-acetyl group by hydrolysis. For this reason Feringa, de Vries, Minnaard and co-workers have investigated the use of other protecting groups for these hydrogenation substrates (Scheme 4). In practice the *N*-formyl group turns out to be a very good choice. The *N*-formyl-protected dehydroamino acid esters were readily prepared in one or two steps by condensation between methyl isocyanoacetate and an aldehyde or ketone using different protocols, depending on the substrates. In the rhodium-catalysed asymmetric hydrogenation, the use of PipPhos (**10**, $R^1$, $R^2 = -(CH_2)_5^-$) gave the best results, and the *N*-formyl amino acid esters were obtained with ee's around 99% for the substrates that were prepared from the aldehydes (Scheme 4). The ketone-derived substrates reacted more sluggishly, and here the ee's did not exceed 85%.

Asymmetric hydrogenation is of particular importance for the production of non-natural amino acids as these are often used in new drugs. Beta-amino acids have been used many times as they have the advantage not to be recognised by peptide hydrolysing enzymes, thus conferring metabolic stability to a peptide-like

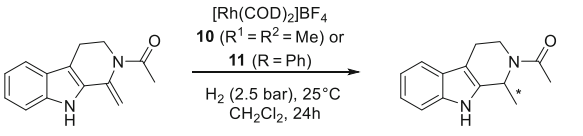



**Scheme 4** Asymmetric hydrogenation of *N*-formyl-dehydroamino acid esters

**Scheme 5** Asymmetric hydrogenation of 2-acetamidomethyl-cinnamic acids using mixtures of ligands



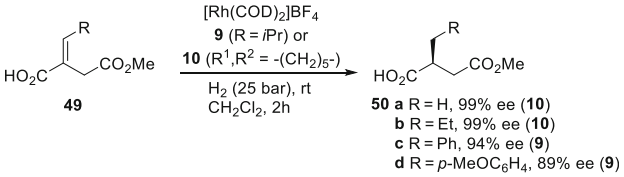

**Scheme 6** Enantiopure 1,2,3,4-tetrahydro-β-carbolines via asymmetric hydrogenation



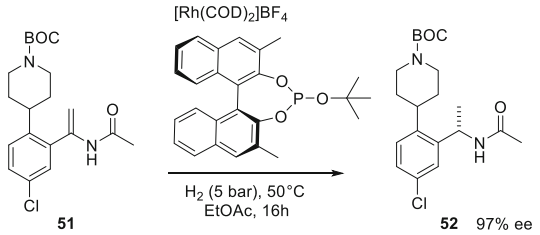

drug. Examples of $\beta^3$-amino acids had already been reported earlier and this area has been reviewed [57]. More recently, Minnaard, Feringa and co-workers reported an asymmetric hydrogenation approach to access the $\beta^2$-amino acids [58]. The substrates were prepared in a three-step sequence entailing a Baylis-Hillman reaction between methyl acrylate and a range of substituted benzaldehydes, followed by a Ritter reaction with acetonitrile and finally hydrolysis of the ester. In order to find a good catalyst, the high-throughput facilities at DSM were used. Not only was a library of monodentate phosphoramidites screened, but additionally also a library in which these monodentate phosphoramidites were combined with monodentate triaryl- or trialkylphosphine ligands. In the end 3,3′-dimethyl-PipPhos in combination with either tri-*para*-tolylphosphine or tri-1-naphthylphosphine gave the best results (ee's 90–91%) in the rhodium-catalysed hydrogenation of a number of methyl 3-acetamido-2-arylidene-propionates (Scheme 5).

Beller and co-workers reported a new approach towards enantiopure 1,2,3,4-tetrahydro-β-carbolines. A range of ligands was tested. Best results, up to 99% ee, were obtained using bidentate phospholane-type ligands. Nevertheless, using MonoPhos **10** ($R^1 = R^2 =$ Me) or phosphepine **11** (R = Ph) on the same substrate gave the product with enantioselectivities of 80 and 44%, respectively (Scheme 6).

Many publications have appeared on the asymmetric hydrogenation of either itaconic acid (**29a**) or its diester (**29b**). Although these substrates serve as useful model compounds, the products are of little synthetic use, also in view of the fact that it is virtually impossible to discriminate between the two carboxylic acid functionalities. For this reason, the monoesters are more interesting substrates since either the acid or the ester functionality can be reduced selectively to the alcohol after hydrogenation of the double bond. De Vries, Rutjes and co-workers were able to synthesise a number of 4-substituted itaconic acid monoesters and screened a range of monodentate phosphoramidites and phosphites in their rhodium-catalysed hydrogenation [59]. Excellent results were obtained with the




**Scheme 7** Asymmetric hydrogenation of substituted itaconic half-esters

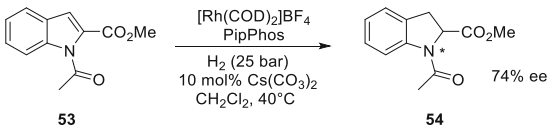



**Scheme 8** Asymmetric hydrogenation of a bulky enamide

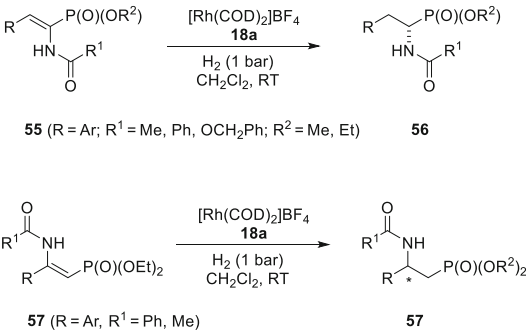
phosphoramidite PipPhos (**10**, $R^1$, $R^2 = -(CH_2)_5^-$) and monodentate phosphite ligand **9** (R = *i*Pr) (Scheme 7).

In the first 5 years after the discovery of the use of monodentate ligands for asymmetric hydrogenation, many groups have reported on the successful enantioselective hydrogenation of a range of enamides. These reactions have potential for the production of enantiopure pharma intermediates that often contain amines and amides. However, these "real-life" substrates often contain a range of other functional groups that may inhibit or slow down substantially the catalysis, either through interaction of the heteroatoms with the metal or through its steric bulk. The latter case was reported by Lefort and co-workers who were faced with the task to achieve both high enantioselectivity as well as high rate in the asymmetric hydrogenation of bulky enamide **51** (Scheme 8) [60]. They initially screened a library of 96 phosphoramidite ligands based on 3 different BINOL backbones and found that useful conversion and enantioselectivity was only obtained with phosphoramidites based on 3,3′-dimethyl-BINOL. For this reason a smaller library of 16 ligands was screened based on this scaffold and 14 amines and 2 alcohols. In the end the phosphite ligand based on *t*-BuOH gave the best results. It was possible to hydrogenate the substrate with a S/C ratio of 521. After 17 h the reaction was complete and the product was obtained in 97% ee. After treatment with activated charcoal and two recrystallisations, **52** was obtained with 99.6% chemical purity, 99.9% ee and a residual rhodium content of only 3 ppm.

Asymmetric hydrogenation of a range of heterocycles has been reported using monodentate phosphoramidites or phosphites usually with ruthenium- or iridium-based catalysts. One class of heterocycles that has been reduced successfully using rhodium catalysts based on monodentate ligands are the 2-substituted indoles. Minnaard, Feringa, de Vries and co-workers reported the rhodium-catalysed




**Scheme 9** Asymmetric hydrogenation of methyl *N*-acetyl 2-indolecarboxylate



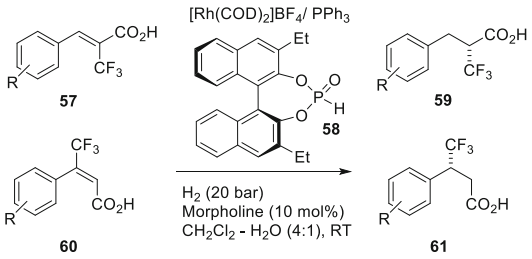

**Scheme 10** Rhodium-catalysed asymmetric hydrogenation of α- and β-enamido phosphonates

asymmetric hydrogenation of methyl *N*-acetyl indole-2-carboxylate (Scheme 9) [61]. The best ligand was PipPhos, but it was necessary to use 10 mol% of $Cs(CO_3)_2$ as additive. They were able to show that high enantioselectivity was obtained only with the doubly protected derivative; the unprotected indole-2-carboxylic acid, its ester and its *N*-acetyl compound were all hydrogenated with poor enantioselectivity.

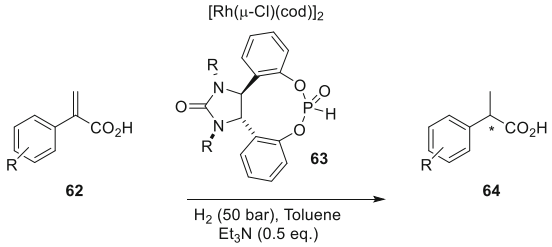
Minnaard and co-workers investigated the rhodium-catalysed asymmetric hydrogenation of thio-ethers that were obtained by the addition of thiols to dimethyl acetylenedicarboxylate [62]. The resulting sulfur-substituted fumarate and maleate esters were subjected to rhodium-catalysed hydrogenation using a range of different ligands. Good yields of the hydrogenated products could be obtained with moderate enantioselectivity using bidentate phosphine ligands. In contrast, the use of monodentate phosphoramidite ligands gave very slow reactions and mainly desulfurisation.

Ding and co-workers subjected α- and β-enamido phosphonates to rhodium-catalysed asymmetric hydrogenation using phosphoramidite ligands (Scheme 10) [63]. Interestingly, only phosphoramidite ligands containing a proton on the nitrogen atom such as **18a** ($R^1 = H$, $R^2 = PhCH_2$ or *i*Pr) were active in this reaction. The (*E*)-α-enamido phosphonates could all be hydrogenated with very good rates and in exceptionally high ee (97–99%) at 1 bar $H_2$. One *Z*-alkene ($R = Ph$, $R^1 = R^2 = Me$) was also hydrogenated and in this case the ee was lower (88%). Hydrogenation of the (*Z*)-β-enamido phosphonates proceeded much more sluggishly, with TOF's in the single digits; nevertheless, the ee was again very high (95–99%). In this series the (*E*)-substrates were hydrogenated with lower enantioselectivity.

**Scheme 11** Asymmetric hydrogenation of trifuoromethyl-substituted cinnamic acids




**Scheme 12** Asymmetric hydrogenation of α-arylated acrylic acids

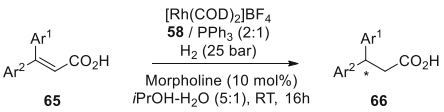



Ding and co-workers extensively investigated the asymmetric hydrogenation of substituted acrylic acids. They screened a range of mixed ligand catalysts based on secondary phosphine oxide (SPO)-type monodentate ligands and triphenylphoshine in the rhodium-catalysed asymmetric hydrogenation of (*Z*)-α-trifluoromethyl-cinnamic acid (Scheme 11) [64]. The SPO based on 3,3′-diethyl-BINOL together with triphenylphosphine (2:1) turned out to be the best combination, and with 1 mol% of catalyst full conversion was achieved after 16 h, and the product was obtained with 98% ee. A range of similar substrates with substituted aromatic or heteroaromatic rings were also hydrogenated with excellent enantioselectivities (96–99% ee). Even trifluoro-methacrylic acid was hydrogenated with 96% ee. Next, the asymmetric hydrogenation of (*E*)-β-trifluoromethyl-cinnamic acid was examined, and here the same catalyst combination gave excellent results. A range of aryl-substituted and heterocyclic derivatives were also hydrogenated with full conversions and ee's between 92 and 99%.

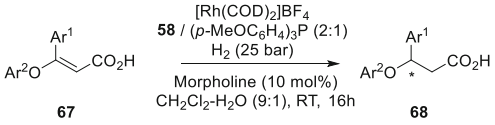
The same group also reported the rhodium-catalysed asymmetric hydrogenation of alpha-arylated acrylic acids [65]. This is of particular relevance as it potentially offers an entry towards enantiopure ibuprofen, naproxen, flurbiprofen as well as ketoprofen. A number of SPOs was screened in combination with different catalyst precursors. Surprisingly, the use of the chlorine containing precursor [Rh(μ-Cl)(cod)]$_2$ induced the highest enantioselectivities. Normally speaking chloride is considered a catalyst poison, and halide-containing catalyst precursors are avoided. The best ligands were **63** in which R was either benzyl or ethyl. The products were obtained in over 99% yield with ee's ranging from 90 to 96% (Scheme 12).

A much more challenging class of substrates which was tackled by the same group are the β,β-diaryl-substituted acrylic acids, in which the two aryl groups are only slightly different as a result of the presence of substituents. Here the authors

**Scheme 13** Asymmetric hydrogenation of β,β-diaryl-substituted acrylic acids




**Scheme 14** Asymmetric hydrogenation of β-aryloxy-cinnamic acid derivatives

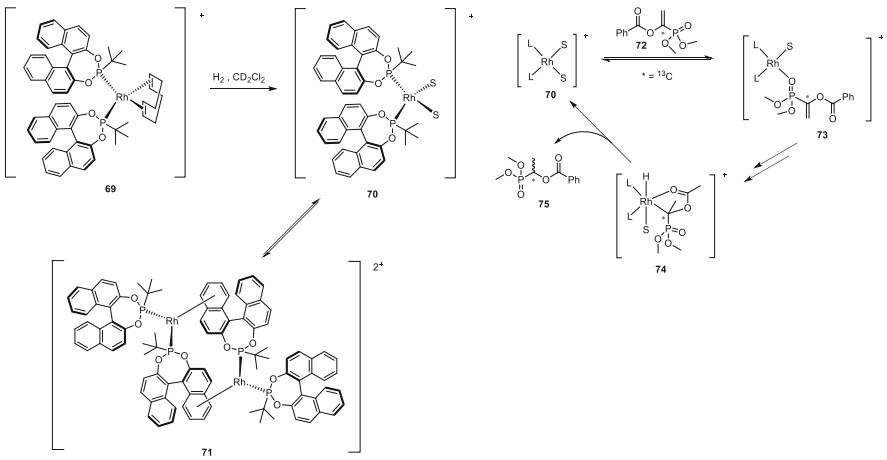



screened the combination of a small library of SPO ligands in combination with triarylphosphines. Surprisingly high enantioselectivities were achieved using a combination of **58** (see Scheme 11) and $PPh_3$ (2:1), and a range of substrates was hydrogenated with ee's ranging from 85 to 96% (Scheme 13).

The asymmetric hydrogenation of β-aryloxy-cinnamic acid derivatives is not unproblematic as the hydrogenation is accompanied by hydrogenolysis to the 3-phenylpropionic acids. The group of Ding found that whereas rhodium in combination with SPOs led to poor conversions and enantioselectivities, a mixed ligand approach in which a combination of an SPO and a triarylphosphine was used worked much better and hydrogenolysis was reduced to about 10% [66]. A small library of six SPOs and seven triarlyphosphines was screened leading to the finding that a combination of SPO **58** with tri-(*p*-methoxyphenyl)phosphine (2:1) gave the 3-aryl-3-aryloxypropionic acids in 92–99% enantioselectivity (Scheme 14). These compounds can be converted into a number of interesting products, such as the psychopharmaceuticals duloxetine and atomoxetine.

## 4 Reaction Mechanism

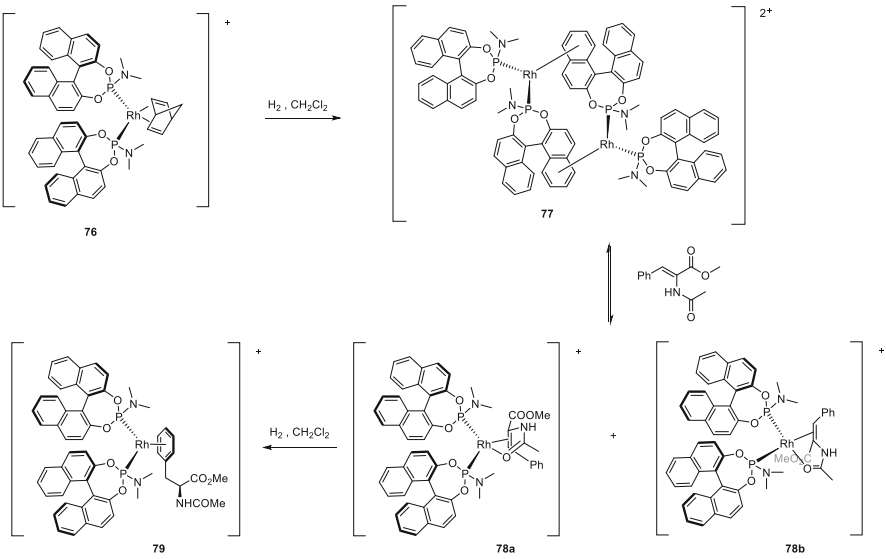
There are some marked differences in the mechanism of the rhodium-catalysed asymmetric hydrogenation of olefins employing monodentate ligands, when compared to the bidentate case. If the reaction were to proceed in a similar fashion, two equivalents of ligand should be coordinated in a *cis* fashion, resembling the coordination geometry of a rhodium-diphosphine complex, which may be the case if the substrate binds in a chelating fashion. In 2005, Reetz et al. showed, for monophosphonites specifically, that in the optimal case, two equivalents of ligand are available to coordinate to rhodium, and a positive non-linear effect ((+)-NLE) was observed in the benchmark hydrogenation of **29b**. The non-linear effect, which corroborates the presence of two monodentate ligands in the active hydrogenation catalyst, was already observed earlier by de Vries and co-workers in the asymmetric hydrogenation with rhodium/MonoPhos (**10**, $R^1$, $R^2$ = Me) [67]. In contrast to chiral diphosphines, DFT calculations showed that the reaction with monodentate phosphite ligands obeys the lock-and-key principle, i.e. that the thermodynamically



**Scheme 15** Mechanism of rhodium-catalysed hydrogenation with a rhodium-bisphosphonite catalyst precursor

more stable catalyst-substrate complex leads to the formation of the enantiomer that is formed in large excess [68]. They proceeded to investigate NLEs of mixtures of chiral monodentate ligands **8** (R = Me) and **8** (R = *t*Bu). At least three complexes should be expected when considering two different ligands, namely, the two homo-combinations, as well as the hetero-combination. They showed that the ee of the hydrogenation of **29b** was enhanced to 96% for the mixture, from 90 and 57% for the exclusively homo-complexes. Additionally, using a racemate of one of the ligands still gave around 90% ee when keeping the other ligand enantiopure, whereas purposefully mismatching the ligand enantiomers showed a drop in enantioselectivity as well as rate. These findings indicated the second monodentate ligand does not necessarily have to be chiral for high enantioselectivity, which was later used to good effect in combinatorial studies [69].

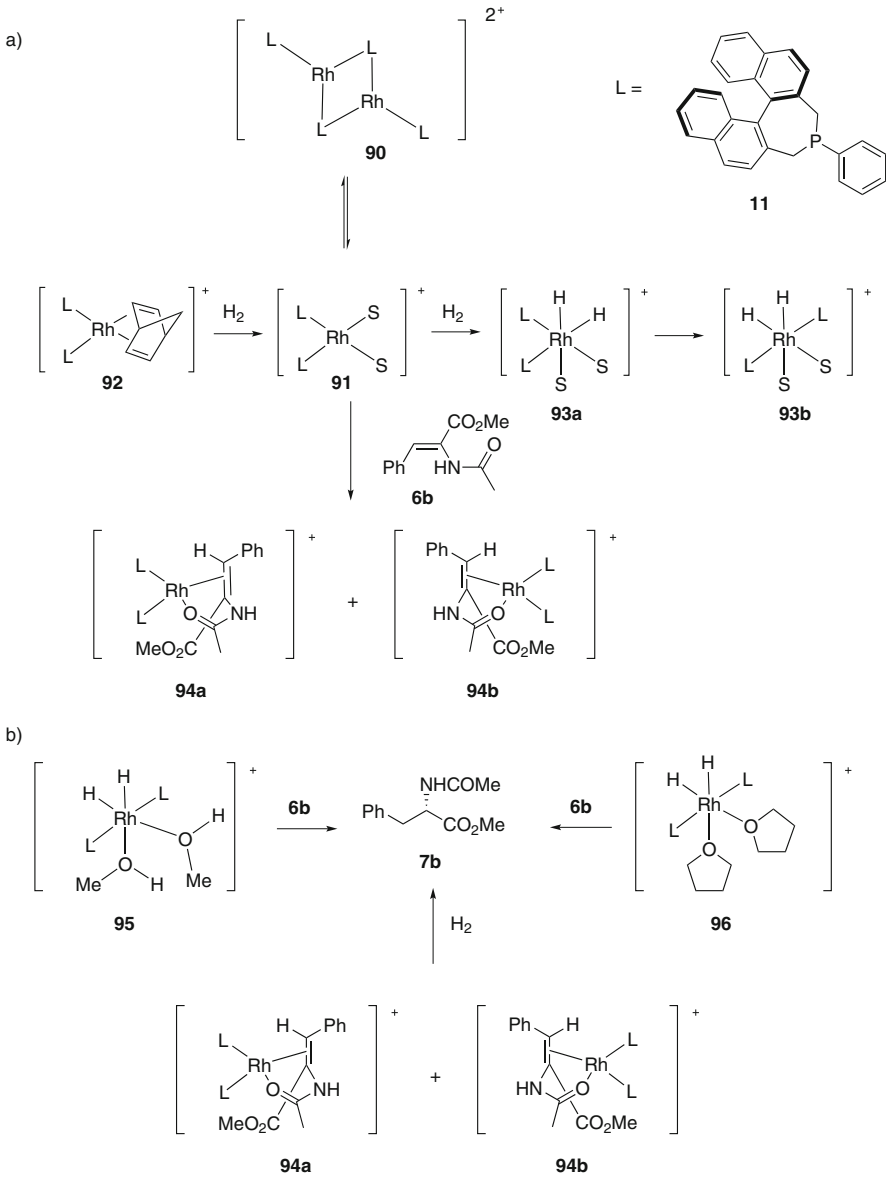
Gridnev et al. hydrogenated a solution of $[Rh(L)_2(cod)]^+$ in $CD_2Cl_2$, where L = **8** (R = *t*Bu) (Fig. 2) and observed two species in equilibrium by $^{31}$P-NMR spectroscopy (Scheme 15) [70]. Based on $J_{P\text{-}Rh}$ values and the nonequivalence of both phosphorus atoms for one of the species, these signals were assigned to the solvento complex $[Rh(L)_2(S)_2]^+$ (**70**) and the η-arene dimeric complex **71**. Addition of methyl 2-acetamido-cinnamate **6b** led to formation of a new doublet in the $^{31}$P NMR; however, the expected chelating substrate complex could not be identified. At temperatures below 243 K, they observed a small concentration of the coordination complex of rhodium with labelled substrate **72**, containing a $^{13}$C-label at the α-olefin position, as well as a phosphonate instead of the methyl ester moiety. Interestingly, no olefin coordination was observed from either the olefin protons or the α-$^{13}$C, in contrast to the analogous Rh-BINAP complex. Applying a hydrogen atmosphere gave rise to the formation of monohydride **74**, with the α-carbon bound to rhodium. Based on comparison with analogous monohydride rhodium-bidentate complexes, this was concluded to be an intermediate in the catalytic cycle,




**Scheme 16** Mechanism of asymmetric hydrogenation of methyl 2-acetamido-cinnamate with rhodium/MonoPhos

establishing that two monophosphonites are coordinated to rhodium during at least part of the reaction [70]. At first glance, this contrasts with the finding that the asymmetric hydrogenation of methyl (*Z*)-2-acetamido-cinnamate **27b** proceeded faster, but without a decrease in enantioselectivity, when the rhodium to ligand ratio was reduced to 1:1. However, this can be explained in terms of an equilibrium between different $[RhL_n]^+$ species, where catalytically inactive $[RhL_3]^+$ and $[RhL_4]^+$ species are less likely to form at lower ligand to metal ratios [67].

Alberico et al. set out to identify catalytic intermediates that form upon hydrogenating the norbornadiene ligand in $[Rh(\mathbf{10})_2(nbd)]^+$ (**76**), and elucidate why the high enantioselectivity of rhodium-monodentate systems seems to depend on the use of non-protic solvents, considering that the bidentate phosphine catalysts typically form solvento complexes with protic solvents (Scheme 16) [71]. Replacing the more usual precursor cod (1,5-cyclooctadiene) with nbd (norbornadiene), they obtained a complex containing two MonoPhos ligands (**10**, $R^1$, $R^2 = Me$) as well as the nbd. In contrast to the cod complexes, these complexes have well-resolved $^{31}P$ NMR and $^1H$ NMR spectra. Catalytically inactive $[Rh(\mathbf{10})_4]^+$ was observed as well, which, by increasing the ligand stoichiometry, was isolated for full characterisation and control experiments. Under hydrogenation conditions in the absence of substrate, **76** turned into the dimeric $[Rh_2(\mathbf{10})_4]^{2+}$ species **77**, without any indication of solvento complex formation. Addition of methyl (*Z*)-2-acetamido-cinnamate (**27b**) to a solution of the dimer gave rise to a mixture of the dimer **77** and a single chelating substrate complex as observed in $^{31}P$ NMR. After lowering the temperature, a few hours later, all **77** had disappeared, and now a minor substrate complex




**Scheme 17** Mechanistic studies of the rhodium-catalysed asymmetric hydrogenation using monodentate phosphepine ligand **11**; (**a**) Formation of hydride as well as substrate complexes are feasible; (**b**) Both hydride complex and substrate complex can lead to product formation

was observed as well. After application of hydrogen, these two complexes disappeared, and a new complex **79** showed up which was identified as the rhodium complex in which the product **7b** was bound via its aromatic ring to the rhodium.

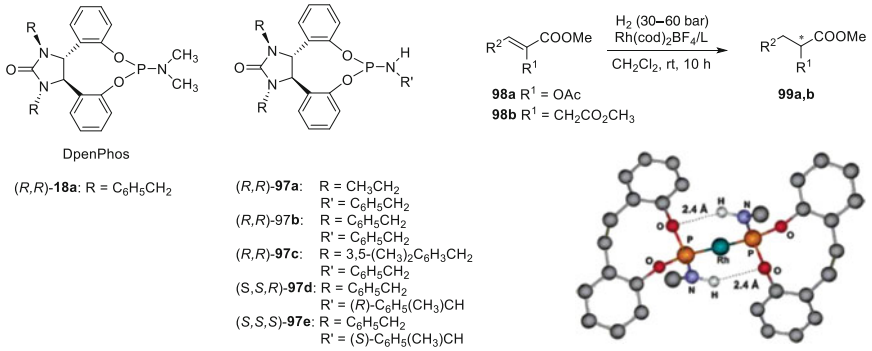
Addition of 5 eq. of **27b** to **79** fully converted this complex back to the mixture of substrate complexes **78**. Their findings suggest an anti-lock-and-key mechanism, in contrast to what Reetz et al. concluded for the phosphite case.

In a similar study from Alberico and Gridnev, the behaviour of the rhodium complex based on the chiral phosphepine **11** (R = Ph) was studied (Scheme 17). Here also a mixture of the dimer (**90**) and the solvato complex $[RhL_2S_2]^+$ (**91**) was observed upon hydrogenation of the catalyst precursor (Scheme 17a). Upon addition of substrate, they could clearly observe the formation of the two diastereomeric chelating substrate adducts (**94a**, **b**). Reaction of this mixture with hydrogen at −90°C gave rise to formation of the product **7b** with 99% ee. If however the catalyst precursor was hydrogenated in a mixture of $CD_2Cl_2$ and a polar solvent such as $CD_3OH$ or THF-$d_8$, the dihydride complexes $[RhL_2S_2H_2]^+$ (**95**, **96**) were observed (Scheme 17b). Oxidative addition of hydrogen to $[RhL_2S_2]^+$ must initially lead to the *cis*(H)-*cis*(P) structure **93a**, but as indicated by $J_{P\text{-}P}$ and $^1H$ chemical shift values for the hydrides, only *cis*(H)-*trans*(P) $[RhH_2L_2S_2]^+$ **93b** was observed. Stoichiometric, low-temperature addition of the substrate again led to formation of the product in >99% ee. Upon raising the temperature, the substrate reappeared coordinated to rhodium, suggesting the reaction steps remain reversible until a late stage [72].

The observation of *trans*-diphosphines is somewhat surprising, as Schiaffino and Ercolani argued that these could be left out of the equation. Their DFT studies indicated that, while thermodynamically more stable, the formation of *trans*-$(PMe_3)_2$ species is essentially blocked with respect to all possible *cis* isomers [73].

## 5 Supramolecular Catalysis Using Monodentate Ligands

Ding and co-workers first recognised the effect of hydrogen bonding in catalysts bearing two monodentate phosphoramidite ligands in which the amine contains only a single substituent (Scheme 18) [74]. These ligands were used in the rhodium-catalysed enantioselective hydrogenation of several (*Z*)-methyl α-(acetoxy)acrylates (**98a**) and (*E*)-β-aryl itaconate (**98b**) derivatives with ee's between 96 and >99%, whereas catalysts using phosphoramidite ligands based on the corresponding secondary amine did not show any reaction with **98a**. Moreover, the asymmetric hydrogenation of substrate **98b** proceeded 1,000 times faster with **97b** as compared to DpenPhos **18a**. They showed in $^1H$-NMR studies that a downfield shift of almost 2 ppm was observed for the NH protons of **97b** upon complexation to rhodium in $CD_2Cl_2$. The addition of $CD_3OD$ left the complex unchanged, whereas the NH signal of the free ligand shifted 0.31 ppm downfield. These findings showed hydrogen-bonding interactions between the ligands, indicating that self-assembly of a chelate complex is the basis for the improved catalytic activity in this type of ligands. A calculated structure of the rhodium complex showing the hydrogen bonds is shown in Scheme 18.




**Scheme 18** Primary amine-based phosphoramidites form chelates through hydrogen bond formation. The calculated structure is reproduced from Liu et al. [74] with permission from the American Chemical Society

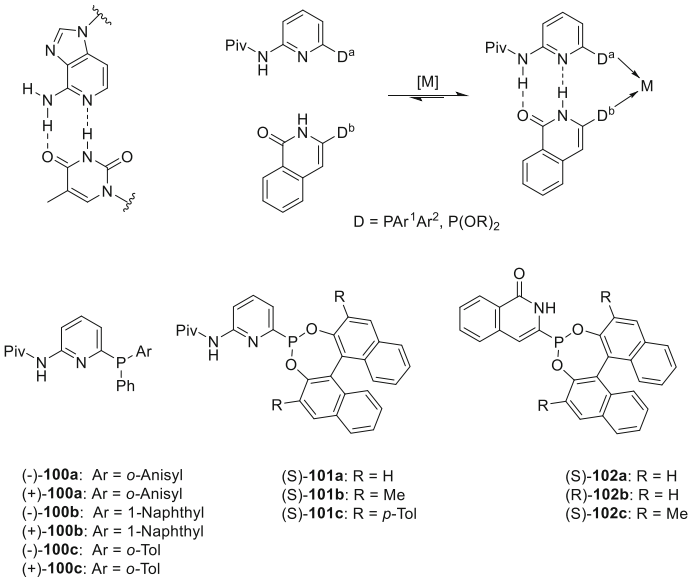
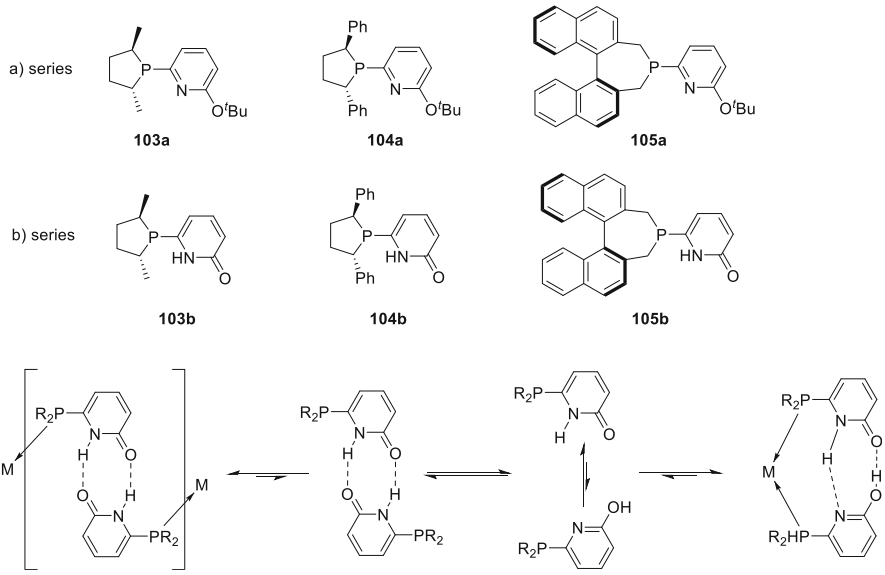



**Fig. 6** Supramolecular library of ligands

Inspired by Watson-Crick base pairing, Breit and co-workers described a combinatorial approach towards the Rh-catalysed asymmetric hydrogenation. A library of chiral amidopyridines and isoquinolin-1(2*H*)-one's equipped with phosphine and phosphinite donor moieties was synthesised (Fig. 6). Supramolecular heterobidentate complexes readily formed upon mixing with $[Rh(cod)_2]BF_4$ (Scheme 19). The optimal combination resulted in full conversion and an ee of 99% when applied in the hydrogenation of methyl 2-acetamido-acrylate **27b** under mild conditions. With different combinations, quantitative conversions and ee's >90% were also obtained

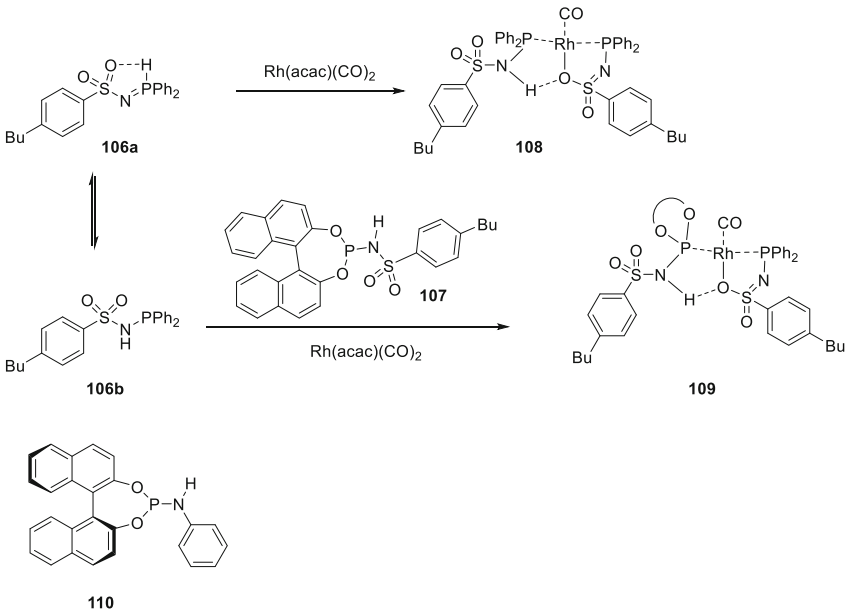



**Scheme 19** Supramolecular phospholane and phosphepine ligands

in the rhodium-catalysed hydrogenation of methyl 2-acetamido-cinnamate (**6b**) and dimethyl itaconate (**29b**) (Scheme 3) [75].

Breit, Börner and co-workers prepared three sets of chiral phospholanes and phosphepines linked to a pyridone, and investigated the complexation behaviour of these ligands with several metals and co-ligands, shown schematically in Scheme 19 [76]. Self-assembly towards a chelate complex was possible with two equivalents of the pyridone ligands, where tautomerisation of the pyridone system to hydroxy-pyridine is key. In the hydrogenation of the benchmark substrates **6b**, **27b** and **29b** (Scheme 3), low enantioselectivities were obtained with the ligands from the a series, which cannot engage in such a supramolecular interaction, whereas hydrogenation using the ligands of series b gave much higher enantioselectivities with the phosphepine ligand clearly as the best one. However, hydrogenation with the ligands of series b was much slower than with the ligands of series a. The authors explained this by assuming the formation of polymeric ensembles.

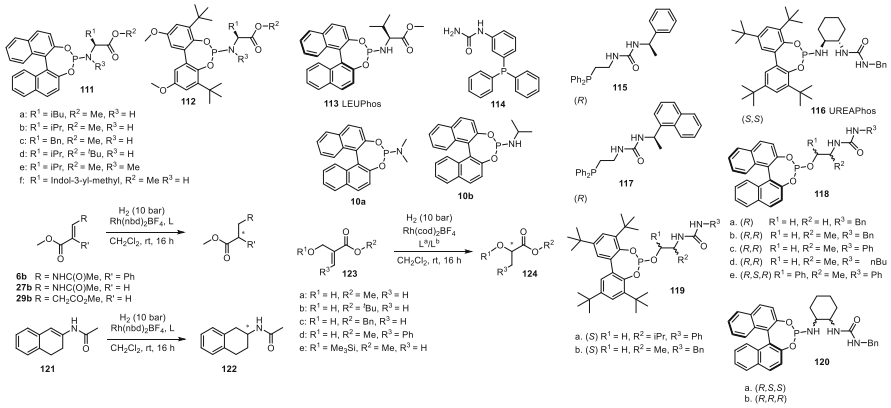
The group of Reek has reported extensively on the development of supramolecular chiral ligands. The so-called METAMORPhos ligands are based on arylsulfonamido-phosphines, such as **106** and phosphoramidites such as **107** (Scheme 20) [77]. When reacted with a rhodium precursor, a homo-bisligated complex, i.e. **108** was obtained through hydrogen bonding of one ligand with its tautomerised form. However, when a 1:1 mixture of **106** and **107** was used, the hetero-complex **109** was formed exclusively. This is a clear advantage of these supramolecular ligands over the classical monodentate ligands were always a mixture of homo- and hetero-complexes is formed. The neutral complexes were inactive in hydrogenation reactions, but could be activated by treatment with




**Scheme 20** METAMORPhos ligands

$HBF_4{\cdot}OMe_2$. Catalytic hydrogenations of **27b** were carried out starting from $[Rh(nbd)_2]BF_4$, however. The homo-complex based on **106**, being non-chiral, showed no ee, and the homo-complex based on **107** induced 99% ee, whereas the hetero-complex based on **106** and **107** induced 91.7% ee, but was reported to be twice as active as the homo-complex based on **107**. Interestingly, the use of the mixture of **106** and **110** led to formation of a mixture of the two homo-complexes.

Reek and co-workers developed another generation of supramolecular ligands by synthesising phosphoramidite ligands based on amino acids **111**, where hydrogen-bonding behaviour can also be expected [78]. Rhodium catalysts based on these ligands enabled full conversions and ee's up to 89% in the hydrogenation of dimethyl itaconate **29b**. It was found that the larger steric bulk of the chiral centre $R^1$ had a positive effect on the ee. Interestingly, the *N*-methylated valine-based ligand **111d**, which should not give rise to hydrogen bonding, outperformed the others in the hydrogenations of methyl 2-acetamido-acrylate (**27b**) (97% ee) and 2-acetamido-cinnamate (**6b**) (84%), whereas it was a poor ligand in the case of dimethyl itaconate (**29b**) (43% conversion, 3% ee.) None of the ligands enabled more than 50% conversion in the conversion of **121**. In a similar vein, the same authors reported the amino acid-based LEUPhos **113**, which was used in combination with achiral phosphines, most notably ureaphosphine **114** [79]. Hydrogen bonding between these two ligands led to the exclusive formation of the hetero supramolecular complex upon mixing with $[Rh(cod)_2]BF_4$. This complex catalysed the hydrogenation of **123** with ee's of 92–99%, outperforming the control experiments with co-ligands without the urea moiety. Furthermore, they highlighted the



**Scheme 21** Urea-based supramolecular ligands

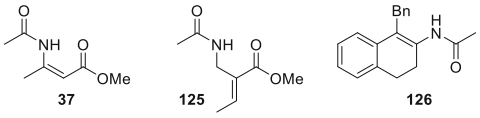


**Fig. 7** Substrates tested with a UREAPhos ligand library

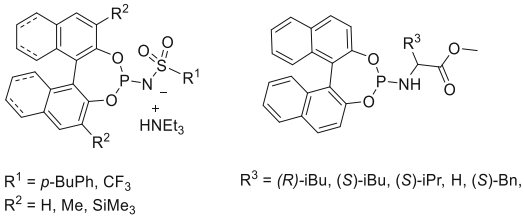
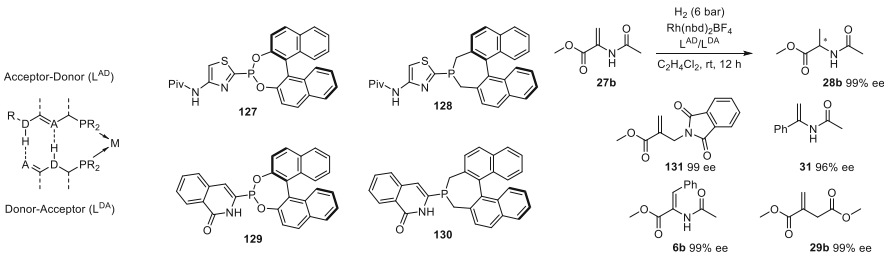


**Fig. 8** Combination of anionic METAMORPhos ligands with amino acid-based phosphoramidites

importance of hydrogen bonding between the substrate and the ligand by DFT calculations, as further evidenced by the trimethylsilyl-protected substrate (**123e**) only giving 52% ee. When the phosphine and urea moieties are separated by a short linker, urea-based ligands such as UREAPhos (**116**) may also be used to self-assemble into homo-bisligated complexes, as shown by Meeuwissen et al. [80] They synthesised a library of 12 phosphoramidites and phosphines (Scheme 21, **115**–**120**) decorated with a urea group and investigated them in a high-throughput setup for the hydrogenation of substrates **37**, **121**, **123a**, and **125**–**126** (Fig. 7). An optimisation screen was performed for substrates **125** (84% conversion, 96% ee) and **126** (84% conversion, 83% ee) using ligand **118b**.

More recently, both paths converged when anionic METAMORPhos ligands were combined with neutral amino acid-based phosphoramidites (Fig. 8),



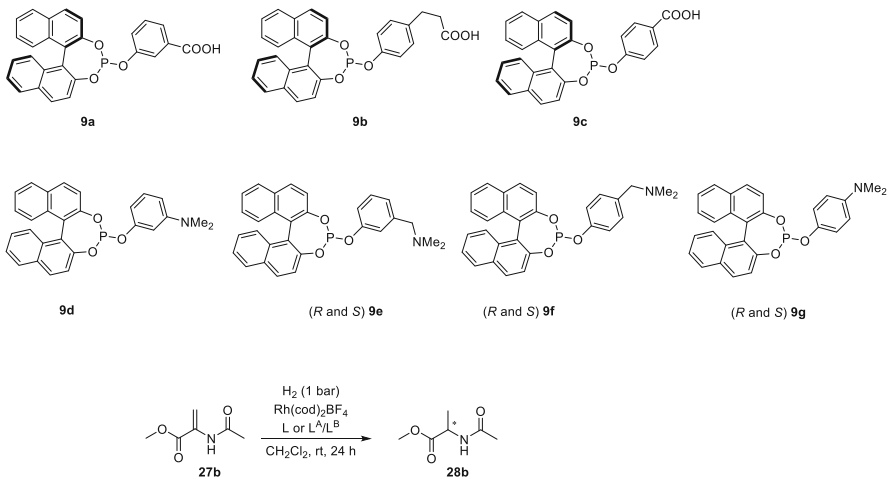

**Scheme 22** Library of donor-acceptor ligands for supramolecular catalysis

increasing the combinatorial scope further [81]. Homo-combinations of anionic METAMORPhos ligands naturally led to negatively charged complexes [Rh $(L)_2(nbd)]HNEt_3$, which dimerised to $[Rh_2(L)_4](HNEt_3)_2$ under hydrogen atmosphere, except for those cases where steric bulk was introduced on the 3,3′ positions of the BINOL. Hetero-combinations with amino acid-based phosphoramidites led to a range of different complexes. Importantly, the dimeric complexes were also active hydrogenation catalysts. A combinatorial screening for a series of substrates led to the conclusion that the hetero-complexes were most active and selective, and ee's around 90% could typically be obtained.

An elegant alternative to high-throughput screening was reported by Wieland and Breit [82]. They performed a diversity-oriented synthesis to generate a library of 12 acceptor-donor and 10 donor-acceptor monodentate ligands (Scheme 22). Enantioselective olefin hydrogenation catalysts were identified by dividing their library into subgroups and identifying the best-performing subgroup in the rhodium-catalysed hydrogenation of **27b** and then iterating this process by dividing the subgroup into further subgroups and repeating the process. The combinations $L^{AD}/L^{DA}$ shown below all induced full conversions and 98–99% ee and were identified after 17 experiments instead of performing the reaction for all 120 combinations. The approach was expanded to give optimal ligand combinations for four more substrates (Scheme 22).

The combination of BINOL-based phosphites equipped with acidic and basic moieties, as described by Gennari and co-workers, only had a modest effect on the enantioselectivity in the rhodium-catalysed hydrogenation of **27b** (Scheme 23) [83]. Homo-combinations induced ee's of 80–87% at full conversion, whereas the hetero-combinations resulted in ee's up to 90%. Use of ligands **9e** and **9f**, containing a benzylic amine, led to reduced conversions of 30% and 89%, respectively. Their strongly basic group possibly acts as a catalyst poison. This effect was partially cancelled out upon mixing with a carboxylic acid-containing ligand. Notably, only 30% ee was obtained in the rhodium-catalysed hydrogenation of **27b** when intentionally mismatching (*R*)-**9a** with (*S*)-**9e**.

The same group designed a library of BINOL-based phosphites connected to a phthalic acid bisamide (Phthalaphos) using several different amino alcohol spacers (Fig. 9) [84, 85]. From this library, highly enantioselective ligands were identified




**Scheme 23** Library of acidic and basic ligands

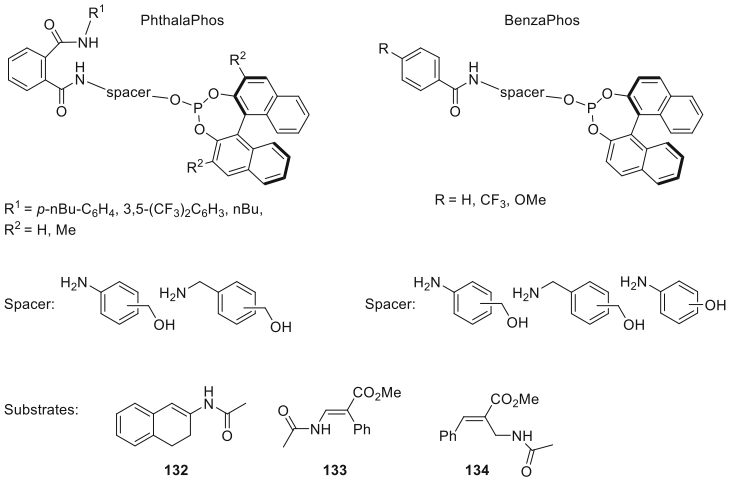
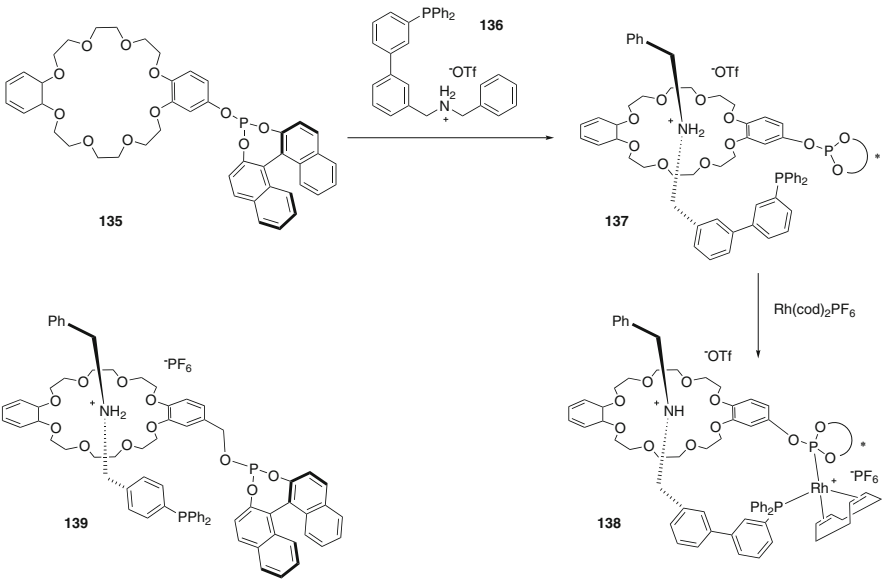



**Fig. 9** PhthalaPhos and BenzaPhos ligand libraries

for substrates **6b**, **27b**, **31** (R = Ph), **121** and **134**; however, for substrates **37**, **123a**, **132** and **133**, only moderate to poor results were obtained. Computational studies and control experiments confirmed the importance of hydrogen bridges between two equivalents of ligand in the homo-bisligated complex, as well as suggesting the formation of ligand-substrate hydrogen bridges in catalytic intermediates. They further simplified these ligands by replacing the phthalic bisamide with benzamides, leading to another library that was dubbed BenzaPhos (Fig. 9) [86]. The first-generation BenzaPhos ligands, i.e. those with unsubstituted benzamides, already led to ee values from 76 to >99% for substrates **6b**, **27b**, **31** (R = Ph), **121** and **123**, thus identifying the optimal spacer. The three most suitable




**Scheme 24** Rotaxane-based supramolecular ligands

ligands were modified by including a *p*-$CF_3$- or *p*-MeO-substituent on the benzamide, further improving the enantioselectivity in these hydrogenations. The influence of hydrogen bridging was again supported by computational studies and control experiments.

Nishibayashi and co-workers [87], as well as Fan and co-workers [88], investigated supramolecular chiral ligands based on the rotaxane principle, i.e. an interaction between a phosphine-linked dibenzyl ammonium salt (the 'axle' moiety) and a phosphite-linked crown ethers (dibenzo[24]crown-8; the 'wheel' moiety) (Scheme 24). These were then employed with $[Rh(cod)_2]PF_6$ or $[Rh(cod)_2]BF_4$ for the room temperature, 1 bar hydrogenation of **6b**, **27b**, several *para*-susbtituted methyl 2-acetamido-cinnamates as well as two naphthyl analogues of **6b**. In the Nishibayashi work, some variations of the position of the phosphine on the axle unit were included, showing that the phosphine-phosphite distance in the resulting supramolecular ligand was crucial for obtaining quantitative conversions and ee's >90%. Replacing the phosphite group on the wheel moiety with a chiral oxazoline dropped the ee to only 15%. In Fan's work, full conversions were also obtained with a range of substituted methyl 2-acetamido-cinnamates, albeit with more modest ee values, varying from 69 to 84%.

Based on the ability of benzene-1,3,5-tricarboxamides (BTA) to form helical rods through $\pi$-$\pi$ stacking as well as hydrogen bridging, Raynal et al. designed several phosphine-functionalised BTAs with zero (**142**), one (**141**, **143**) or two remote chiral centres (**140**) in the side chains (Fig. 10) [89]. These were shown to self-assemble into chiral helices and in combination with $[Rh(cod)_2]BAr_F$ catalysed

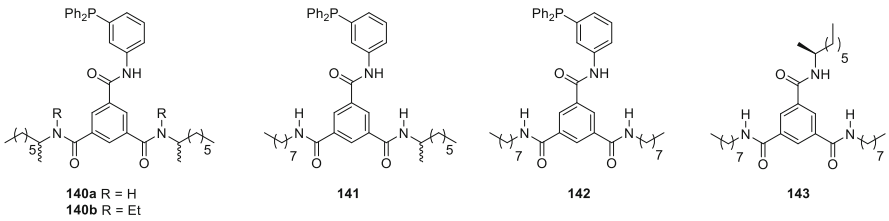



**Fig. 10** Precursors for helical supramolecular ligands

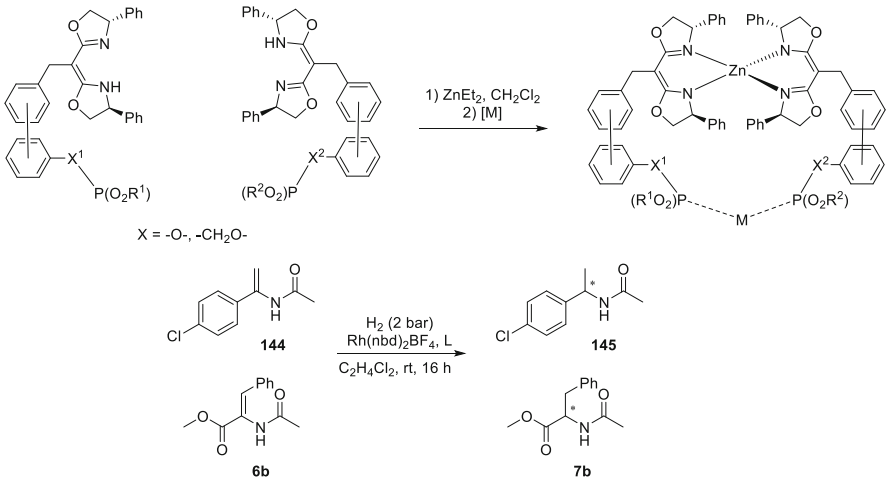
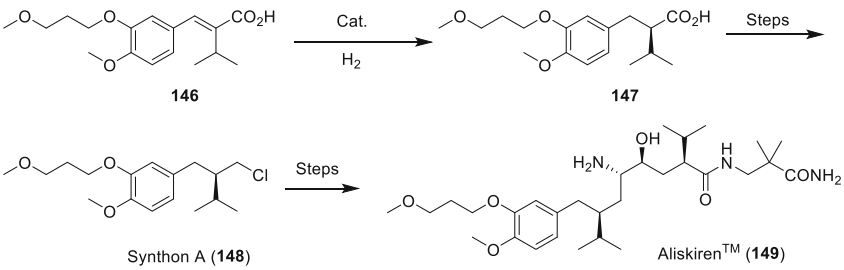



**Fig. 11** Supramolecular ligands linked by zinc

the asymmetric hydrogenation of **29b** in hexane. Up to 88% ee was obtained, but only where all amides in the side chain contained an N-H functionality. Additionally, when the reactions were repeated in increasingly polar solvents or with more polar counterions, enantioselectivity was lost, presumably through breaking up the chiral assemblies.

Instead of hydrogen bridging, Takacs and co-workers used complexation of chiral bisoxazolines to Zn(II) for the self-assembly of modular supramolecular ligands [90]. The bisoxazolines were connected to bisphenol- or bis-naphthol-based phosphites via varying spacers (Fig. 11). In combination with $[Rh(nbd)_2]BF_4$ as rhodium source, this led to a library of >150 catalysts, which were then screened in the hydrogenation of **6b** and **144** as model substrates. In general, most catalysts containing a flexible linker gave nearly quantitative conversions and ee's around 90%, whereas the more constrained linkers performed worse than control experiments with two equivalents of the monodentate phosphite ligand **9** (Fig. 2, R = Ph).

In summary, the self-assembly of monodentate ligands to form de facto supramolecular chiral bidentate ligands has been investigated mainly from a

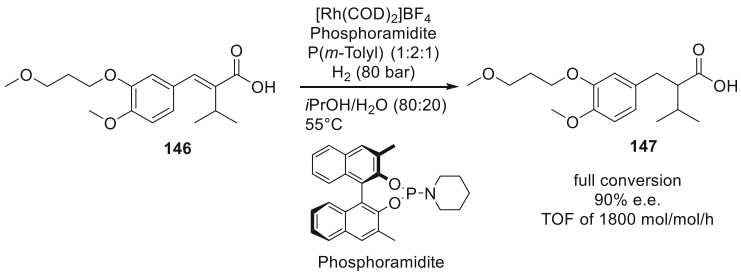



**Scheme 25** Asymmetric hydrogenation step in the production of Aliskiren™

combinatorial point of view. Several different strategies for self-assembly have been highlighted. Monodentate ligands are often easier to synthesise than, especially unsymmetrical, bidentate ones, and self-assembly lends itself well for generating large libraries of catalyst combinations. Considering the difficulty of rationally designing catalysts for a given substrate, such a combinatorial approach may well prove successful, as was shown in the asymmetric hydrogenation of a range of acrylates and enamides.

## 6 Industrial Application

Although there were probably several processes where monodentate ligands have been used on the 10–100 kg scale, we are aware of only one ton-scale process. At DSM a process was developed for the production of Synthon A (**147**), an intermediate for the production of the renin-inhibitor Aliskiren™ (**149**), a blood pressure-lowering agent developed by Novartis and Speedel (Scheme 25) [91]. In the medicinal chemistry route, the asymmetric hydrogenation was performed with rhodium and Walphos, a ferrocene-based bidentate phosphine ligand. At DSM the high-throughput screening equipment was used to screen libraries of monodentate phosphoramidite ligands. In a first screen, it became obvious that the catalysts not only delivered the product in a rather low ee, but far worse, the rate of the reaction was so low that an industrial process seemed impossible. Since it is known that the rate determining step in rhodium-catalysed homogeneous hydrogenation is the oxidative addition of hydrogen, the researcher screened combinations of phosphoramidite ligands with electron-rich phosphine ligands as electron-rich ligands are known to accelerate oxidative addition reactions. This strategy paid off. After a number of screens, a ligand combination was found of 3,3′-dimethyl-PipPhos and tri-*m*-tolylphosphine, which allowed hydrogenation of the substrate with a turnover frequency of 1,800 $h^{-1}$ (Scheme 26). In addition, the product was formed in 90% ee, which could be easily upgraded by crystallisation in the subsequent steps. This process was implemented at DSM on ton scale.




**Scheme 26** Ton-scale rhodium-catalysed asymmetric hydrogenation using a mixed monodentate ligand catalyst

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