28
Enantioselective Alkene Hydrogenation: Monodentate Ligands

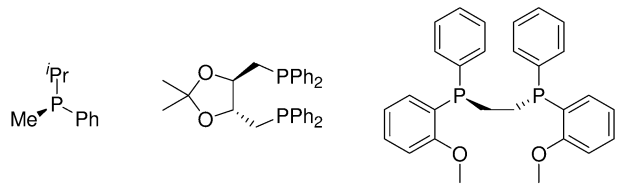
Michel van den Berg, Ben L. Feringa, and Adriaan J. Minnaard

28.1
Introduction

In 1968, Knowles et al. [1] and Horner et al. [2] independently reported the use of a chiral, enantiomerically enriched, monodentate phosphine ligand in the rhodium-catalyzed homogeneous hydrogenation of a prochiral alkene (Scheme 28.1). Although enantioselectivities were low, this demonstrated the transformation of Wilkinson's catalyst, $Rh(PPh_3)_3Cl$ [3] into an enantioselective homogeneous hydrogenation catalyst [4].

In order to enhance enantioselective induction by preventing rotation around the rhodium–phosphorus bond, Dang and Kagan developed a chelating bidentate phosphine; DIOP [5]. By using tartaric acid as a starting material from the chiral pool, and by situating the chirality in the backbone, and not on phosphorus, synthesis of the ligand was simplified. In addition, it was the first example of a C_2 symmetric ligand, designed in this way to minimize the number of diastereomeric rhodium–ligand–substrate complexes. This strategy proved to be very effective, being confirmed several years later by Knowles et al. in the dimerization of PAMP to DIPAMP, which raised the enantioselectivity in the hydrogenation of methyl 2-acetamido-cinnamate from 55% to 95% [6].

The trend to develop chiral ligands devoid of chirality on phosphorus simplified the synthesis and led to the preparation of literally hundreds of chiral bi-



Scheme 28.1 Some of the first monodentate and bidentate ligands in enantioselective hydrogenation.

The Handbook of Homogeneous Hydrogenation.
Edited by J.G. de Vries and C.J. Elsevier

ISBN: 978-3-527-31161-3

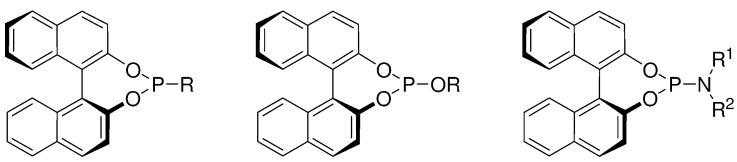
sphosphines [7]. Together with the application of DIPAMP and Ph-β-Glup in commercial processes for L-DOPA [8], this established the use of bidentate phosphorus ligands as a *conditio sine qua non* for high ee-values in asymmetric hydrogenation. This was apparently underscored by the development of the very successful ligands BINAP, especially versatile with ruthenium, and DuPhos.

Knowles et al. had shown that the use of the P-chiral monodentate CAMP gave rise to an *e.e.* of 88% [9] in the formation of *N*-acyl-phenylalanine. However, due to the superior results obtained using bidentate ligands and the difficult preparation of P-chiral phosphines, this route was rarely followed for a long time [10, 11].

It thus came as a surprise that in the year 2000, three groups independently reported the use of three new classes of monodentate ligands (Scheme 28.2) [12]. The ligands induced remarkably high enantioselectivities, comparable to those obtained using the best bidentate phosphines, in the rhodium-catalyzed enantioselective alkene hydrogenation. All three being based on a BINOL backbone, and devoid of chirality on phosphorus, these monophosphonites [13], monophosphites [14] and monophosphoramidites [15] are very easy to prepare and are equipped with a variable alkyl, alkoxy, or amine functionality, respectively.

These reports announced the rapid development of a large variety of monodentate ligands for rhodium-catalyzed enantioselective hydrogenation. It was shown that the substrate scope for catalysts based on monodentate ligands is most probably at least as big as for their bidentate counterparts. Also, initial doubts about the activity and stability of the monodentate ligand-catalysts have been taken away. Several reports show that substrate : catalyst ratios (SCRs) of 10^3 or higher, essential for industrial application, are possible. In addition, reaction rates are in the studied cases comparable to those reached by catalysts based on state-of-the-art bidentate ligands [16].

The mechanism of the rhodium-catalyzed enantioselective hydrogenation has been thoroughly studied, and a wealth of information is now available. Logically, these studies have been performed using bidentate ligands. It will be very interesting to see whether catalytic cycles that have been proposed will also hold for catalysts equipped with monodentate ligands. Although a mechanistic study is still lacking [17], Zhou et al. performed a kinetic study of hydrogenations using the monodentate phosphoramidite SIPHOS [18]. As noticed earlier for MonoPhos,



Scheme 28.2 New classes of monodentate ligands used in asymmetric hydrogenation. R = alkyl or aryl.

the enantioselectivity of the reactions was shown to be independent of the hydrogen pressure (e.g., hydrogen concentration) between 1 and 50 bar. This seems to be more general for monodentate ligands. In addition, the enantioselectivity decreases slightly with increasing temperature, and *vice versa*. Both observations disagree with the "major/minor" diastereomer part of the Halpern mechanism.

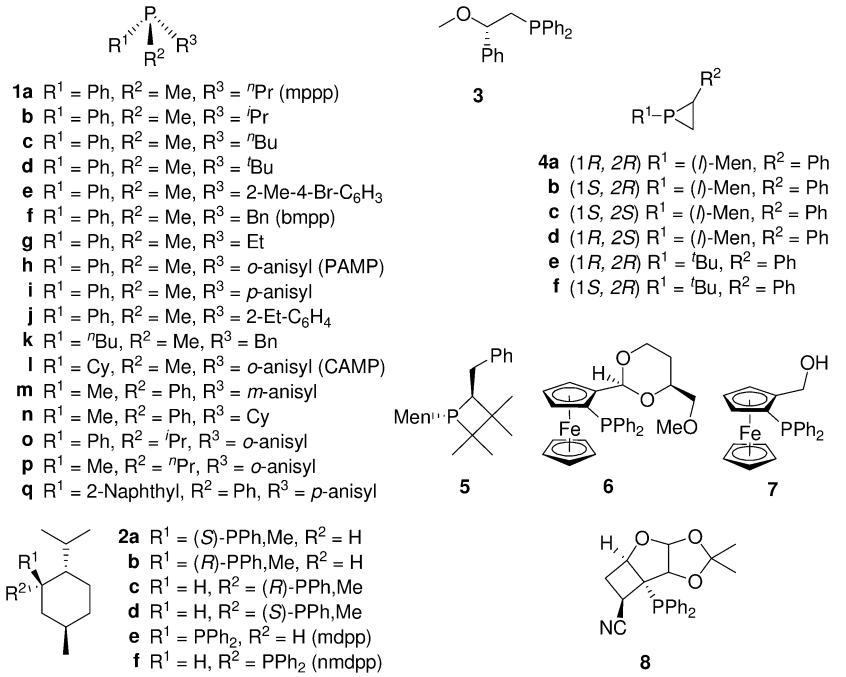
Both for MonoPhos and SIPHOS, a positive non-linear effect was observed with respect to the ee of the ligand. The observation that for several ligands a ligand:rhodium ratio of 1 : 1 gives a faster reaction than a L : Rh ratio of 2 : 1, with preservation of ee, tempted Zhou et al. to propose a mechanism with only one ligand on rhodium in the enantiodiscriminating step. This seems to contradict the recent results obtained using mixtures of ligands, a synergy that logically can only arise from a catalyst containing two different ligands. The application of these mixtures of monodentate ligands in catalysis, first shown by the group of Reetz and discussed in Chapter 36, in a number of cases affords higher ee-values than the corresponding pure ligands [19]. Very recent reports show that also the combination of chiral and achiral ligands can lead to unprecedented ee-values in enantioselective hydrogenation [20]. Combined with the modular construction of most monodentate ligands, and therefore the easy variation of their structure, this offers a tremendous opportunity for high throughput catalyst screening, as discussed in Chapter 36.

The present chapter provides a comprehensive overview of the literature relating to monodentate ligands in enantioselective hydrogenation until the end of 2004. Patent literature has not been covered. As the large majority of the ligands is available in both enantiomeric forms, the absolute configuration of the products has not been indicated. As most authors focus on the enantioselectivity of their catalysts, this will be reflected in this chapter. Whenever possible, attention will be given to turnover frequencies (TOF) and turnover numbers (TON). Parts of this chapter have been covered recently by a review of Jerphagnon, Renaud and Bruneau [21] and by De Vries and Ager [22].

28.2 Monodentate Phosphines

Although, in the past, most attention was paid to the use of bidentate phosphines, a number of monodentate phosphines has also been developed and applied in the rhodium-catalyzed hydrogenation of alkenes. These earlier-developed ligands are chiral on phosphorus (**1**) [9] and usually equipped with a phenyl and a methyl moiety (Scheme 28.3). The third substituent varies in size in order to maximize the chiral induction in the hydrogenation. The enantioselectivity in the hydrogenation of substrates such as the precursors of L-DOPA varies over a broad range, from 1% to 90% *e.e.* using ligands **1m** and **1l** (CAMP), respectively. The results of the other ligands fall between these values.

Ligands **2a–2d**, which are also chiral on phosphorus, and **3**, were used in the chemo- and enantioselective hydrogenation of (*E*)-3,7-dimethyl-2,6-dienoic acid

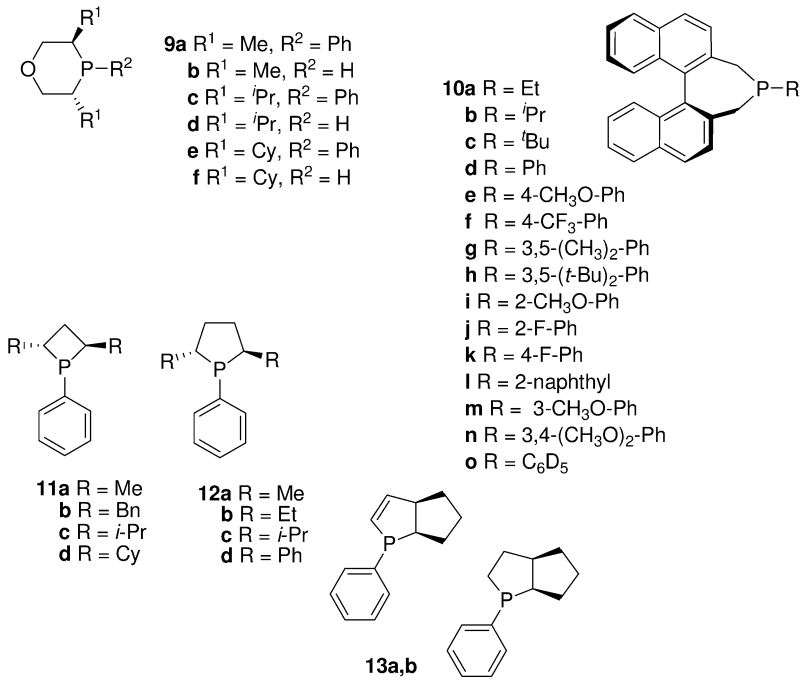


Scheme 28.3 Chiral monodentate phosphine ligands (men = menthyl, see **2**).

[23]. The *e.e.*-values were moderate, an improved result of 79% *e.e.* being obtained with nmdpp (**2f**) which is not chiral on phosphorus. The use of the other, non P-chiral, ligand mdpp (**2e**) gave low enantioselectivity. Ligand **2f** was also successfully used in the hydrogenation of 2-methylcinnamic and (*E*)-3-methylcinnamic acid [24].

Both ligands **4** [25] and **5** [26], in which phosphorus is part of a ring, were tested in the hydrogenation of α-acetamidocinnamic acid. Of these phosphirane ligands, only **4b** possessing a *trans*-configuration was able to induce reasonable enantioselectivities. Ferrocenyl-based monodentate phosphine **6**, used in a 4:1 ratio with $[Rh(COD)Cl]_2$, afforded an ee of 87% in this reaction, albeit with incomplete conversion [27]. Using ligand **7** under identical conditions, full conversion was reached, though with an *e.e.*-value of only 30%. Ligand **8**, derived from a carbohydrate, has also been applied with reasonable success [28].

Cyclic, C_2-symmetric monodentate phosphines with the phosphorus atom in a four-, five-, six-, or seven-membered ring have frequently been used in enantioselective hydrogenation (Scheme 28.4). The use of the six-membered oxaphosphiranes **9**, demonstrates that with these secondary phosphines high ee-values can be obtained in the hydrogenation of dehydroamino esters and methyl itaconate [29]. The atropisomeric ligands **10a–o** show a large effect of the size of the substituent on the enantioselectivity of the hydrogenation. Low ee-values in the hydrogenation of methyl *N*-acylcinnamate are obtained using ligand **10c** which



Scheme 28.4 Cyclic monodentate phosphine ligands.

contains a bulky *t*-Bu group [30]. When this group is replaced by a phenyl moiety, the *e.e.* obtained is 90%. After optimization by varying the substituent, excellent ee-values could be obtained [31]. Using these ligands, the first highly enantioselective ruthenium-catalyzed hydrogenation of *β*-ketoesters with monodentate ligands was also achieved [32].

As for ligands **11**, containing a four-membered ring [33, 34], ligands **12** which also contain a five-membered ring afford good enantioselectivities [35], especially **12d**. One could consider these ligands as monodentate analogues of DuPhos. The group of Fiaud [36] reported the existence of **12d** a year before the publication of the BINOL-based monodentate phosphonite, phosphite and phosphoramidite ligands.

Recently, two new P- and C-chiral monodentate phosphines **13** were reported. The ligands were applied in a number of transition metal-catalyzed reactions, though ee-values in the rhodium-catalyzed hydrogenation of *N*-acyl dehydrophenylalanine were only moderate [37].

28.3
Monodentate Phosphonites

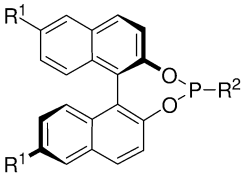
Rhodium-catalyzed enantioselective hydrogenation using monodentate phosphonite ligands was first reported by the group of Pringle [13], followed by the group of Reetz (Scheme 28.5) [38]. The reported ligands are easily synthesized from an alkyl- or arylphosphorus dichloride and the appropriate BINOL or 9,9′-bisphenanthrol. The ligands are easily hydrolyzed in the presence of moisture, but are considerably more stable as their rhodium complexes [39].

Enantioselectivities obtained in the hydrogenation of methyl 2-acetamido-cinnamate, methyl 2-acetamido-acrylate and dimethyl itaconate are surprisingly high (up to 94% *e.e.*). The TOFs of the hydrogenation reactions using these monodentate phosphonites is fairly high, with most of the reactions with a SCR of 500 reaching TOFs of 250–300 mol $mol^{-1} \cdot h$ and full conversion at 1.5 bar. In addition, ligand **15d** has been studied in the rhodium- and iridium-catalyzed hydrogenation of a benzyl imine, but no chiral induction was observed [40].

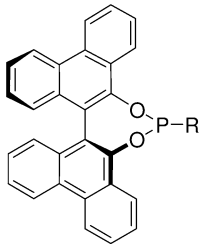
The first – and until now only – case of ruthenium-catalyzed enantioselective ketone hydrogenation using monodentate ligands concerns phosphonite ligands [41]. In several cases, but especially with **15f**, excellent ee-values are obtained. The simple synthesis of these phosphonites makes them an interesting class of ligands for the synthesis of a ligand library for high-throughput experimentation (HTE). In addition, mixtures of ligands can be used (see Chapter 36).

28.4
Monodentate Phosphites

The chiral monodentate phosphites presented in Scheme 28.6 are easily prepared from a diol, phosphorus trichloride, and an alcohol. Usually, the diol is converted into the corresponding phosphoro chloridite, followed by reaction



15a R^1 = H, R^2 = Me
b R^1 = H, R^2 = Et
c R^1 = H, R^2 = ^{t}Bu
d R^1 = H, R^2 = Ph
e R^1 = H, R^2 = *o*-biphenyl
f R^1 = H, R^2 = *o*-BrPh
g R^1 = H, R^2 = *o*-Tol
h R^1 = H, R^2 = *o*-Anisyl
i R^1 = H, R^2 = *c*-C_6H_{11}
j R^1 = H, R^2 = Cl
k R^1 = C_6F_{13}, R^2 = Ph



16a R = Me
b R = ^{t}Bu
c R = Ph

Scheme 28.5 Monodentate phosphonite ligands.

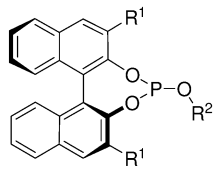
with the appropriate alcohol. The reversed approach – for example, reaction of a phosphoric dichloride with a diol – has also been used.

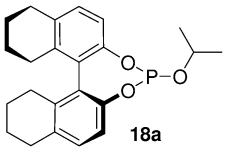
The application of monodentate phosphites as ligands in the rhodium-catalyzed enantioselective hydrogenation was first reported by the group of Reetz [14]. Initially, bidentate phosphites based on dianhydro-D-mannitol and two BINOL moieties were used, but it transpired that by substituting one of the BINOL moieties for methanol, leading to **17bh** and **17bi**, enantioselectivities in the rhodium-catalyzed hydrogenation were surprisingly high.

Based on a comparison of matched and mismatched ligands, it was shown that the BINOL moiety had the largest influence on the enantioselectivity of the reaction. Elaborating on this finding, a number of simple BINOL-based monodentate phosphite ligands was synthesized. The use of these ligands in the rhodium-catalyzed hydrogenation revealed their excellent behavior, resulting in high *e.e.*-values in the products. The group of Xiao reported monodentate phosphite ligands based on BINOL and L-menthol, **17bc** and **17bd** [42], while more recently Bakos et al. reported ligands derived from octahydro-BINOL, **18a** and **18b** [43] and the groups of Börner [44] and Helmchen [45] reported substituted BINOL-based phosphites. Large, helicene-like phosphites **19** have also been reported recently [46].

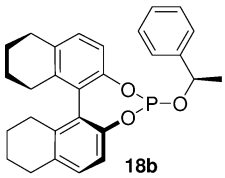
The initial report of Reetz describes the use of a Rh : L ratio of 1 : 1, although more recent experiments were conducted using a ratio of 1 : 2. Within this range, the enantioselectivities are unaffected. The combination of rhodium with ligands **17** used in the hydrogenation of methyl 2-acetamido cinnamate afforded enantioselectivities ranging from 2% to 99%. However, the majority of the results ranged from 75% to 99%. The use of ligands **17am** and **17an** gave the highest ee-values. Particularly striking was the influence of the BINOL moiety, which completely dominate the configuration of the product. The chiral alcohol present does not seem to have any influence. Similar to the use of monodentate phosphonites, the hydrogenations using monodentate phosphites are best performed in non-protic solvents. The rate of the reactions is high; even at a hydrogen pressure of 1.3 bar rates of 300 mol $mol^{-1} \cdot h$ were obtained. At an elevated pressure of 20 bar, TOFs up to 120 000 mol $mol^{-1} \cdot h$ were obtained in the hydrogenation of dimethyl itaconate with **18a**. This increase in pressure had only a marginal, if any, effect on the enantioselectivity. Recently, Reetz et al. reported the use of the "parent" phosphite ligand **17be** (a phosphoric acid diester) which led to *e.e.*-values of up to 85%. This was only slightly lower than the results obtained using ligand **17aa** [47]. The related phosphite **20**, based on TADDOL, was tested in an iridium-catalyzed imine hydrogenation but produced disappointing results [48].

Besides the phosphite ligands based on BINOL, phosphite ligands based on bisphenol are also used in rhodium-catalyzed hydrogenation. These ligands are shown in Scheme 28.7 and consist of a bisphenol with different substituents on the 3,3′,5,5′, and 6,6′-positions. The ligands without substituents on the 6,6′-positions are only fluxionally chiral. The use of readily available chiral alcohols (**21aa–21aj**) such as menthol in combination with bisphenol was thought to induce one of the bisphenol conformations in preponderant amounts [49]. The





18a

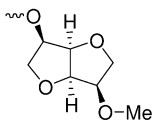


18b

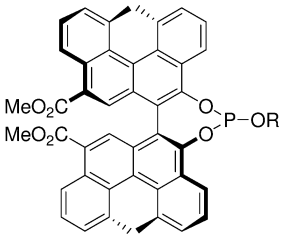
17aa R^1 = H, R^2 = Me
ab R^1 = H, R^2 = Et
ac R^1 = H, R^2 = Ph
ad R^1 = H, R^2 = ^{i}Pr
ae R^1 = H, R^2 = *c*-C_5H_9
af R^1 = H, R^2 = *c*-C_6H_{11}
ag R^1 = H, R^2 = Bn
ah R^1 = H, R^2 = ^{t}Bu
ai R^1 = H, R^2 = ^{i}Bu [(*R*)-BINOL]
aj R^1 = H, R^2 = 9-Fluorenyl
ak R^1 = H, R^2 = $CH_2C(CH_3)_3$ [(*R*)-BINOL]
al R^1 = H, R^2 = $CH_2CH(C_2H_5)_2$ [(*R*)-BINOL]
am R^1 = H, R^2 = ^{i}Bu
an R^1 = H, R^2 = (*S*)-^{i}Bu [(*R*)-BINOL]
ao R^1 = H, R^2 = (*S*)-$CH_2CH(CH_3)C_2H_5$
ap R^1 = H, R^2 = (*S*)-$CH_2CH(CH_3)C_2H_5$ [(*R*)-BINOL]
aq R^1 = H, R^2 = (*R*)-$CH(CH_3)Ph$
ar R^1 = H, R^2 = (*S*)-$CH(CH_3)Ph$
as R^1 = H, R^2 = (*rac*)-$CH(CH_3)Ph$
at R^1 = H, R^2 = (*S*)-$CH(OCH_3)Ph$
au R^1 = H, R^2 = $CH_2CH_2N[CH(CH_3)_2]_2$
av R^1 = H, R^2 = $CH_2CH_2OCH_3$

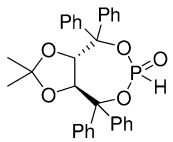
17aw R^1 = H, R^2 = $CH_2CH_2OCH_3$ [(*R*)-BINOL]
ax R^1 = H, R^2 = CH_2CH_2Cl [(*R*)-BINOL]
ay R^1 = H, R^2 = CH_2CCl_3 [(*R*)-BINOL]
az R^1 = H, R^2 = 2-Br-Ph
ba R^1 = H, R^2 = 2,6-(CH_3)-Ph
bb R^1 = H, R^2 = 2,6-$(Ph)_2$-Ph
bc R^1 = H, R^2 = *L*-Menthyl
bd R^1 = H, R^2 = *L*-Menthyl [(*R*)-BINOL]
be R^1 = R^2 = H
bf R^1 = H, R^2 = $C(O)CH_3$ [(*R*)-BINOL]
bg R^1 = H, R^2 = C(O)Ph [(*R*)-BINOL]
bh R^1 = H, R^2 = see below [(*R*)-BINOL]
bi R^1 = H, R^2 = see below
bj R^1 = Br, R^2 = C(O)Ph [(*R*)-BINOL]
bk R^1 = Me, R^2 = C(O)Ph [(*R*)-BINOL]
bl R^1 = Ph, R^2 = C(O)Ph [(*R*)-BINOL]
bm R^1 = $SiMe_3$, R^2 = C(O)Ph [(*R*)-BINOL]

OR^2 in **17bh**, **17bi** =



19a (*M*,*M*,*S*,*L*), R = *L*-Menthyl
b (*M*,*M*,*S*,*S*), R = 1-(*S*)-Phenylethyl
c (*M*,*M*,*S*,*R*), R = 1-(*R*)-Phenylethyl
d (*M*,*M*,*R*,*S*), R = 1-(*S*)-Phenylethyl
e (*M*,*M*,*R*,*R*), R = 1-(*R*)-Phenylethyl



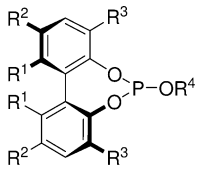


20

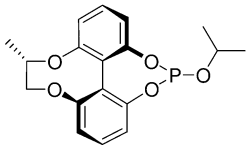
Scheme 28.6 Monodentate phosphite ligands derived from BINOL or related diols.

2:1 complexation of **21 ac** with rhodium resulted in a 5:1 diastereomeric mixture of $[Rh(\mathbf{21ac})_2COD]BF_4$. Within the two complexes, the bisphenol part of the ligands has the same conformation, and no complexes were found in which the two bisphenol parts have different conformations.

The axially chiral ligands **21 ak–21 ba** were recently reported by Ojima et al. [50]. In addition, the group of Driessen-Hölscher prepared a series of monodentate phosphites based on 5-Cl-6-MeO-bisphenol (**21 bb–21 bf**) [51]. Both series of ligands are successful. The use of phosphite ligand **22**, which has a chiral diol

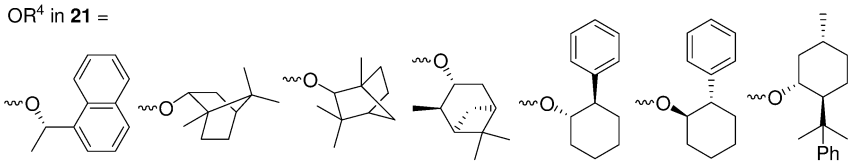


21aa-ad $R^1 = R^2 = R^3 = H$, R^4 = see below
ae-ah $R^1 = H$, $R^2 = R^3 = {}^t$Bu, R^4 = see below
ai $R^1 = R^2 = R^3 = H$, R^4 = *L*-Menthyl
aj $R^1 = H$, $R^2 = R^3 = {}^t$Bu, R^4 = *L*-Menthyl
ak $R^1 = R^2 = Me$, $R^3 = H$, $R^4 = Ph$
al $R^1 = R^2 = Me$, $R^3 = {}^t$Bu, $R^4 = Ph$
am $R^1 = R^2 = Me$, $R^3 = H$, R^4 = 2-naphthyl
an $R^1 = R^2 = Me$, $R^3 = {}^t$Bu, R^4 = 2-naphthyl
ao $R^1 = R^2 = Me$, $R^3 = H$, R^4 = see below
ap $R^1 = R^2 = Me$, $R^3 = {}^t$Bu, R^4 = see below
aq $R^1 = R^2 = Me$, $R^3 = H$, R^4 = see below
ar $R^1 = R^2 = R^3 = Me$, R^4 = see below
as $R^1 = R^2 = Me$, $R^3 = Br$, R^4 = see below
at $R^1 = R^2 = Me$, $R^3 = {}^t$Bu, R^4 = see below
au $R^1 = R^2 = Me$, $R^3 = Ph$, R^4 = see below
av $R^1 = R^2 = Me$, $R^3 = H$, R^4 = *L*-Menthyl
aw $R^1 = R^2 = Me$, $R^3 = {}^t$Bu, R^4 = *L*-Menthyl
ax $R^1 = R^2 = Me$, $R^3 = {}^t$Bu, R^4 = see below
ay $R^1 = R^2 = Me$, $R^3 = H$, R^4 = *L*-Menthyl [(*R*)-biphenyl]
az $R^1 = R^2 = Me$, $R^3 = {}^t$Bu, R^4 = *L*-Menthyl [(*R*)-biphenyl]
ba $R^1 = R^2 = Me$, $R^3 = {}^t$Bu, R^4 = see below [(*R*)-biphenyl]
bb $R^1 = OMe$, $R^2 = Cl$, $R^3 = H$, $R^4 = {}^i$Pr
bc $R^1 = OMe$, $R^2 = Cl$, $R^3 = H$, $R^4 = Cy$
bd $R^1 = OMe$, $R^2 = Cl$, $R^3 = H$, R^4 = (*R*)-Phenethyl
be $R^1 = OMe$, $R^2 = Cl$, $R^3 = H$, $R^4 = Ph$
bf $R^1 = OMe$, $R^2 = Cl$, $R^3 = H$, R^4 = 2,6-$(CH_3)_2$-Ph



22

OR^4 in **21** =



aa, ae **ab, af** **ac, ag** **ad, ah** **ao, ap** **aq - au** **ax, ba**

Scheme 28.7 Monodentate phosphite ligands derived from bisphenol.

bridging the 6,6′ position of the bisphenol backbone locking its conformation, was reported recently [52]. The use of **22** resulted in an excellent *e.e.* of 96% in the hydrogenation of dimethyl itaconic acid.

In general, the results obtained with monodentate ligands based on bisphenol are comparable to those obtained using ligands based on BINOL. Large substituents on the 3,3′-positions of the bisphenol results in lower ee-values. In some cases even the absolute configuration of the products is reversed. This is unfortunate, as bulky substituents on the 3,3′-positions increase the stability of the ligands towards hydrolysis, though the rate of the hydrogenation is not greatly influenced. The result of hydrogenations using these ligands is very solvent-dependent. The preferred solvents are dichloromethane and 1,2-dichloroethane, but when other solvents such as tetrahydrofuran, methanol, ethyl acetate or

chloroform are used, no enantioselectivity is observed. The factor determining the configuration of the product is, as in the case using BINOL-based ligands, the configuration of the biaryl moiety.

Rhodium-catalyzed hydrogenation of enamides has been successfully performed using monodentate phosphites **17**, with enantioselectivities of up to 95% being obtained [53]. The rate of hydrogenation is low; in order to reach full conversion with a SCR of 500, hydrogenation is performed at a pressure of 60 bar for 20 h. The use of ligand **17am** in the rhodium-catalyzed hydrogenation of aromatic enamides resulted in ee-values of up to 95%.

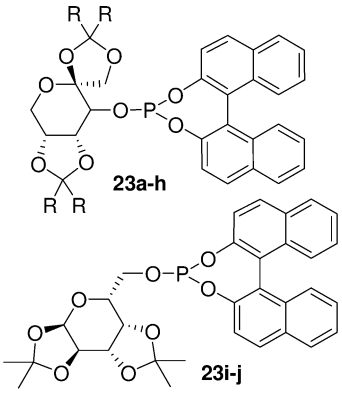
Monodentate phosphites have been used very successfully in the hydrogenation of enol-esters by the group of Reetz [54]. The use of ligands **17** which consist of a BINOL moiety and a simple alcohol gave only moderate results, from 21% to 65% *e.e.* Monodentate phosphite ligands derived from carbohydrates (**23** and **24**), however, afforded considerably higher enantioselectivities in the hydrogenation of enol esters derived from aliphatic alkynes (Scheme 28.8). Especially using an enol ester based on 2-furanoic acid, 90% ee was obtained. Performing the same reaction at –20 °C resulted in an ee of 94%. Thus far, the highest ee-value was obtained using (bidentate) Ru/PennPhos in the hydrogenation of the enol acetate based on 2-hexanone (75%) [55]. As for the *N*-acyl enamides, enol esters are hydrogenated at low rates. To reach full conversion, similar conditions were needed, with a SCR of 200 and a hydrogen pressure of 60 bar for 20 h.

The use of monodentate phosphite ligands in the hydrogenation of *β*-acylamino acrylates, affording derivatives of *β*-amino acids, has been demonstrated by Bruneau et al. [56]. Ligand **17bc** is clearly more effective in the hydrogenation of substrates with an *E*-configuration. In contrast, ligand **17bd**, a diastereomer of **17bc**, affords better results in the hydrogenation of substrates with the *Z*-configuration.

The carbohydrate ligands **23** and **24** were also applied in the hydrogenation of itaconate and enamides [57]. Also here, the configuration of the products is predominantly determined by the configuration of the BINOL moiety in the ligand. An extensive study, including the hydrogenation of *N*-acyl *β*-dehydroamino esters, using carbohydrate-derived monophosphites (also **25** and **26**) was recently reported by Zheng et al. [58].

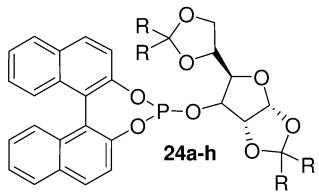
Very recently, the group of Reetz published details of a monodentate phosphite ligand **27** (together with a large number of comparable phosphoramidite ligands) in which the BINOL unit bears a single *ortho*-substituent. This creates an additional stereocenter at phosphorus, which leads to mixtures of diastereomers. The ligand was found to be very successful in the hydrogenation of *N*-acyl dehydroalanine methyl ester [59].

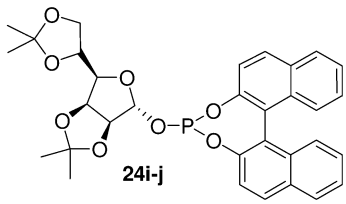
As described for monodentate phosphonite ligands, monodentate phosphite ligands have also been used in a monodentate ligand combination approach.

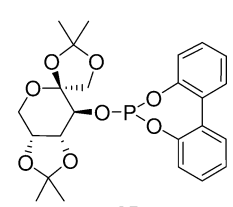


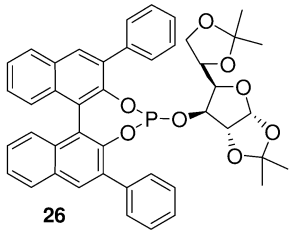
23a 4-(*S*), R = CH_3, (*R*)-BINOL
b 4-(*S*), R = CH_3, (*S*)-BINOL
c 4-(*S*), R = -$(CH_2)_5$-, (*R*)-BINOL
d 4-(*S*), R = -$(CH_2)_5$-, (*S*)-BINOL
e 4-(*R*), R = CH_3, (*R*)-BINOL
f 4-(*R*), R = CH_3, (*S*)-BINOL
g 4-(*R*), R = -$(CH_2)_5$-, (*R*)-BINOL
h 4-(*R*), R = -$(CH_2)_5$-, (*S*)-BINOL
i (*R*)-BINOL
j (*S*)-BINOL

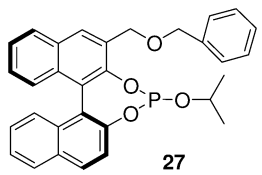
24a 3-(*S*), R = CH_3, (*R*)-BINOL
b 3-(*S*), R = CH_3, (*S*)-BINOL
c 3-(*S*), R = -$(CH_2)_5$-, (*R*)-BINOL
d 3-(*S*), R = -$(CH_2)_5$-, (*S*)-BINOL
e 3-(*R*), R = CH_3, (*R*)-BINOL
f 3-(*R*), R = CH_3, (*S*)-BINOL
g 3-(*R*), R = -$(CH_2)_5$-, (*R*)-BINOL
h 3-(*R*), R = -$(CH_2)_5$-, (*S*)-BINOL
i (*R*)-BINOL
j (*S*)-BINOL











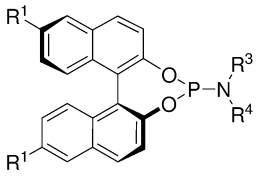
Scheme 28.8 Monodentate phosphite ligands based on carbohydrates.

28.5
Monodentate Phosphoramidites

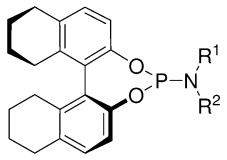
The use of monodentate phosphoramidites in enantioselective hydrogenation was first reported in 2000, together with reports on the use of phosphites and phosphonites [15]. Phosphoramidites are prepared in a variety of ways, but the most common route is the treatment of a diol with PCl_3, followed by addition of an amine [60, 61]. MonoPhos (**29a**), the first reported phosphoramidite used as a ligand, is prepared from BINOL and HMPT in toluene [62]. Phosphoramidites, especially

those based on BINOL, have the distinct advantage of being resistant to water and oxygen (Scheme 28.9). Although sensitive to acidic conditions, this is hardly a handicap as their rhodium complexes are considerably less sensitive. This is revealed in the successful hydrogenation of dehydroamino acids. Together with their ease of preparation – mostly in one or two steps – this feature makes them very versatile, and has been employed successfully in HTE using ligands of phosphoramidites and in the use of ligand-mixtures (see Chapter 36).

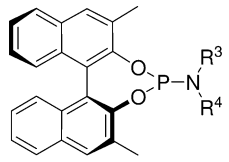
The majority of the reported phosphoramidite ligands consist of BINOL and a diversity of readily available amines. Excellent enantioselectivities in the hydrogenation of *a*- and *β*-dehydroamino acids, itaconates and enamides [63, 64] have been reported. In a recent full report, the group of Minnaard, De Vries and Feringa noted that especially the BINOL-derived ligands containing a piperidine or



29a $R^1 = R^2 = H$, $R^3 = R^4 = Me$ (MonoPhos)
b $R^1 = R^2 = H$, $R^3 = R^4 = Et$
c $R^1 = R^2 = H$, $R^3 = R^4 = n$-Pr
d $R^1 = R^2 = H$, $R^3 = Me$, $R^4 = Bn$
e $R^1 = R^2 = H$, $R^3 = Me$, $R^4 = (R)$-$CH(CH_3)Ph$
f $R^1 = R^2 = H$, $R^3 = R^4 = (S)$-$CH(CH_3)Ph$
g $R^1 = R^2 = H$, $R^3 = H$, $R^4 = (R)$-$CH(CH_3)Ph$
h **ha - hl** $R^1 = R^2 = H$, R^3 - R^4 = see below
j $R^1 = Br$, $R^2 = H$, $R^3 = R^4 = Me$
k $R^1 = R^2 = R^3 = H$, R^4 = 4-vinylphenyl
l $R^1 = R^2 = R^3 = H$, R^4 = 8-quinoline
m $R^1 = R^2 = R^3 = H$, R^4 = 2-MeO-C_6H_4
n $R^1 = R^2 = H$, R^3 = 2-MeO-C_6H_4, R^4 = 4-vinylphenyl
o $R^1 = C_6F_{13}$, $R^2 = H$, $R^3 = Me$

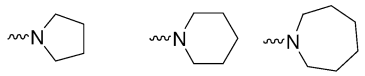


30a $R^1 = R^2 = Me$
b $R^1 = R^2 = Et$
c $R^1 = H$, $R^2 = (R)$-$CH(CH_3)Ph$
d $R^1 = Me$, $R^2 = (R)$-$CH(CH_3)Ph$
e **ea - ee** R^1 - R^2 = see below

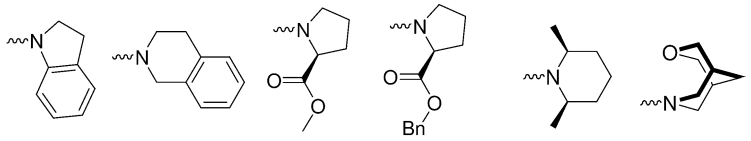


31a $R^1 = R^2 = Me$
b,c,d see below

NR^3R^4 in **29, 30** =



29ha **31b**
29hb (PipPhos) **30ea** **31c**
29hc **30eb**
29hd (MorfPhos) **30ec** **31d**
29he
29hf **30 ed**



29hg
29hh **30ee**
29hi
29hj
29hk
29hl

Scheme 28.9 Monodentate phosphoramidites based on BINOL.

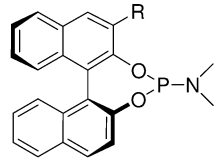
a morpholine substituent (PipPhos **29hb** and MorfPhos **29hd**, respectively) are the most privileged ligands [65]. Variations on this theme comprise the use of substituted BINOLs and octahydro-BINOL (H_8-BINOL) [17, 66]. In some cases these ligands afford higher ee-values. Very recently, it was shown that enol acetates and enol carbamates can also be hydrogenated, with excellent ee-values to the corresponding alcohol derivatives using PipPhos **29hb** [67]. Phosphoramidite ligand **29hl**, based on a combination of BINOL and oxa-bispidine, has been reported by the group of Waldmann [68].

Very recently, Reetz, Ma and Goddard reported phosphoramidites based on BINOL bearing a single *ortho*-substituent (Scheme 28.10) [69]. These ligands are also chiral on phosphorus, such that the synthesis results mostly in diastereomers which have to be separated. In several cases, however, one of the diastereomers was formed exclusively. Some of the ligands afford high ee-values in the hydrogenation of methyl *N*-acyl dehydroalanine and dimethyl itaconate.

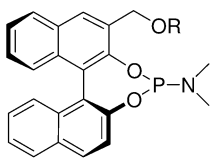
Zhou et al. have reported extensively on the use of a spiro-biindanediol as the backbone in the ligands **35a–f** (Scheme 28.11, SIPHOS) [70]. Excellent results are obtained for a variety of substrates, and recently a full report has appeared on the use of these ligands [71]. Synthesis of the diol backbone requires a number of steps, including a resolution [72]. An additional and successful spiro-diol-derived phosphoramidite **39** has recently been disclosed by the group of Zhang [73].

Phosphoramidite ligands based on TADDOL (**36**) and on D-mannitol (**37**) [74] have also been used (Scheme 28.11). However, the enantioselectivities reported for the hydrogenation of α-dehydroamino acids and itaconates were generally lower compared to the ligands based on BINOL. A different strategy is the use of ligands **38a–g** based on the achiral diol catechol, and chiral amines [75].

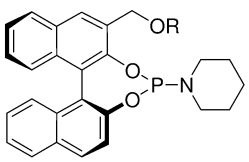
The rate of hydrogenation of dehydroamino acids using [Rh(MonoPhos)$_2$-COD]BF_4 is not very high at 1 bar of hydrogen, though this can be overcome by applying higher pressure. Reactions performed with 5 bar reach TOFs of 200 to 600 mol mol$^{-1}\cdot$h. This increase in rate also allows for a reduction in the amount of catalyst needed to about 0.02–0.1 mol%. The increase in hydrogen pressure, up to 100 bar, does not affect the enantioselectivity; this is in contrast to the de-



32a R = Me
b R = Ph
c R = SPh
d R = $SiMe_3$
e R = $SiPh_3$

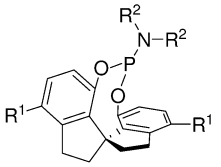


33a R = C(O)Ph
b R = Me
c R = Bn

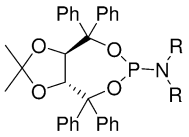


34a R = C(O)Ph
b R = Me
c R = Bn

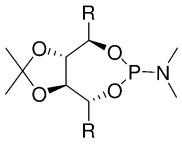
Scheme 28.10 Monodentate phosphoramidites based on monosubstituted BINOL.



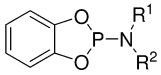
35a R^1 = H, R^2 = Me (SIPHOS)
b R^1 = H, R^2 = Et
c R^1 = H, R^2 = ^{i}Pr
d R^1 = H, R^2 = -$(CH_2)_4$-
e R^1 = Br, R^2 = Me
f R^1 = Ph, R^2 = Me
g R^1 = OMe, R^2 = Me



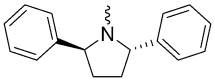
36a R = ^{i}Pr
b R = Bn



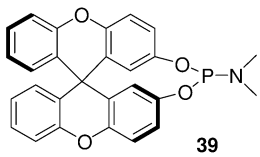
37a R = H
b R = Me
c R = Et
d R = ^{i}Bu
e R = Ph
f R = Me (*S*,*S*,*S*,*S*)
g R = Ph (*S*,*S*,*S*,*S*)



NR^{1}R^2 in **38g** =



38a R^1 = (*S*)-$CH(CH_3)Ph$, R^2 = H
b R^1 = (*S*)-$CH(CH_3)Ph$, R^2 = Me
c R^1 = (*S*)-$CH(CH_3)Ph$, R^2 = Et
d R^1 = (*R*)-$CH(CH_3)Ph$, R^2 = ^{i}Pr
e R^1 = (*S*)-$CH(CH_3)Ph$, R^2 = Bn
f R^1 = (*S*)-$CH(CH_3)Ph$, R^2 = (*S*)-$CH(CH_3)Ph$
g R^1 - R^2 = see above



39

Scheme 28.11 Phosphoramidite ligands based on alternative backbones.

crease in *e.e.* which is seen upon increasing hydrogen pressure when using most bidentate ligands, and is a distinct advantage.

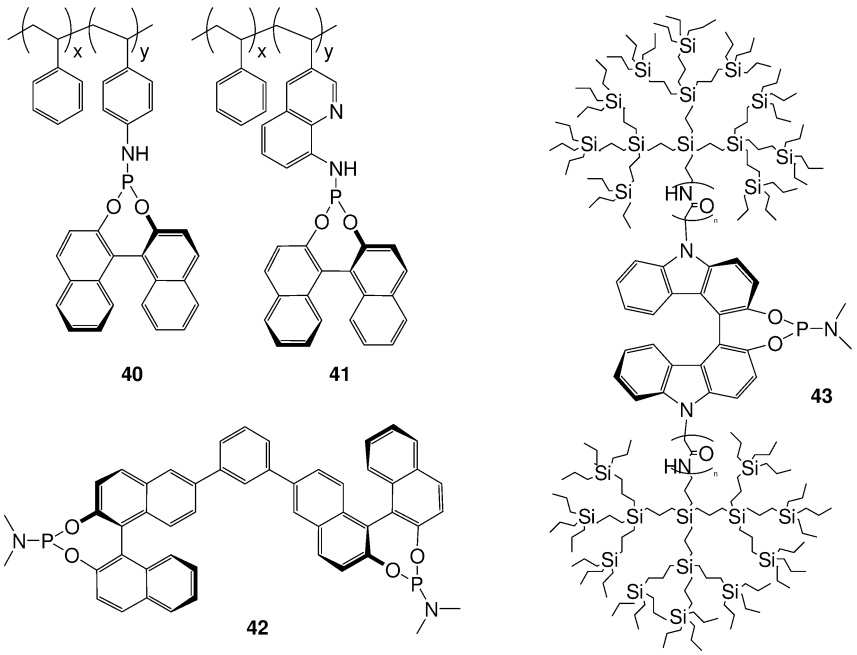
Initially, it was not clear whether monodentate ligands could, apart from enantioselectivity, compete with the established bidentate ligands. Activity and stability of the catalyst are also important parameters. Using MonoPhos **29a** and related phosphoramidites, it has been shown that monodentate ligands can (at least in a number of cases) keep up with the best bidentate ligands. Itaconic acid has been hydrogenated using $[Rh(MonoPhos)_2COD]BF_4$ at a SCR of 10 000 on 100-g scale. This reaction gave full conversion in 3 h, with 97.5% *e.e.* [76]. In the hydrogenation of *β*-dehydroamino esters, the reaction rates of MonoPhos **29a** and **29g** were compared with the bidentate ligands DuPhos, JosiPhos and PhanePhos; subsequently, the reactions with ligand **29g**, together with DuPhos, proved to be the fastest [16].

Monodentate phosphoramidite ligands were also employed in the rhodium-catalyzed hydrogenation of enamides. These hydrogenations generally require longer reaction times and higher hydrogen pressures (e.g., 1 to 20 h at 10 to 20 bar with 0.1–2 mol% catalyst). Good to excellent enantioselectivities are obtained using a variety of phosphoramidites. Very high enantioselectivities were reached using PipPhos **29hb**, MorfPhos **29hd** and members of the SIPHOS family.

Phosphoramidite ligands have also been very successful in the asymmetric hydrogenation of *β*-dehydroamino esters. As with bidentate ligands, there is a large difference in behavior during hydrogenation of the *E*- and *Z*-substrates. The *E*-isomer is generally hydrogenated more easily, and with a higher ee-value. However, by varying the ligand's structure and solvent, both *E*- and *Z*-*β*-dehydroamino esters could be hydrogenated with excellent ee-values using **29d** and **29g**, thereby surpassing – at that time – the bidentate ligands [77]. Recently, the SIPHOS ligands have also been shown as successful in the hydrogenation of *E*- and *Z*-*β*-dehydroamino esters.

Since monodentate phosphoramidites are so successful in asymmetric hydrogenation – both because of their performance and their ease of preparation – a logical extension is their application in recyclable systems. Doherty et al. were the first to prepare polymer-supported phosphoramidites by using the monomers **40** and **41** (Scheme 28.12); these led to high ee-values which fell somewhat upon polymerization [78]. The catalyst was shown to be capable of being recycled at least four times.

One highly successful approach was demonstrated by Ding et al., using self-supporting heterogeneous catalysts consisting of ligands such as **42** to create a polymer-type catalyst [79]. Both "dents" in the ligand coordinate to different rhodium ions. The results obtained using this self-supporting catalyst were comparable or better than those obtained using the analogous monomers. The reusability of the catalyst was at least seven cycles.



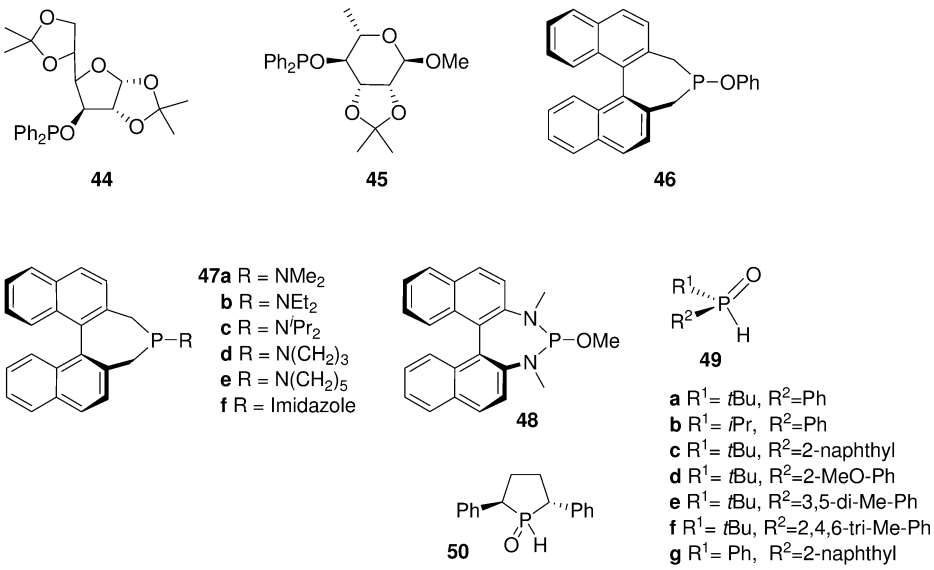
Scheme 28.12 Immobilized phosphoramidite ligands.

The immobilization of catalysts on a solid support is a well-known approach to render a system recycleable, and this has been performed recently by the immobilization of rhodium-MonoPhos **29a** on aluminosilicate AlTUD-1. The resultant system showed high efficiency in water, and could be recycled [80].

Another way of retaining the catalyst is to create dendrimer-supported ligands, thereby allowing separation of the product and catalyst by membranes. Based on the readily modified BICOL backbone, two dendrimer-ligands **43** were prepared that had performance comparable to that of MonoPhos **29a** in the hydrogenation of methyl *N*-acyl dehydrophenylalanine [81].

28.6
Monodentate Phosphinites, Aminophosphinites, Diazaphospholidines and Secondary Phosphine Oxides

In the quest for effective ligands in enantioselective hydrogenation, a number of groups have varied the atoms surrounding the phosphorus atom in order to develop new and hopefully successful ligands. An additional argument for ligand development is to circumvent existing patent literature. Next to phosphines, phosphonites, phosphites and phosphoramidites, attention has been paid to monodentate phosphinites. Surprisingly, as early as 1986 an excellent ee was reported in the hydrogenation of dimethyl itaconate using phosphinite **45** (Scheme 28.13) [82]. Most likely because ee-values were determined somewhat



44 45 46 47a–f 48 49 50

Scheme 28.13 Monodentate phosphinites, aminophosphinites, diazaphospholidines and secondary phosphine oxides.

inaccurately by measuring optical rotations, this result was generally overlooked. Nevertheless, it must be considered as an early example of a successful monodentate ligand. Other monodentate phosphinites, **44** and the recently reported **46** [83], were much less successful. Although phosphinites are rather stable in air, rapid hydrolysis takes place in the presence of moisture.

Monodentate aminophosphines **47** have been developed recently in analogy to the other BINOL-based ligands and related bidentate aminophosphines. Although the scope of these ligands has not been studied in depth, good ee-values can be obtained in rhodium-catalyzed enantioselective hydrogenation [84]. One recent study reports the preparation and use of diazaphospholidine **48** as a logical extension of the BINOL-based phosphites and phosphoramidites [85]. This ligand has not yet been studied in depth, mainly because the synthesis is rather laborious and the ligand is sensitive to hydrolysis.

Secondary phosphine oxides are known to be excellent ligands in palladium-catalyzed coupling reactions and platinum-catalyzed nitrile hydrolysis. A series of chiral enantiopure secondary phosphine oxides **49** and **50** has been prepared and studied in the iridium-catalyzed enantioselective hydrogenation of imines [48] and in the rhodium- and iridium-catalyzed hydrogenation functionalized olefins [86]. Especially in benzyl substituted imine-hydrogenation, **49a** ranks among the best ligands available in terms of *e.e.*

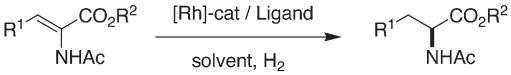
28.7
Hydrogenation of N-Acyl-α-Dehydroamino Acids and Esters

The hydrogenation of methyl *N*-acyl-dehydrophenylalanine **52a** and methyl *N*-acyl-dehydroalanine **53a** to their corresponding amino acid derivatives **54a** and **55a** are the benchmark reactions for rhodium-catalyzed enantioselective hydrogenation. Most newly developed ligands are tested in the hydrogenation of these substrates, and good enantioselectivities are often obtained. As the number of reports is overwhelming, a selection of the results is presented in Table 28.1. Only ligands that afford ee-values of 95% and higher have been included.

It transpires that most classes of monodentate ligands include members that are able to induce high enantioselectivity in the hydrogenation of the two benchmark substrates **52a** and **53a**. It is not clear whether their corresponding acids **52b** and **53b** have been studied or, alternatively, if the authors decided not to include (disappointing) ee-values. For phosphoramidite MonoPhos (**29a**), however, the ee-values are invariably excellent. Overall, the TOFs range from 50 to 170 h^{-1}, but have not been optimized in most cases. Unfortunately, with one exception [87], the hydrogenation of dehydroamino esters in which R^1 is a (functionalized) alkyl substituent has not been studied, probably because of their difficult accessibility.

As the hydrogenation of substituted dehydrophenylalanines is important from an industrial point of view, and the substrates are easily accessible, some phosphoramidites have been screened against a series of these substrates. According

Table 28.1 Enantioselective hydrogenation of *N*-acyl-dehydrophenylalanine and *N*-acyl-dehydroalanine.



52a R^1 = Ph, R^2 = Me
52b R^1 = Ph, R^2 = H
53a R^1 = H, R^2 = Me
53b R^1 = H, R^2 = H

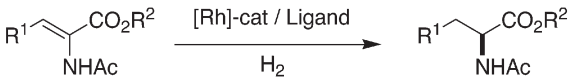
54a R^1 = Ph, R^2 = Me
54b R^1 = Ph, R^2 = H
55a R^1 = H, R^2 = Me
55b R^1 = H, R^2 = H

Entry	Ligand	54a (54b) ee [%]	55a (55b) ee [%]
1	**10d** [h]	95	67
2	**10h** [h]	95	94
3	**15b** [a]	89	94
4	**17ac** [b]		95
5	**17ae** [b]		97
6	**17af** [b]		95
7	**17ah** [b]		95
8	**17am** [b]		96
9	**17an** [b]		96
10	**17aq** [b]		96
11	**17at** [b]		96
12	**29a** [c]	97 (97)	>99 (>99)
13	**29b** [d]	98	97
14	**29hb** [g]	>99	>99
15	**29hc** [g]	97	97
16	**29hd** [g]	98	99
17	**29hf** [g]	97	96
18	**29hh** [g]	99	99
19	**30a** [e]	94	>99
20	**30ea** [g]	>99	97
21	**30eb** [g]	96	
22	**30ec** [g]	99	95
23	**30ed** [g]	99	96
24	**30ee** [g]	98	96
25	**35a** [f]	98	97
26	**35d** [f]	98	
27	**35e** [f]	98	
28	**35f** [f]	97	
29	**33a** [i]		>98
30	**33b** [i]		>98
31	**39** [j]	98	98

a) Reactions carried out with SCR 500, in CH_2Cl_2, $p(H_2) = 1.5$ bar, 25 °C, 3 h.
b) Reactions carried out with SCR 1000, in CH_2Cl_2 or $ClCH_2CH_2Cl$, $p(H_2) = 1.3$ bar, 25 °C, 20 h.
c) Reactions carried out with SCR 100 or 1000, in CH_2Cl_2 or EtOAc, $p(H_2) = 1$ bar, 25 °C, 1–3 h.
d) Reactions carried out in THF.
e) Reactions carried out in acetone.
f) Reactions carried out in toluene.
g) Reactions carried out with SCR 50, in CH_2Cl_2, $p(H_2) = 5$ bar, 25 °C, 3 h.
h) Reactions carried out with SCR 100, in toluene + SDS, $p(H_2) = 1$ bar, 25 °C, t/2 = 0.5–3 h.
i) Reactions carried out with pure diastereomers, SCR 200, in CH_2Cl_2, $p(H_2) = 1.3$ bar, 20 h.
j) Reactions carried out with SCR 100, in CH_2Cl_2, $p(H_2) = 1.3$ bar, r.t., 12 h.

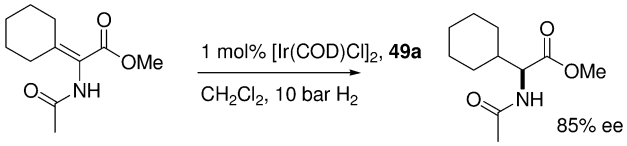
to the data in Table 28.2, it is safe to assume that a large variety of sterically and electronically different substituents are tolerated without repercussions on the ee-value. This also leads to the assumption, for example, that the recently developed PipPhos **29hb** and MorfPhos **29hd**, being the second generation of MonoPhos **29a**, will perform very well. On average, TOFs using MonoPhos **29a** are around 500 h^{-1} at 5 bar, increasing to 1700 h^{-1} at 60 bar. In the case of a cyano substituent, a strongly decreased rate was observed, probably because of coordination of this group to rhodium. For SIPHOS **35** and **39**, the TOFs are about 50 to 100 h^{-1} at 1 bar.

Table 28.2 Enantiomeric hydrogenation of substituted methyl *N*-acyl-dehydrophenylalanine.



Entry	Substituent	29a	29b	30a	35a	39
1	R^1 = 3-MeO-Ph, R^2 = Me	97				
2	R^1 = 4-MeO-Ph, R^2 = Me	94	99	94	96	
3	R^1 = 3-MeO-4-AcO-Ph, R^2 = Me	96		96		
4	R^1 = 4-F-Ph, R^2 = Me	96	>99			>99
5	R^1 = 4-F-Ph, R^2 = H	93				
6	R^1 = 3-F-Ph, R^2 = Me	95				
7	R^1 = 3-F-Ph, R^2 = H	96				
8	R^1 = 2-F-Ph, R^2 = Me	95				
9	R^1 = 4-Cl-Ph, R^2 = Me	94	99	98	99	99
10	R^1 = 4-Cl-Ph, R^2 = H			83		
11	R^1 = 3,4-Cl_2-Ph, R^2 = H	97				
12	R^1 = 3,4-Cl_2-Ph, R^2 = Me	99				
13	R^1 = 3-NO_2-Ph, R^2 = Me	95			99	
14	R^1 = 4-NO_2-Ph, R^2 = Me	95	>99	96	99	
15	R^1 = 3-NO_2-4-F-Ph, R^2 = Me	95				
16	R^1 = 4-biphenyl, R^2 = Me	95				
17	R^1 = 3-F-4-biphenyl, R^2 = Me	93				
18	R^1 = 4-Ac-Ph, R^2 = Me	99	99			
19	R^1 = 4-Bz-Ph, R^2 = Me	94				
20	R^1 = 4-CN-Ph, R^2 = Me	92[a)]				
21	R^1 = 1-naphthyl, R^2 = Me	93				
22	R^1 = 4-Br-Ph, R^2 = Me		99	91		
23	R^1 = 2-Cl-Ph, R^2 = Me		99	93	97	99
24	R^1 = 3-Cl-Ph, R^2 = Me		99			
25	R^1 = 3-Cl-Ph, R^2 = H			74		
26	R^1 = 4-Me-Ph, R^2 = Me		98		98	
27	R^1 = 3-Br-Ph, R^2 = Me					>99
28	R^1 = 2-naphthyl, R^2 = Me					>99

a) Very slow reaction was observed.



Scheme 28.14 Enantioselective hydrogenation of methyl *N*-acyl dehydrocyclohexylglycine.

Studies have been limited to substrates containing the *N*-acyl or *N*-benzoyl stereodirecting groups. On occasion, for further synthetic applications, a carbamate protecting group is preferred [88]. Substrates possessing two substituents at the *β*-position have also been ignored, with one exception (Scheme 28.14) [84]. In that report, secondary phosphine oxide **49a** induced 85% ee in the iridium-catalyzed hydrogenation of methyl *N*-acyl dehydrocyclohexylglycine, with a low TOF (1 h^{-1}). This (sub)class of substrates clearly deserves further investigation, as the number of bidentate ligands that induces excellent enantioselectivity is also limited.

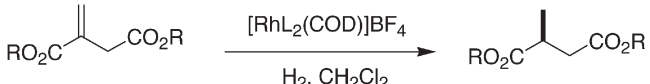
28.8 Hydrogenation of Unsaturated Acids and Esters

Next to the hydrogenation of *α*-dehydroamino acids and esters, the hydrogenation of itaconic acid **56** and its corresponding dimethyl ester **57** is considered to be a benchmark reaction. In addition, the substrates are cheap and the products are valuable intermediates in natural product synthesis. A large number of monodentate ligands has been reported to give good and often excellent results in the hydrogenation of itaconic acid and its corresponding dimethyl ester; hence, only a selection is provided here.

All classes of ligands have members that perform well, although excellent ee-values are rare when phosphines are used, with the exception of ligand **9f** developed by the group of Helmchen. A large number of phosphite ligands has been explored, and both ligands based on BINOL and bisphenols give excellent ee-values. Only **57** has been used as a substrate, and not itaconic acid **56**. Phosphoramidites also perform extremely well, especially PipPhos **29hb**, MorfPhos **29hd**, and related ligands. One remarkable finding was the 100-g scale hydrogenation of itaconic acid **56** using a SCR of 10 000 (TOF 5000 h^{-1}) with MonoPhos **29a** at high pressure, giving quantitative yield and 97% ee [89] (Table 28.3). An even more impressive result was the hydrogenation of **57** with a S/C of 10 000 (TOF 40 000 at 20 bar, 98% ee) when applying phosphite **18a**. As mentioned previously, phosphinite **45** is an early example of a successful monodentate ligand in the hydrogenation of dimethyl itaconate. On average, TOFs range from 20 to 50 h^{-1} at 1 bar, and to 1300 h^{-1} at 10 bar.

Although some attention has been paid to the hydrogenation of *β*-substituted itaconates, that can be prepared by Stobbe condensation, this class of com-

Table 28.3 Enantioselective hydrogenation of itaconic acid and its dimethyl ester.



56 R = H
57 R = Me

58 R = H
59 R = Me

Entry	Ligand	58 [%]	59 [%]	Entry	Ligand	58	59
1	**9f**[a]	96		25	**21bd**[d]		99
2	**17ac**[b]		98	26	**22**[d]		96
3	**17ad**[b]		99	27	**23e**[e]		>99
4	**17ae**[b]		99	28	**23f**[e]		99
5	**17af**[b]		97	29	**23g**[e]		99
6	**17ai**[b]		99	30	**24b**[e]		99
7	**17aj**[b]		96	31	**24d**[e]		97
8	**17am**[b]		99	32	**29a**[f]	97	94
9	**17an**[b]		99	33	**29hb**[g]		99
10	**17ap**[b]		97	34	**30ea**[g]		99
11	**17aq**[b]		99	35	**29hd**[g]		98
12	**17ar**[b]		99	36	**30ec**[g]		98
13	**17as**[b]		99	37	**30ed**[g]		99
14	**17aw**[b]		95	38	**29hh**[g]		97
15	**17bc**[b]		95	39	**30ee**[g]		95
16	**17bh**[b]		95	40	**33a**[h]		96
17	**17bi**[b]		98	41	**33b**[h]		95
18	**18a**[b]		99	42	**33c**[h]		96
19	**18b**[b]		98	43	**34a**[h]		96
20	**21ak**[c]		97	44	**34b**[h]		96
21	**21am**[c]		96	45	**34c**[h]		97
22	**21as**[c]		97	46	**45**		99
23	**21au**[c]		98				
24	**21bb**[d]		97				

a) Reactions carried out with SCR 500, in CH_2Cl_2, $p(H_2) = 1.1$ bar, 20 °C, 24 h.
b) Reactions carried out with SCR 1000, in CH_2Cl_2, $p(H_2) = 1.3$ bar, 20 °C, 20 h.
c) Reactions carried out with SCR 200, in CH_2Cl_2 or CH_2ClCH_2Cl, $p(H_2) = 7$ bar, 25 °C, 20 h. In some cases $[Rh(COD)_2]SbF_6$ was used instead of $[Rh(COD)_2]BF_4$ at 50 °C.
d) Reactions carried out with SCR 1000, in CH_2Cl_2, $p(H_2) = 3$ bar, 25 °C, 20 h. $[Rh(COD)_2]SbF_6$ was used instead of $[Rh(COD)_2]BF_4$ at 50 °C.
e) Reactions carried out with SCR 100, in CH_2Cl_2, $p(H_2) = 10$ bar, 25 °C, 12 h.
f) The reaction with itaconic acid was carried out on 100-g scale with SCR 10 000, in CH_2Cl_2, $p(H_2) = 100$ bar, 25 °C (at the start of the reaction), 2 h.
g) Reactions carried out with SCR 50, in CH_2Cl_2, $p(H_2) = 5$ bar, 25 °C, 4 h. For **29hb**, reaction carried out with SCR 1000, in CH_2Cl_2, $p(H_2) = 10$ bar, 25 °C, TOF 1300 h^{-1}.
h) Reactions carried out with SCR 200, in CH_2Cl_2, $p(H_2) = 1.3$ bar, 25 °C, 20 h.

pounds seems to have escaped attention in the hydrogenation using monodentate ligands, until now.

In general, unsaturated esters and acids have hardly been studied in rhodium-catalyzed hydrogenation. This is not surprising, as a carbonyl group at a suitable position is generally thought to be essential for obtaining high ee-values [90]. Using monodentate ligands, some studies were performed during the early years of asymmetric hydrogenation, with most providing low ee-values. An exception was the hydrogenation of (*E*)-3,7-dimethyl-2,6-dienoic acid that afforded the product in 79% ee using monophosphine **2f**. All the more surprising, therefore, was a recent study in which tiglic acid and a series of substituted cinnamic acids were hydrogenated using a combination of a monodentate phosphoramidite and a monodentate phosphine [91]. The rates were very high and excellent ee-values were obtained (details of this study are provided in Chapter 36).

28.9 Hydrogenation of *N*-Acyl Enamides, Enol Esters and Enol Carbamates

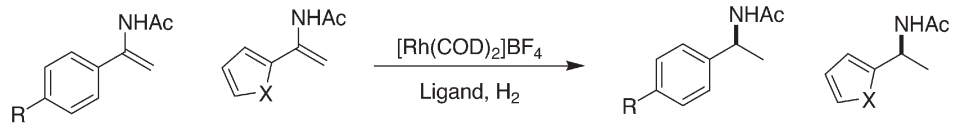
Rhodium-catalyzed enantioselective hydrogenation of *N*-acyl enamides provides access to enantioenriched amides which can be hydrolyzed to the free amines. The synthesis of the substrates is considerably less straightforward than that of *N*-acyl dehydroamino acids, which explains the smaller number of reports devoted to *N*-acyl enamides.

Nevertheless, a number of monodentate ligands have shown good performance in this hydrogenation. A selection of results for the hydrogenation of acyclic terminal enamides is listed in Table 28.4. Only the most successful ligands in terms of ee-value are reported, though both phosphites and phosphoramidites perform very well. The phosphite ligands are based on BINOL, and in particular **23c**, which contains a carbohydrate unit, provides excellent ee-values. As phosphoramidites, PipPhos **29hb**, SIPHOS **35a** and the phosphoramidite ligand based on catechol **38g** are excellent ligands. On average, the TOFs are approximately 25 h^{-1} at pressures of 10 to 25 bar, though PipPhos **29hb** is especially impressive, with a TOF of 250 h^{-1} at 25 bar.

N-Acyl enamides substituted at C2 and cyclic enamides have received considerably less attention. A selection of the results is listed in Table 28.5. Phosphite ligand **23c** appears to be the only ligand that gives excellent ee-values for both **62*Z*** and **62*E*** (the mixture was used). PipPhos **29hb** is the monodentate ligand of choice in the hydrogenation of cyclic enamides, and ranks between the best bidentate ligands that can handle these substrates. Clearly, **63** – and especially **67** – are substrates that escape selective hydrogenation with these ligands, until now. The TOFs generally range from 10 to 25 h^{-1}.

The rhodium-catalyzed enantioselective hydrogenation of enol esters is an alternative to the asymmetric reduction of ketones. Although enol esters are accessible both from ketones and alkynes, the number of studies reporting successful asymmetric hydrogenation has been limited. It appears that, compared

Table 28.4 Enantioselective hydrogenation of acyclic terminal *N*-acyl enamides.



60a R = H
b R = Cl
c R = MeO
d R = CF_3
e 2-naphthyl

60f X = S
g R = O

61a R = H
b R = Cl
c R = MeO
d R = CF_3
e R = 2-naphthyl

61f X = S
g R = O

Entry	Ligand	61a [%]	61b [%]	61c [%]	61d [%]	61e [%]	61f [%]	61g [%]
1	**17ag**[a)]	95				94		
2	**17am**[a)]	95						
3	**23c**[f)]	95	98	96	98	97		
4	**29b**[b)]	97	90	98	99			
5	**29hb**[c)]	99	99	99				
6	**29hd**[c)]	99	99	99				
7	**29hf**[c)]	99	99	98				
8	**30a**[b)]	96	86	92	99			81
9	**30ea**[c)]	98	98	99				
10	**30ec**[c)]	97	97	98				
11	**35a**[d)]	98	99		99		96	99
12	**35d**[d)]	97	99					
13	**35e**[d)]	98	98					
14	**35f**[d)]	95	94					
15	**38g**[e)]	97	94	97				

a) Reactions carried out with SCR 500, in CH_2Cl_2, $p(H_2) = 60$ bar, 30 °C, 20 h.

b) Reactions carried out with SCR 200, in THF, $p(H_2) = 20$ bar, 5 °C, 8 h. More substrates were tested than shown in the table.

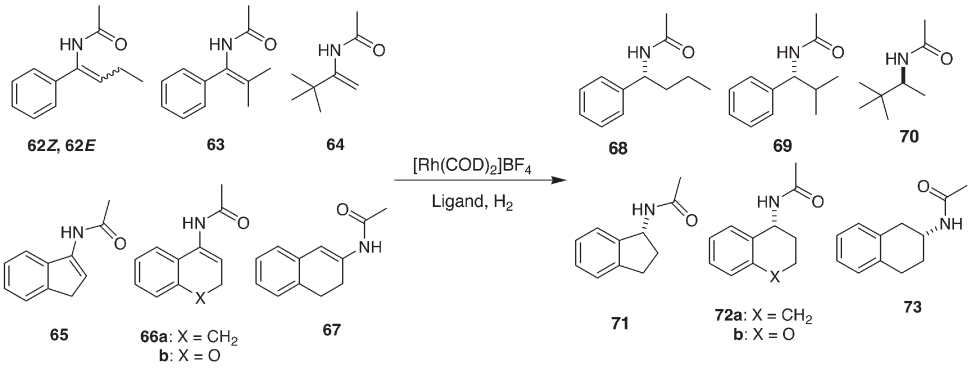
c) Reactions carried out with SCR 50, in CH_2Cl_2, $p(H_2) = 25$ bar, 25 °C, 20 h. One substrate was hydrogenated using **29hb** at SCR 1000 with an overall TOF of 250 h^{-1} giving the same ee and full conversion.

d) Reactions carried out with SCR 100, in toluene, $p(H_2) = 50$ bar, 5 °C, 12 h. More substrates were tested than shown in the table.

e) Reactions carried out with SCR 100, in EtOAc, $p(H_2) = 25$ bar, 25 °C, 16 h. More substrates were tested than shown in the table.

f) Reactions carried out with SCR 100, in CH_2Cl_2, $p(H_2) = 10$ bar, 25 °C, 12 h.

Table 28.5 Enantioselective hydrogenation of cyclic and substituted *N*-acyl enamides.



Entry	Ligand	68 [62*Z*]	68 [62*E*]	69 [%]	70 [%]	71 [%]	72a [%]	72b [%]	73 [%]
1	**17aq** [a]	97	76						
2	**23c** [b]	97	97						
3	**29hb** [c]	96	3	–17	82*	98*	98	99	21
4	**30ea** [c]	97	5	–1	44	82		99	28
5	**29hd** [c]	98	23		27	97*	97*	99	13
6	**30ec** [c]	99	26		13	89	88	99	15
7	**29hf** [c]	98	17		21	87	82	99	8
8	**35a** [d]					94			
9	**38g** [e]	99	88		70		35		9

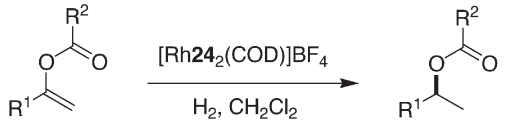
a) Reactions carried out with SCR 500, in CH_2Cl_2, $p(H_2) = 60$ bar, 30 °C, 20 h.
b) Reactions carried out with SCR 100, in CH_2Cl_2, $p(H_2) = 10$ bar, 25 °C, 12 h.
c) Reactions carried out with SCR 50, in CH_2Cl_2, $p(H_2) = 25$ bar, 25 °C, 20 h.
d) Reactions carried out at $p(H_2) = 100$ bar, 0 °C. The 5-bromo- and 6-methoxy-substituted compounds were obtained in 88% and 95% ee, respectively.
e) Reactions carried out with SCR 100, in CH_2Cl_2, $p(H_2) = 25$ bar, 25 °C, 16 h.
* Reactions carried out at –20 °C.

to the corresponding *N*-acyl enamides, the enantioselective hydrogenation of enol esters is considerably more difficult in terms of TOF and *e.e.*. An exception is the hydrogenation of enol esters derived from *α*-keto esters. Nevertheless, a limited number of bidentate ligands have been reported that afford *e.e.*-values >90% in aryl-, vinyl- or trifluoromethyl-substituted enol esters. For alkyl-substituted enol esters, the *e.e.*-values have only been moderate [92].

Reetz and Goossen et al. reported recently the asymmetric hydrogenation of a series of enol esters using monodentate phosphite ligands **17** and **24** based on a combination of BINOL and carbohydrates or simple alcohols; the results of these studies are shown in Table 28.6.

Unprecedented *e.e.*-values were obtained using ligand **24b** in the hydrogenation of aliphatic enol esters. A furyl substituent on the carboxylate is apparently

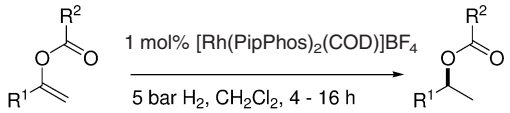
Table 28.6 Enantioselective hydrogenation of aliphatic enol esters.



74a R^1 = ^{n}Bu, R^2 = Ph — **75a-h**
b R^1 = ^{n}Bu, R^2 = Me
c R^1 = ^{n}Bu, R^2 = Et
d R^1 = ^{n}Bu, R^2 = ^{t}Bu
e R^1 = ^{n}Bu, R^2 = 2-Furyl
f R^1 = Et, R^2 = Ph
g R^1 = Et, R^2 = 2-*N*-Me-pyrrolyl
h R^1 = Et, R^2 = 2-Furyl

Entry	Ligand	Product							
		75a	**75b**	**75c**	**75d**	**75e**	**75f**	**75g**	**75h**
1	**24b**[a)]	86	74	74	42	90*	80	72	84
2	**24f**[a), b)]	13	32	6	10	22	11	5	34

a) Reactions carried out with SCR 200, in CH_2Cl_2, $p(H_2) = 60$ bar, 30 °C, 20 h (TOF = 5 h^{-1}).
b) Using ligand **24f** the conversion was between 76% and 100%.
* At –20 °C, 94% ee was obtained.



		ee%
74i	R^1 = Ph, R^2 = Me	**75i** 90
j	R^1 = Ph, R^2 = NEt_2	**j** 96
k	R^1 = 4-Cl-Ph, R^2 = Me	**k** 90
l	R^1 = 4-NO_2-Ph, R^2 = Me	**l** 98
m	R^1 = 4-NO_2-Ph, R^2 = NEt_2	**m** 98
n	R^1 = ^{n}Bu, R^2 = NEt_2	**n** 63
o	R^1 = Bn, R^2 = NEt_2	**o** 73
p	R^1 = Me_3Si, R^2 = NEt_2	**p** 43
q	R^1 = 1*E*-heptenyl, R^2 = NEt_2	**q** 97
r	R^1 = styryl, R^2 = NEt_2	**r** 76

Scheme 28.15 Enantioselective hydrogenation of enol acetates and enol carbamates.

beneficial for the enantioselectivity. The reactions are most likely not very fast, which is also the case using bidentate ligands.

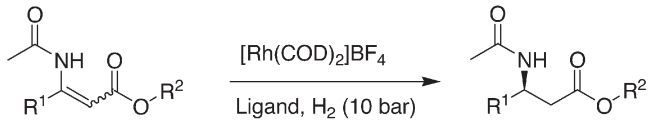
In order to mimic the electronic properties of the corresponding *N*-acyl enamide, enol carbamate **74j** (Scheme 28.15) has been introduced in the enantioselective hydrogenation using rhodium and a series of secondary phosphinoxide ligands **49**. The use of 2 mol% of Rh/L and 1 bar of hydrogen gave full conversion and 81% *e.e.* in a slow reaction. Unfortunately, the *e.e.*-values fell upon increasing the hydrogen pressure.

Very recently, however, the use of Rh/PipPhos **29hb** was reported as an excellent catalyst for the hydrogenation of both enol acetates and enol carbamates (Scheme 28.15). The carbamate group induced higher enantioselectivities compared to the corresponding acyl group, and the hydrogenations were faster (TOFs up to 25 h^{-1} at 5 bar). Remarkably, dienol carbamates **74q** and **74r** were hydrogenated to the corresponding allylic carbamate, leaving the additional double bond intact.

28.10
Hydrogenation of *N*-Acyl-*β*-Dehydroamino Acid Esters

Enantiopure *β*-amino acids can efficiently be obtained using rhodium-catalyzed asymmetric hydrogenation. The substrates are synthesized by reacting the *β*-keto esters with NH_4OAc and subsequent acylation with acetic anhydride. This reaction generally results in a mixture of double bond isomers [93]. Compared to the corresponding *α*-dehydroamino acids and esters, their *β*-analogues are considerably more challenging. There is a large difference in behavior of the hydrogenation of the *E*- and *Z*-stereoisomers. The *E*-isomer is generally hydrogenated at higher rate and with considerably higher ee than the *Z*-isomer. A few monodentate ligands have been studied for the rhodium-catalyzed hydrogenation of this class of compounds. Phosphites **17bc** and **24c** induce high ee-values but require a high catalyst loading and long reaction times. In addition, for **24c** the conversion is incomplete. Better results have been obtained using phosphoramidites; for example, it has been shown that using BINOL-based phosphoramidites, different ligands and different solvents were necessary to hydrogenate the different double bond isomers. Excellent ee-values were obtained, however. In particular for the Z-isomers, **29g** was the best ligand available at the time, also taking into account the bidentate ligands. SIPHOS ligand **35a** also provides high ee-values, with the advantage that mixtures of *E* and *Z* substrates can be used (Table 28.7). The reactions are slow (TOF 1 h^{-1} at 100 bar), however. In general, the TOFs vary considerable among the ligands, ranging from 3 h^{-1} at 15 bar to 200 h^{-1} at 10 bar.

Table 28.7 Enantioselective hydrogenation of *N*-Acyl-*β*-dehydroamino acid esters.



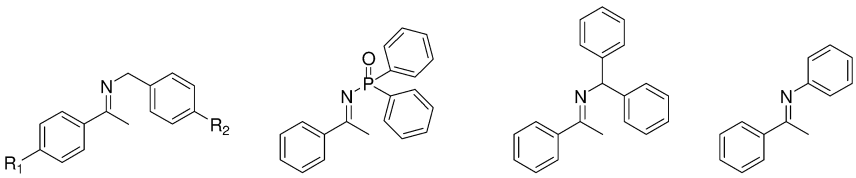
78a R^1 = Me, R^2 = Me — **79a-m**
b R^1 = Me, R^2 = Et
d R^1 = Ph, R^2 = Et
e R^1 = Et, R^2 = Me
f R^1 = ^{i}Pr, R^2 = Et
g R^1 = *p*-F-Ph, R^2 = Me
h R^1 = *o*-Br-Ph, R^2 = Me
i R^1 = *m*-Br-Ph, R^2 = Me
j R^1 = *p*-Br-Ph, R^2 = Me
k R^1 = *p*-Cl-Ph, R^2 = Me
l R^1 = *p*-Me-Ph, R^2 = Me
m R^1 = *p*-MeO-Ph, R^2 = Me

	Ligand	79a *E/Z*	79b *E/Z*	79d *Z*	79e *E/Z*	79f *E/Z*	79g *Z*	79h	79i	79j	79k	79l	79m
1	**17bc**[a]	91/55	94/38	52									
2	**24c**[b]	96/–	96/–	93	98/–								
3	**29a**[c]	91/–											
4	**29d**[c]	99/–	98/–		99/–	99/–							
5	**29g**[d]	–/95	–/94	92	–/94	–/92	94						
6	**35**[e]	89	87	90				91	92	94	91	91	93

a) Reactions carried out with SCR 100, in CH_2Cl_2, $p(H_2)$ = 15 bar, 30 h.
b) Reactions carried out with SCR 50, in CH_2Cl_2, $p(H_2)$ = 30 bar, 12–48 h. Conversions were incomplete.
c) Reactions carried out with SCR 50, in CH_2Cl_2, $p(H_2)$ = 10 bar, 4 h or SCR of 200, in CH_2Cl_2, $p(H_2)$ = 25 bar, 6 h.
d) Reactions carried out with SCR 50, in *i*-PrOH, $p(H_2)$ = 10 bar, 0.3 h or with SCR 200, in *i*-PrOH, $p(H_2)$ = 10 bar, 1 h.
e) Reactions carried out with SCR 50, in CH_2Cl_2, $p(H_2)$ = 100 bar, 48 h. Mixtures of *Z* and *E* were used.

28.11 Hydrogenation of Ketones and Imines

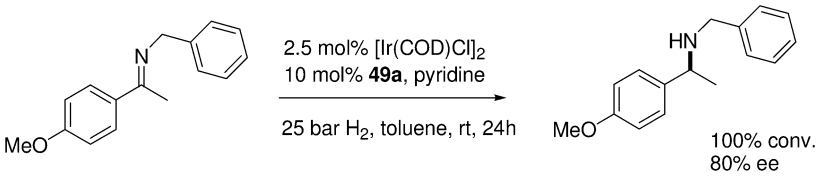
Although this chapter is devoted to the hydrogenation of alkenes, it is interesting to include the studies that have appeared on the hydrogenation of imines and ketones. Surprisingly, the enantioselective imine hydrogenation using monodentate ligands has been reported in only a few studies. BINOL-based monodentate phosphonite ligand **15d** has been studied in the rhodium- and iridium-catalyzed hydrogenation of benzyl imine **80** (Scheme 28.16) [40]. No chiral



80 $R_1 = R_2 = H$
81 $R_1 = OMe$, $R_2 = H$
82 $R_1 = H$, $R_2 = OMe$
83 $R_1 = H$, $R_2 = Cl$
84 $R_1 = Cl$, $R_2 = H$

85 **86** **87**

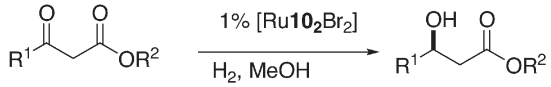
Scheme 28.16 Imines for enantioselective hydrogenation.



Scheme 28.17 Enantioselective hydrogenation of benzyl imines using iridium/secondary phosphinoxide ligands.

induction was observed. In a thorough study, secondary phosphine oxide ligands **49** and **50** were used in the iridium-catalyzed hydrogenation of a series of imines [48]. Enantioselectivities up to 80% and full conversion were reached with Ir/**49a** in the hydrogenation of benzyl imine **81** in toluene, adding pyridine as a co-ligand (Scheme 28.17). This places the catalyst among the best catalysts

Table 28.8 Enantioselective hydrogenation of β-keto esters using monodentate phosphine ligands.

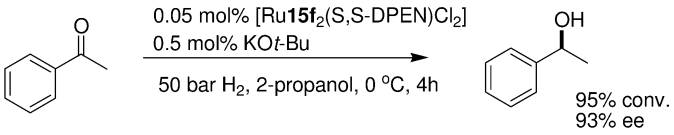


88a $R^1 = Me$, $R^2 = Me$
88b $R^1 = Et$, $R^2 = Me$
88c $R^1 = CH_2Cl$, $R^2 = Et$
88d $R^1 = Ph$, $R^2 = Et$

89a $R^1 = Me$, $R^2 = Me$
89b $R^1 = Et$, $R^2 = Me$
89c $R^1 = CH_2Cl$, $R^2 = Et$
89d $R^1 = Ph$, $R^2 = Et$

Entry	Ligand	Substrate	Yield [%]	ee [%]
1	**10d**[a)]	**88a**	95	84
2	**10e**[a)]	**88a**	97	92
3	**10e**[a)]	**88b**	99	94
4	**10e**[a)]	**88c**	77	38
5	**10e**[a)]	**88d**	99	95
6	**10o**[a)]	**88a**	98	64

a) Reactions carried out with SCR 1000, in MeOH, $p(H_2) = 40–80$ bar, at 50 °C, 16 h.



Scheme 28.18 Enantioselective hydrogenation of aryl-methyl ketones.

known for benzyl imine hydrogenation in terms of enantioselectivity, although the reactions are slow. Low *e.e.*-values were obtained with *N*-diphenylphosphinoyl ketimine **85**, benzhydryl imine **86** and aryl imine **87**. A chiral phosphoric acid diester **20**, based on TADDOL was also tested, but gave very low *e.e.*-values.

At the same time, however, the iridium-catalyzed hydrogenation of **80** was reported using chiral phosphoric acid diester **17be** based on BINOL [47a]. Full conversion and a maximum *e.e.* of 50% was observed, again in a slow reaction. Interestingly, a catalyst based on palladium and **17be** afforded 39% *e.e.* and full conversion in the hydrogenation of aryl imine **87**.

In an early report, the *β*-keto ester methyl acetylacetate was hydrogenated with 71% ee using Rh/CAMP [94]. In a thorough study, the group of Beller reported excellent results in the ruthenium-catalyzed hydrogenation of *β*-keto esters using monodentate phosphines based on the binaphthyl skeleton. The phosphoramidite MonoPhos **29a** and a related phosphonite gave only low ee-values in this reaction. A selection of the results is presented in Table 28.8. One remarkable point was the difference between the non-deuterated ligand **10d** and its deuterated analogue **10o**.

Recently, the first report was made on the ruthenium-catalyzed enantioselective hydrogenation of aryl-methyl ketones using monodentate phosphonites (Scheme 28.18). In particular, ligand **15f** induced excellent ee-values. One very early report on rhodium-catalyzed hydrogenation of ketones using the monophosphine bmpp **1f** met with a low *e.e.* [95].

28.12 Conclusions

It is safe to state that monodentate ligands have rapidly found their place in rhodium-catalyzed enantioselective hydrogenation, and the high speed at which new ligands appear continuously is the best illustration of their versatility. On the one hand, the straightforward preparation and the use of ligand libraries (see Chapter 36) makes the rapid development of tailor-made ligands possible. On the other hand, it clear from the information provided in this chapter that certain ligands, such as PipPhos **29hb**, SIPHOS **35a**, and some BINOL and biphenol-based phosphites, are so-called privileged ligands with a large scope.

Nevertheless, there remains a plethora of substrates that have not yet been studied using the monodentate ligand approach. In the application of asymmetric hydrogenation, it is very important to go beyond the benchmark substrates, and several studies have already shown that the scope of enantioselective hydrogenation might be much broader than was originally assumed.

One especially underexposed aspect in most reports is that of the TOF and TON of the catalyst. Not only from a scientific point of view, but also because of the costs of the precious metals used, this must be an important characteristic of catalytic systems.

Abbreviations

HTE high-throughput experimentation
TOF turnover frequency
TON turnover number

References

1 (a) W. S. Knowles, M. J. Sabacky, *J. Chem. Soc. Chem. Commun.* **1968**, 1445; (b) W. S. Knowles, *Acc. Chem. Res.* **1983**, *16*, 106.
2 L. Horner, H. Siegel, H. Büthe, *Angew. Chem. Int. Ed. Engl.* **1968**, *7*, 942.
3 J. A. Osborn, F. H. Jardine, J. F. Young, G. Wilkinson, *J. Chem. Soc. A* **1966**, 1711.
4 For an excellent overview of the field of enantioselective hydrogenation, see: J. M. Brown, in: E. N. Jacobsen, A. Pfaltz, H. Yamamoto (Eds.), *Comprehensive Asymmetric Catalysis*, Springer, Berlin, **1999**, Vol. 1, Chapter 5.1.
5 (a) T. P. Dang, H. B. Kagan, *J. Chem. Soc. Chem. Commun.* **1971**, 481; (b) H. B. Kagan, T. P. Dang, *J. Am. Chem. Soc.* **1972**, *94*, 6429.
6 B. D. Vineyard, W. S. Knowles, M. J. Sabacky, G. L. Bachman, D. J. Weinkauff, *J. Am. Chem. Soc.* **1977**, *99*, 5946.
7 (a) H. Brunner, W. Zettlmeier, *Handbook of Enantioselective Catalysis,* VCH, Weinheim, **1993**; (b) R. Noyori, *Asymmetric Catalysis in Organic Synthesis,* Wiley, New York, **1993**; (c) H. B. Kagan, in: J. D. Morrison (Ed.), *Asymmetric Synthesis*, Academic Press, Inc., Orlando, **1985**, Volume 5; (d) H. Brunner, *Top. Stereochem.* **1988**, *18*, 129; (e) H.-U. Blaser, C. Malan, B. Pugin, F. Spindler, H. Steiner, M. Studer, *Adv. Synth. Catal.* **2003**, *345*, 103.
8 H. U. Blaser, E. Schmidt (Eds.), *Asymmetric Catalysis on Industrial Scale: Challenges, Approaches and Solutions,* Wiley-VCH, **2004**.
9 (a) W. S. Knowles, M. J. Sabacky, B. D. Vineyard, *J. Chem. Soc. Chem. Commun.* **1972**, 10; (b) J. Solodar, *J. Org. Chem.* **1978**, *43*, 1787.
10 For a discussion on this topic, see: X. Zhang, *Enantiomer* **1999**, *4*, 541.
11 For a review on the use of chiral monodentate phosphines in asymmetric catalysis, see: F. Lagasse, H. B. Kagan, *Chem. Pharm. Bull.* **2000**, *48*, 315.
12 For a perspective on the use of chiral monodentate phosphorus ligands in enantioselective olefin hydrogenations see: I. V. Komarov, A. Börner, *Angew. Chem. Int. Ed.* **2001**, *40*, 1197. As a forerunner, the development of a new, though less enantioselective, monodentate phosphine ligand was reported; F. Guillen, J.-C. Fiaud, *Tetrahedron Lett.* **1999**, *40*, 2939.
13 C. Claver, E. Fernandez, A. Gillon, K. Heslop, D. J. Hyett, A. Martorell, A. G. Orpen, P. G. Pringle, *Chem. Commun.* **2000**, 961.
14 M. T. Reetz, G. Mehler, *Angew. Chem. Int. Ed.* **2000**, *39*, 3889.
15 M. van den Berg, A. J. Minnaard, E. P. Schudde, J. van Esch, A. H. M. de Vries, J. G. de Vries, B. L. Feringa, *J. Am. Chem. Soc.* **2000**, *122*, 11539.
16 D. Peña, A. J. Minnaard, A. H. M. de Vries, J. G. de Vries, B. L. Feringa, *Org. Lett.* **2003**, *5*, 475.
17 For an initial study using the phosphoramidite MonoPhos, see: M. van den Berg, A. J. Minnaard, R. M. Haak, M. Leeman, E. P. Schudde, A. Meetsma, B. L. Feringa,

A. H. M. de Vries, C. E. P. Maljaars, C. E. Willans, D. Hyett, J. A. F. Boogers, H. J. W. Henderickx, J. G. de Vries, *Adv. Synth. Catal.* **2003**, *345*, 308.
18 Y. Fu, X. X. Guo, S. F. Zhu, A. G. Hu, J. H. Xie, Q. L. Zhou, *J. Org. Chem.* **2004**, *69*, 4648.
19 M. T. Reetz, T. Sell, A. Meiswinkel, G. Mehler, *Angew. Chem. Int. Ed.* **2003**, *42*, 790.
20 (a) M. T. Reetz, X. Li, *Angew. Chem. Int. Ed.* **2005**, *44*, 2959; (b) see Ref. 91.
21 T. Jerphagnon, J.-L. Renaud, C. Bruneau, *Tetrahedron; Asymm.* **2004**, *15*, 2101.
22 J. G. de Vries, in: D. Ager (Ed.), *Handbook of Chiral Chemicals*, M. Dekker, **2004**.
23 D. Valentine, Jr., K. K. Johnson, W. Priester, R. C. Sun, K. Toth, G. Saucy, *J. Org. Chem.* **1980**, *45*, 3698.
24 (a) J. D. Morrison, R. E. Burnett, A. M. Aguiar, C. J. Morrow, C. Phillips, *J. Am. Chem. Soc.* **1971**, *93*, 1301; (b) J. D. Morrison, W. F. Masler, *J. Org. Chem.* **1974**, *39*, 270.
25 A. Marinetti, F. Mathey, L. Ricard, *Organometallics* **1993**, *12*, 1207.
26 A. Marinetti, L. Ricard, *Organometallics* **1994**, *13*, 3956.
27 O. Riant, O. Samuel, T. Flessner, S. Taudien, H. B. Kagan, *J. Org. Chem.* **1997**, *62*, 6733.
28 S. Saito, Y. Nakamura, Y. Morita, *Chem. Pharm. Bull.* **1985**, *33*, 5284.
29 M. Ostermeier, J. Priess, G. Helmchen, *Angew. Chem. Int. Ed.* **2002**, *41*, 612.
30 K. Junge, G. Oehme, A. Monsees, T. Riermeier, U. Dingerdissen, M. Beller, *Tetrahedron Lett.* **2002**, 43, 4977.
31 K. Junge, B. Hagemann, S. Enthaler, A. Spannenberg, M. Michalik, G. Oehme, A. Monsees, T. Riermeier, M. Beller, *Tetrahedron; Asymm.* **2004**, *15*, 2621.
32 K. Junge, B. Hagemann, S. Enthaler, G. Oehme, M. Michalik, A. Monsees, T. Riermeier, U. Dingerdissen, M. Beller, *Angew. Chem. Int. Ed.* **2004**, *43*, 5066.
33 A. Marinetti, J.-P. Gent, *C. R. Chimie* **2003**, *6*, 507.
34 A. Marinetti, S. Jus, F. Labrue, A. Lemarchand, J.-P. Gent, L. Ricard, *Synthesis*, **2001**, 2091.
35 M. J. Burk, J. E. Feaster, R. L. Harlow, *Tetrahedron; Asymm.* **1991**, *2*, 569. Ligands **12b** and **12c** have not been tested in asymmetric hydrogenation.
36 (a) F. Guillen, M. Rivard, M. Toffano, J. Y. Legros, J. C. Daran, J. C. Fiaud, *Tetrahedron* **2002**, *58*, 5895; (b) see Ref. 12; (c) C. Dobrota, M. Toffano, J. C. Fiaud, *Tetrahedron Lett.* **2004**, *45*, 8153.
37 Z. Pakulski, O. M. Demchuk, J. Frelek, R. Luboradzki, K. M. Pietrusiewicz, *Eur. J. Org. Chem.* **2004**, 3913.
38 M. T. Reetz, T. Sell, *Tetrahedron Lett.* **2000**, *41*, 6333.
39 S. Trinkhaus, R. Kadyrov, R. Selke, J. Holz, L. Götze, A. Borner, *J. Mol. Cat. A. Chem.* **1999**, *144*, 15.
40 A. Martorell, C. Claver, E. Fernandez, *Inorg. Chem. Comm.* **2000**, *3*, 132.
41 Y. Xu, N. W. Alcock, G. J. Clarkson, G. Docherty, G. Woodward, M. Wills, *Org. Lett.* **2004**, *6*, 4105.
42 W. Chen, J. Xiao, *Tetrahedron Lett.* **2001**, *42*, 2897.
43 I. Gergely, C. Hegedüs, H. Gulyás, Á. Szöllösy, A. Monsees, T. Riermeier, J. Bakos, *Tetrahedron: Asymmetry* **2003**, *14*, 1087.
44 A. Korostylev, A. Monsees, C. Fischer, A. Börner, *Tetrahedron: Asymmetry* **2004**, *15*, 1001.
45 M. Ostermeier, B. Brunner, C. Korff, G. Helmchen, *Eur. J. Org. Chem.* **2003**, 3453.
46 D. Nakano, M. Yamaguchi, *Tetrahedron Lett.* **2003**, *44*, 4969.
47 (a) M. T. Reetz, T. Sell, R. Goddard, *Chimia* **2003**, *57*, 290; (b) M. T. Reetz, *Russ. J. Org. Chem.* **2003**, *39*, 392.
48 X.-B. Jiang, A. J. Minnaard, B. Hessen, B. L. Feringa, A. L. L. Duchateau, J. G. O. Andrien, J. A. F. Boogers, J. G. de Vries, *Org. Lett.* **2003**, *5*, 1503.
49 W. Chen, J. Xiao, *Tetrahedron Lett.* **2001**, *42*, 8737.
50 Z. Hua, V. C. Vassar, I. Ojima, *Org. Lett.* **2003**, *5*, 3831.
51 B. Meseguer, T. Prinz, U. Scholz, H.-C. Militzer, F. Agel, B. Driessen-Hölscher EP 1 298 136, 2003, to Bayer AG.
52 P. Hannen, H.-C. Millitzer, E. M. Vogl, F. A. Rampf, *Chem. Commun.* **2003**, 2210.

53 M.T. Reetz, G. Mehler, A. Meiswinkel, T. Sell, *Tetrahedron Lett.* **2002**, *43*, 7941.

54 M.T. Reetz, L.J. Goossen, A. Meiswinkel, J. Paetzold, J. Feldthusen Jensen, *Org. Lett.* **2003**, *5*, 3099.

55 Q. Jiang. D. Xiao, P. Cao, X. Zhang, *Angew. Chem. Int. Ed.* **1998**, *37*, 1100.

56 T. Jerphagnon, J.-L. Renaud, P. Demonchaux, A. Ferreira, C. Bruneau, *Adv. Synth. Catal.* **2004**, *346*, 33.

57 H. Huang, Z. Zheng, H. Luo, C. Bai, X. Hu, H. Chen, *Org. Lett.* **2003**, *5*, 4137.

58 (a) H. Huang, X. Liu, S. Chen, H. Chen, Z. Zheng *Tetrahedron: Asymm.* **2004**, *15*, 2011; (b) Note added in proof: a new class of monodentate phosphites based on a combination of D-mannitol and BINOL or bisphenols affords excellent ee s in the hydrogenation of *α*-and *β*-*α*-acyldehydroamino esters, *N*-acyl enamides and itaconates, see: H. Huang, Z. Zheng, H. Luo, C. Bai, X. Hu, H. Chen, *J. Org. Chem.* **2004**, *69*, 2355.

59 M.T. Reetz, J.-A. Ma, R. Goddard, *Angew. Chem. Int. Ed.* **2005**, *44*, 412.

60 (a) K. Nozaki, N. Sakai, T. Nanno, T. Higashijima, S. Mano, T. Horiuchi, H. Takaya, *J. Am. Chem. Soc.* **1997**, *119*, 4413; (b) A. Duursma, J.-G. Boiteau, L. Lefort, J.A.F. Boogers, A.H.M. de Vries, J.G. de Vries, A.J. Minnaard, B.L. Feringa, *J. Org. Chem.* **2004**, *69*, 8045.

61 For alternative routes, see: (a) Ref. 17; (b) A. van Rooy, D. Burgers, P.C.J. Kamer, P.W.N.M. van Leeuwen, *Recl. Trav. Chim. Pays-Bas* **1996**, *115*, 492.

62 R. Hulst, N.K. de Vries, B.L. Feringa, *Tetrahedron: Asymmetry* **1994**, *5*, 699.

63 M. Van den Berg, R.M. Haak, A.J. Minnaard, A.H.M. de Vries, J.G. de Vries, B.L. Feringa, *Adv. Synth. Catal.* **2002**, *344*, 1003.

64 (a) X. Jia, X. Li, L. Xu, Q. Chi, X. Yao, A.S.C. Chan, *J. Org. Chem.* **2003**, *68*, 4539; (b) X. Jia, R. Guo, X. Li, X. Yao, A.S.C. Chan, *Tetrahedron Lett.* **2002**, *43*, 5541.

65 H. Bernsmann, M. van den Berg, R. Hoen, A.J. Minnaard, G. Mehler, M.T. Reetz, J.G. de Vries, B.L. Feringa, *J. Org. Chem.* **2005**, *70*, 943.

66 (a) Q. Zeng, H. Liu, X. Cui, A. Mi, Y. Jiang, X. Li, M.C.K. Choi, A.S.C. Chan, *Tetrahedron: Asymmetry* **2002**, *13*, 115; (b) Q. Zeng, H. Liu, A. Mi, Y. Jiang, X. Li, M.C.K. Choi, A.S.C. Chan, *Tetrahedron* **2002**, *58*, 8799; (c) X. Li, X. Jia, G. Lu, T.T.-L. Au-Yeung, K.-H. Lam, T.W.H. Lo, A.S.C. Chan, *Tetrahedron: Asymmetry* **2003**, *14*, 2687.

67 L. Panella, B.L. Feringa, J.G. de Vries, A.J. Minnaard, *Org. Lett.* **2005**, *7*, 4177.

68 O. Huttenloch, J. Spieler, H. Waldmann, *Chem. Eur. J.* **2000**, *6*, 671.

69 M.T. Reetz, J.-A. Ma, R. Goddard, *Angew. Chem. Int. Ed.* **2005**, *44*, 412.

70 (a) A.-G. Hu, Y. Fu, J.-H. Xie, H. Zhou, L.-X. Wang, Q.-L. Zhou, *Angew. Chem. Int. Ed.* **2002**, *41*, 2348; (b) Y. Fu, J.-H. Xie, A.-G. Hu, H. Zhou, L.-X. Wang, Q.-L. Zhou, *Chem. Commun.* **2002**, 480; (c) S.-F. Zhu, Y. Fu, J.-H. Xie, B. Liu, L. Xing, Q.-L. Zhou, *Tetrahedron: Asymmetry* **2003**, *14*, 3219.

71 Y. Fu, X.-X. Guo, S.-F. Zhu, A.-G. Hu, J.-H. Xie, Q.-L. Zhou, *J. Org. Chem.* **2004**, *69*, 4648.

72 V.B. Birman, A.L. Rheingold, K.-C. Lam, *Tetrahedron: Asymmetry* **1999**, *10*, 125.

73 S. Wu, W. Zhang, Z. Zhang, X. Zhang, *Org. Lett.* **2004**, *6*, 3565.

74 A. Bayer, P. Murszat, U. Thewalt, B. Rieger, *Eur. J. Inorg. Chem.* **2002**, 2614.

75 R. Hoen, M. van den Berg, H. Bernsmann, A.J. Minnaard, J.G. de Vries, B.L. Feringa, *Org. Lett.* **2004**, *6*, 1433.

76 M. van den Berg, PhD. Thesis **2005**, University of Groningen, The Netherlands.

77 D. Peña, A.J. Minnaard, J.G. de Vries, B.L. Feringa, *J. Am. Chem. Soc.* **2002**, *124*, 14552.

78 S. Doherty, E.G. Robins, I. Pál, C.R. Newman, C. Hardacre, D. Rooney, D.A. Mooney, *Tetrahedron: Asymmetry* **2003**, *14*, 1517. Of course, once polymerized the ligands are no longer monodentate.

79 X. Wang, K. Ding, *J. Am. Chem. Soc.* **2004**, *126*, 10524.

80 C. Simons, U. Hanefeld, I.W.C.E. Arends, A.J. Minnaard, T. Maschmeyer, R.A. Sheldon, *Chem. Comm.* **2004**, 2830.

81 P.N.M. Botman, A. Amore, R. van Heerbeek, J.W. Back, H. Hiemstra, J.N.H. Reek, J.H. van Maarseveen *Tetrahedron Lett.* **2004**, *45*, 5999.

82 M. Yamashita, M. Kobayashi, M. Sugiura, K. Tsunekawa, T. Oshikawa, S. Inokawa, H. Yamamoto, *Bull. Chem. Soc. Jpn.* **1986**, *59*, 175.

83 Y. Chi, X. Zhang, *Tetrahedron Lett.* **2002**, *43*, 4849.

84 K. Junge, G. Oehme, A. Monsees, T. Riermeier, U. Dingerdissen, M. Beller, *J. Organomet. Chem.* **2003**, *675*, 91.

85 M.T. Reetz, H. Oka, R. Goddard, *Synthesis* **2003**, 1809.

86 X.-B., Jiang, M. van den Berg, A.J. Minnaard, B.L. Feringa, J.G. de Vries, *Tetrahedron: Asymmetry* **2004**, *15*, 2223.

87 The methyl-substituted substrate has been hydrogenated with SIPHOS in excellent ee; see: Ref. [68b].

88 MonoPhos **29a** has shown to give the same ee-values for *N*-acyl, *N*-BOC and *N*-Z protection (unpublished results).

89 M. van den Berg, E.P. Schudde, A.J. Minnaard, B.L. Feringa, J. G. de Vries (unpublished results).

90 (a) E. Farrington, M.C. Franchini, J.M. Brown, *Chem. Comm.* **1998**, 277; (b) J.M. Brown, *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 191.

91 R. Hoen, J.A.F. Boogers, H. Bernsmann, A.J. Minnaard, A. Meetsma, T.D. Tiemersma-Wegman, A.H.M. de Vries, J.G. de Vries, B.L. Feringa, *Angew. Chem. Int. Ed.* **2005**, *44*, 4209.

92 N.W. Boaz, *Tetrahedron Lett.* **1998**, *39*, 5505.

93 See, however J. You, H.-J. Drexler, S. Zhang, C. Fischer, D. Heller, *Angew. Chem. Int. Ed.* **2003**, *42*, 913 for an in-depth study of the synthesis of these stereoisomers.

94 (a) J. Solodar, *Chemtech* **1975**, 421. For the enantioselective hydrogenation of cyclopenta-1,3,4,-trione using Rh/CAMP, see (b) C.J. Sih, J.B. Heather, G.P. Peruzzotti, P. Price, R. Sood, L.-F.H. Lee, *J. Am. Chem. Soc.* **1973**, *95*, 1676.

95 P. Bonvicini, A. Levi, G. Modena, G. Scorrano, *J. Chem. Soc., Chem. Comm.* **1972**, 1188.