BINOL-derived phosphoramidites in asymmetric hydrogenation: can the presence of a functionality in the amino group influence the catalytic outcome?

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In discovering the remarkable catalytic properties of BINOL-derived phosphoramidites (binoP–NR_2), Dutch researchers recently achieved a long-awaited breakthrough in asymmetric catalysis. For the first time, easily accessible *monodentate* chiral P(III) ligands turned out to provide high enantioselectivities when used in rhodium-catalysed olefin hydrogenation. The simplest ligand representative of this family is MonoPhos™, which can be made straightforwardly from BINOL and hexamethylphosphorous triamide. Since the first publication dealing with such catalysts (*J. Am. Chem. Soc.*, 2000), a variety of binoP–NRR′ ligands have been reported in which the amino group bears a functional substituent or a stereogenic centre. This *critical review* examines the impact of the presence of such a functionality in the amino group on catalytic olefin hydrogenation reactions.

1 Introduction

In 1965, Osborn and Wilkinson discovered that unsaturated substrates, in particular olefins, can be hydrogenated homogeneously and under mild conditions in the presence of the complex $[RhCl(PPh_3)_3]$.[1] Three years later, Horner and coworkers showed that similar hydrogenation reactions could be observed with catalytic systems based upon tertiary phosphines other than PPh_3. Their studies were carried out by using a combination of $[RhCl(ethene)_2]_2$ and various triaryl- and trialkyl-phosphines as well as alkyl-arylphosphines.[2] All these ligands were achiral. The first use of a chiral phosphine (Fig. 1) in catalytic hydrogenation was by Knowles *et al.* in 1968.[3] In fact, the phosphine used by Knowles for these hydrogenation experiments was not enantiomerically pure, yet it produced a mixture in which there was 15 per cent more of one enantiomer than the other.[4] Although this excess was modest, the result was of fundamental importance in proving that it was possible to achieve catalytic asymmetric hydrogenation.

In 1971, Kagan and Dang published the synthesis of the enantiomerically pure diphosphine (*R*,*R*)-DIOP, obtained from (*R*,*R*)-tartaric acid.[6] This ligand gave, for that time, remarkably high ee's—up to 72%—in the rhodium(I)-catalyzed hydrogenation of (*Z*)-*N*-acetamidocinnamic acid. These experiments were carried out under 1 bar pressure of H_2 and at room temperature. After this discovery, which established the apparent superiority of diphosphines over that of monophosphines, and for a quarter of a century, the chemistry of the metal-catalyzed hydrogenation of prochiral substrates was dominated by complexes containing chiral bidentates.

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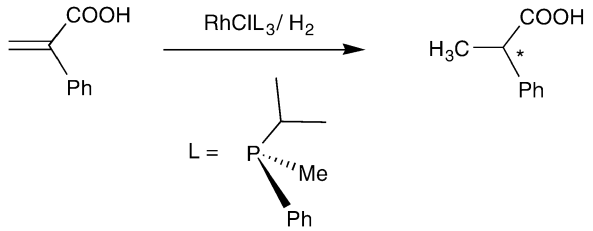


Fig. 1 First use of a chiral phosphine in the catalytic hydrogenation of an olefin. Ligands similar to the one used by Knowles had previously been synthesized by Horner.[5]

Hundreds of chiral diphosphines, most where the P(III) centre itself is not the source of chirality, are therefore nowadays commercially available.[7] Prominent representatives include DIPAMP,[8] DuPHOS,[9] chiraphos,[10] NORPHOS,[11] Josiphos,[12] BINAP,[13] Phenyl-β-GLUP,[14] BIPNOR,[15] SEGPHOS,[16] C_1-Tunephos,[17] and SYNPHOS[18] (Fig. 2).

Knowles' DIPAMP was the first diphosphine employed industrially, namely for the preparation of L-DOPA, which serves as prodrug for increasing dopamine levels for the treatment of Parkinson's desease. L-DOPA was obtained in 95% ee after hydrogenation of the appropriate olefinic precursor. This synthesis is still performed by EGIS in Hungary.[19]

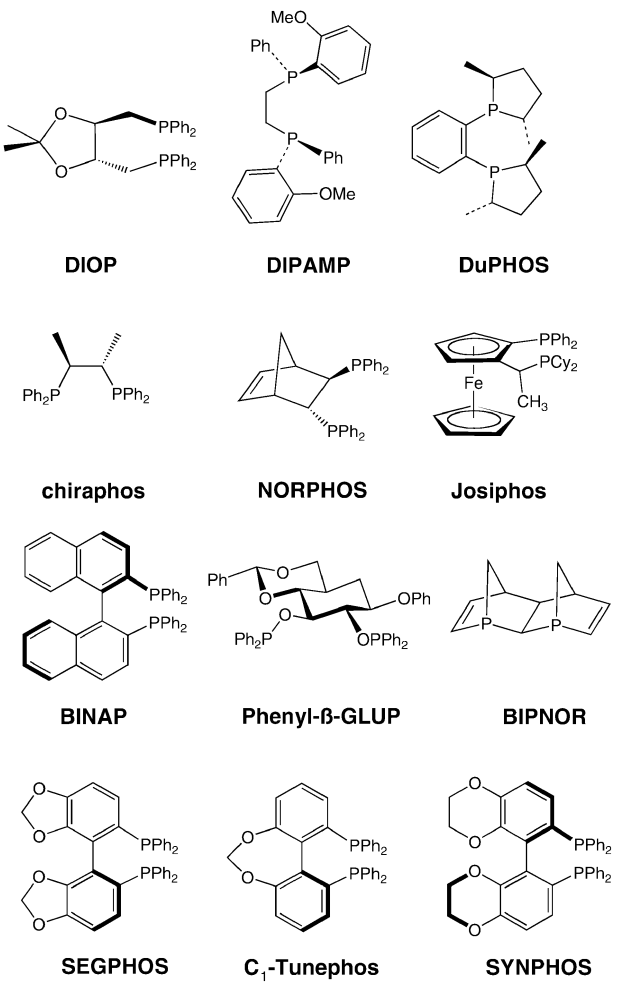
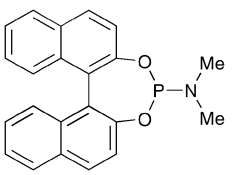


Fig. 2 Common, chiral di-P(III) ligands.

The general belief that bidentate ligands, when used in catalysis, systematically result in higher ee's than monodentate ones persisted until 2000, when Pringle[20] and Reetz[21] independently found that some monodentate phosphonites derived from optically active 1,1′-bi-2-naphthol (BINOL)[24–26] may lead to ee's up to 94% in olefin hydrogenation. A few weeks later Dutch researchers[22] published their results on the phosphoramidite MonoPhos™,[23] another BINOL-derived monodentate ligand. For the first time, ee's up to 99% were obtained with a chiral monodentate P(III) ligand in the fast enantioselective hydrogenation of olefins.[27,28] It is interesting that MonoPhos, which was first synthesised by B. L. Feringa *et al.*,[23] had originally been used for the determination of the enantiomeric excess of various chiral compounds. Its effectiveness in asymmetric olefin hydrogenation was discovered later, in the laboratory of J. G. de Vries, by M. van den Berg and A. Minnaard.[27] Since de Vries' finding, a plethora of monodentate (and also some bidentate) phosphoramidites containing the 3,5-dioxa-4-phosphacycloheptadinaphthyl unit, termed hereafter "binoP", has been synthesized and assessed in asymmetric olefin hydrogenation. In the following, monophosphoramidites containing such a binoP moiety are termed BINOL-derived phosphoramidites.



MonoPhos (or binoPNMe$_2$)

Herein, we examine whether functional organic groups or stereogenic centres present in the amino group may be useful for improving the catalytic outcome in asymmetric hydrogenation reactions. Bidentate systems containing at least one binoPNRR′ moiety will also be discussed. It must be emphasised that only derivatives of the unsubstituted 1,1′-bi-2-naphthol are considered in this review, although it is now established that variation of the latter may also considerably enhance the catalytic performance.[29,30] We wish to draw the readers attention to the fact that several excellent publications connected to this topic have already appeared. These are either restricted to the use of MonoPhos in asymmetric catalysis,[31,32] or report on the properties of selected phosphoramidites in asymmetric hydrogenation.[33–36] Whenever possible, the catalytic performance of these ligands will be compared to those of MonoPhos.

2. Preparation of BINOL-derived phosphoramidites

BINOL-derived phosphoramidites can be easily obtained (in at most two steps) from optically active BINOL according to three different methods (Fig. 3). In method *a*, BINOL is first reacted with hexamethylphosphorous triamide ($P(NMe_2)_3$) in refluxing toluene, to afford *quantitatively*[23] air-stable MonoPhos. Replacement of the residual NMe_2 moiety by another amino group may be achieved in a second step by reaction with a secondary amine in the presence of 1-tetrazole. In

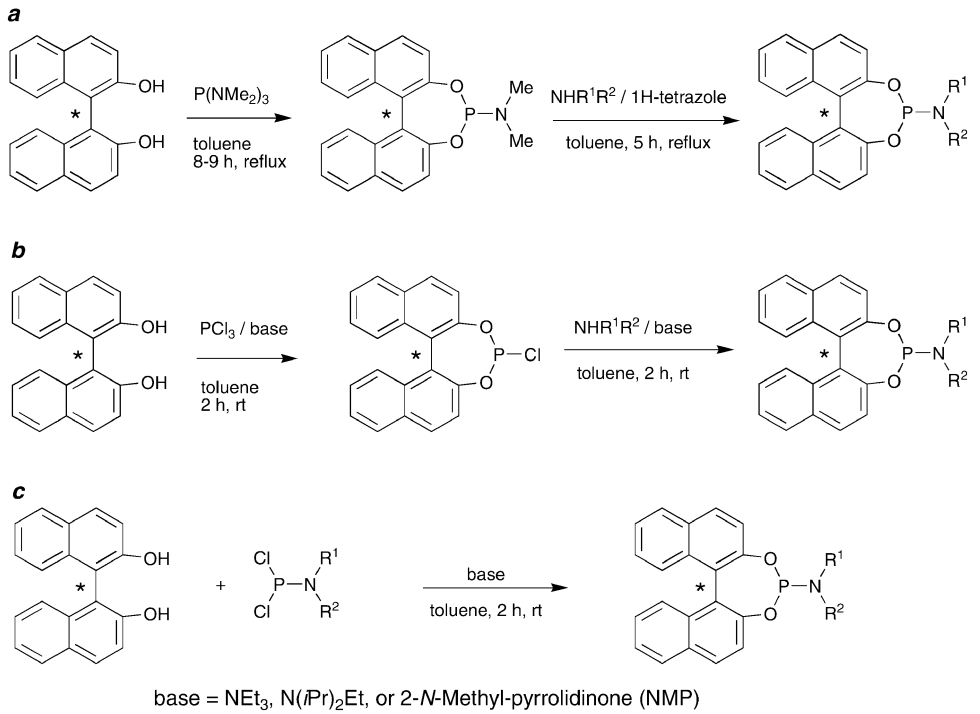


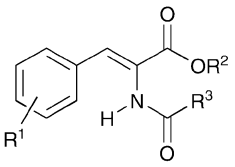
Fig. 3 Typical syntheses of BINOL-derived phosphoramidites.

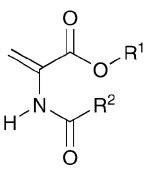
method *b*, BINOL is reacted with trichlorophosphine (PCl_3) in refluxing toluene to yield (1,1′-binaphthalene-2,2′-diyl)chlorophosphite (binoPCl). Subsequent treatment at room temperature of this chlorophosphite with a secondary amine leads to the desired compound. The less-used route, method *c*, consists in reacting a dichloroaminophosphine with BINOL in the presence of a base. The most frequently used method is method *b*, leading often to overall isolated yields of 70–85% (the first step is nearly quantitative).[37] For the other two methods, the yields do not surpass 50%. Most phosphoramidites are stable towards oxygen, but some of them were reported[38,39] to easily undergo P–N cleavage in the presence of protic solvents (note that MonoPhos is stable in MeOH[31] and towards hydrolysis).[33] In all these ligands, the phosphorus atom is part of a heterocyclic ring, a feature which certainly contributes to the good stability towards air.

3. Prochiral substrates tested in hydrogenation reactions (H_2) involving MonoPhos and its derivatives

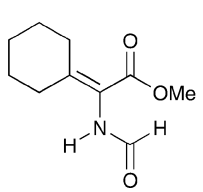
MonoPhos derivatives in which the amino part contains a functional group have been used for a wide variety of prochiral alkenes. Most of the latter are olefins substituted by both an amido and a carboxylic acid (or an ester) group (**1–46**). The corresponding hydrogenation products are important chiral building-blocks for the industrial synthesis of peptides as well as for numerous biomedical and medicinal applications.[40] The second most studied group of substrates are olefins containing an amide function as the sole functional group (**47–62**). Other studies have focused on olefins substituted only by an acid or an ester function (*e.g.* **63–65**), or on some special ketones such as **66–69**.

Typically, hydrogenation runs carried out with the substrates mentioned above have been performed at temperatures in the range 0–25 °C and at hydrogen pressures between 1 and 10 bar. The catalyst performance frequently strongly depends upon the solvent used, which generally is chosen from the following ones: CH_2Cl_2, EtOAc, *i*-PrOH. In some rare cases, the best results were obtained using an isopropanol–water mixture.[29,41] In the case of MonoPhos, using alcohols for the hydrogenation of methyl 2-acetamido cinnamate turned out to result in significantly lower ee's than using CH_2Cl_2, EtOAc, THF, or toluene.[27] The amount of catalyst metal (rhodium in most cases) usually does not exceed 5 mol%. In many literature reports, the experiments were carried out using a phosphoramidite : metal ratio of 2 : 1, which corresponds to the hypothetical formation of a $[RhL_2(COD)]^+$ complex.[27] Higher L : Rh ratios, which may result in the formation of RhL_3 and RhL_4 species, generally lead to a reaction rate decrease. In one example, it was found that using a 1 : 1 metal : ligand ratio increased the activity without changing the enantioselectivity, suggesting that a monoligand complex may be operative beside a "RhL_2" complex, but this was not demonstrated.[31] Interestingly, Giacomina, de Vries *et al.* have recently shown that an iridium(I) complex containing a single monophosphoramidite ligand may act as a good hydrogenation catalyst. However, whether the active catalyst is a monodentate complex is a matter of debate. The formation of a *P,C*-chelate complex, obtained after CH activation, cannot be formally excluded in this specific case.[42] Finally, it must be mentioned that in some particular hydrogenations (*vide infra*) mixing a chiral phosphoramidite and an achiral phosphine was shown to increase both the activity and the enantioselectivity. This suggests the occurrence of several equilibria involving a mixed RhLL′ species which in turn should be responsible for the observed performance.[43]





1 R^1 = H, R^2 = R^3 = Me
2 R^1 = *m*-Cl, R^2 = R^3 = Me
3 R^1 = *p*-Br, R^2 = R^3 = Me
4 R^1 = *p*-Me, R^2 = R^3 = Me
5 R^1 = *p*-F, R^2 = R^3 = Me
6 R^1 = *p*-Cl, R^2 = R^3 = Me
7 R^1 = *o*-Cl, R^2 = R^3 = Me
8 R^1 = *o*-OMe, R^2 = R^3 = Me
9 R^1 = *p*-OMe, R^2 = R^3 = Me
10 R^1 = 2-Napht, R^2 = R^3 = Me
11 R^1 = *p*-NO_2, R^2 = R^3 = Me
12 R^1 = *o*-Me, R^2 = R^3 = Me
13 R^1 = *p*-F, R^2 = Me, R^3 = Ph
14 R^1 = *p*-Cl, R^2 = Me, R^3 = Ph
15 R^1 = R^2 = H, R^3 = Me
16 R^1 = H, R^2 = Et, R^3 = Me
17 R^1 = *p*-Cl, R^2 = Et, R^3 = Me
18 R^1 = R^2 = Me,
19 R^1 = H, R^2 = Me
20 R^1 = R^2 = H



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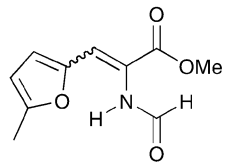

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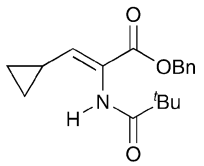

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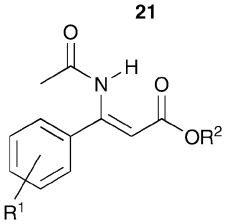
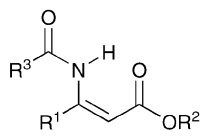
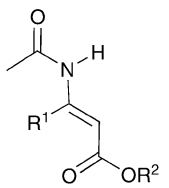


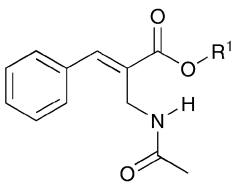
24 R^1 = *p*-Cl, R^2 = Me
25 R^1 = *p*-Cl, R^2 = Et
26 R^1 = H, R^2 = Et
27 R^1 = *m*-OMe, R = Me
28 R^1 = *p*-OMe, R^2 = Me
29 R^1 = *p*-OMe, R^2 = Et
30 R^1 = *p*-Me, R^2 = Me
31 R^1 = *p*-Me, R^2 = Et
32 R^1 = *p*-F, R^2 = Me



33 R^1 = R^2 = R^3 = Me
34 R^1 = Ph, R^2 = R^3 = Me
35 R^1 = R^3 = Me, R^2 = Et
36 R^1 = Et, R^2 = R^3 = Me
37 R^1 = R^2 = Me, R^3 = Ph
38 R^1 = *i*-Pr, R^2 = R^3 = Me
39 R^1 = *i*-Pr, R^2 = Et, R^3 = Me
40 R^1 = Ph, R^2 = Et, R^3 = Me



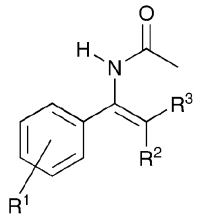
41 R^1 = R^2 = Me
42 R^1 = Me, R^2 = Et
43 R^1 = Et, R^2 = Me
44 R^1 = *i*-Pr, R^2 = Me



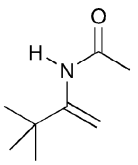
45 R^1 = Me
46 R^1 = H

4. Varying the amino group of BINOL-derived phosphoramidites

This section examines the changes induced in hydrogenation by introducing functional groups into the amino group of a binoPNRR′ phosphoramidite. The results presented show only trends, each ligand considered having not necessarily been optimised in a specific case. The fact that a ligand does not make a specific product with high ee does not mean that the ligand is useless for hydrogenation of other substrates. Two types of amino groups will be considered: those in which the amino moiety contains an auxiliary functional group, and those in which the amino group bears a stereogenic centre. Thus, the discussion excludes NRR′ moieties where R or R′ are simple alkyls. Whenever possible, the results obtained for a given phosphoramidite will be compared to a similar run carried out with the reference ligand, binoPNMe_2 (*i.e.* MonoPhos). The latter, as well as related dialkylamino phosphoramidites, usually turned out to provide good hydrogenation rates.[28] However, it is worth mentioning here that some particular dialkylaminophosphoramidites may lead to higher hydrogenation rates, at least for specific substrates. For example, in a publication of 2003, Peña *et al.* showed that the hydrogenation of **1** occurred *ca.* 10 times faster with



47 $R^1 = R^2 = R^3 = H$,
48 $R^1 = p$-Cl, $R^2 = R^3 = H$,
49 $R^1 = p$-OMe, $R^2 = R^3 = H$,
50 $R^1 = p$-Me, $R^2 = R^3 = H$,
51 $R^1 = p$-CF_3, $R^2 = R^3 = H$,
52 $R^1 = p$-Br, $R^2 = R^3 = H$,
53 $R^1 = m$-OMe, $R^2 = R^3 = H$,
54 $R^1 = p$-F, $R^2 = R^3 = H$,
55 $R^1 = R^2 = H$, $R^3 = Et$,
56 $R^1 = R^3 = H$, $R^2 = Et$,
57 $R^1 = H$, $R^2 = R^3 = Me$



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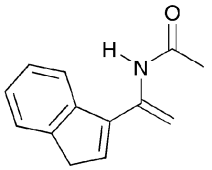

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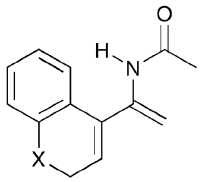
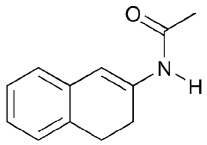


60 X = CH_2,
61 X = O



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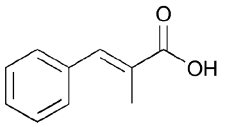

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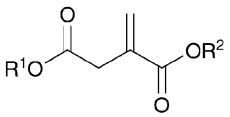
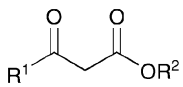


64 $R^1 = R^2 = H$
65 $R^1 = R^2 = Me$



66 $R^1 = R^2 = Me$,
67 $R^1 = Ph$, $R^2 = Et$,
68 $R^1 = Et$, $R^2 = Me$,
69 $R^1 = Me$, $R^2 = Et$

binoPNH(CHMePh) than with binoPNMe$_2$.[44] We note that in most BINOL-derived monophosphoramidites for which the solid state structure was established, the nitrogen atom adopts a planar structure.[45] In some rare examples slight deviation from planarity was observed, thus making the nitrogen, when heterosubstituted, a stereogenic centre.[46]

4.1 Amino groups containing ether or thioether functions

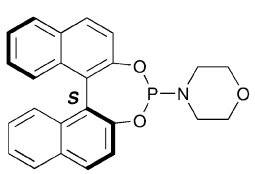
To date, thirteen phosphoramidites bearing an ether or a thioether group have been reported. In **70–75**, the nitrogen atom is part of a heterocycle. In **70–72** the chalcogen is incorporated into the heterocycle, while in **73–75** it belongs to a pendent group. The morpholine derivative **70** (MorfPhos) is the most studied ligand in this category. This is not only due to the easy access to this ligand, but also to its good performance. The reaction rates observed with this ligand in the hydrogenation of the α-dehydroamino esters **1** and **18**, the *N*-formyl dehydroamino esters **21** and **22**, and dimethyl itaconate (**65**) are similar to those obtained with MonoPhos. In most instances, the enantioselectivities obtained with ligand **70** were better than with MonoPhos (Table 1, entries 1–5).[47,48] For example, an ee increase of 17% was observed in the hydrogenation of the cyclohexylidene olefin **21**.

Similarly good performance was observed with **70** in the asymmetric reduction of the cyclic and acyclic enamides **47–62**, the ee's increasing up to 18% with respect to MonoPhos (Table 1, entries 7–21).[48] It should be noted that lowering the temperature led to slightly higher ee's, but concomitantly the TOF's decreased (Table 1, entries 15, 16, 18 and 19). Phosphoramidite **70** led also to better results in the enantioselective hydrogenation of the enamides **47–62** than common bidentate ligands, such as, *e.g.*, DIOP or DuPhos.[9,49] However, the reduction of the enamides **56–58**, and **62** gave mediocre results in terms of enantiodiscrimination (Table 1, entries 11–13 and 21). Interestingly, low enantioselectivities were also observed for these latter enamides when using MonoPhos.[48] These results are further consistent with observations made by Reetz *et al.*, who obtained poor enantioselectivities by hydrogenating the enamides **56** (*E*-configuration) and **57** with related *phosphites*.[50] The asymmetric reduction of olefin **63** with ligand **70** turned out

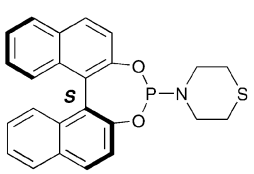
Table 1 Rhodium-catalysed olefin hydrogenation with phosphoramidites **70–75**

Entry	Ligand	Olefin	$P(H_2)$ (bar)	Olefin : Rh : L	Time (h)	Conv (%)	Ee (%) (*config*)
1	**70**	**1**	5	100 : 2 : 4	4	100	98 (*R*)
2	**70**	**18**	5	100 : 2 : 4	4	100	99 (*R*)
3	**70**	**21**	5	100 : 5 : 10	16	54	42 (*R*)
4	**70**	**22**	5	100 : 5 : 10	16	100	88 (*R*)
5	**70**	**65**	5	100 : 2 : 4	4	100	98 (*S*)
6	**70**	**63**	25	100 : 1 : 2	5	72	0
7	**70**	**47**	25	100 : 2 : 4	8	100	>99 (*R*)
8	**70**	**48**	25	100 : 2 : 4	8	100	99 (*R*)
9	**70**	**49**	25	100 : 2 : 4	8	100	99 (*R*)
10	**70**	**55**	25	100 : 2 : 4	8	100	98 (*R*)
11	**70**	**56**	25	100 : 2 : 4	8	100	23 (*R*)
12	**70**	**57**	25	100 : 2 : 4	8	70	5
13	**70**	**58**	25	100 : 2 : 4	8	100	27 (*S*)
14	**70**	**59**	25	100 : 2 : 4	8	100	90 (*R*)
15	**70**[a]	**59**	55	100 : 2 : 4	8	100	95 (*R*)
16	**70**[b]	**59**	55	100 : 2 : 4	8	89	97 (*R*)
17	**70**	**60**	25	100 : 2 : 4	8	100	87 (*R*)
18	**70**[a]	**60**	55	100 : 2 : 4	8	100	94 (*R*)
19	**70**[b]	**60**	55	100 : 2 : 4	8	94	97 (*R*)
20	**70**	**61**	25	100 : 2 : 4	8	100	>99
21	**70**	**62**	25	100 : 2 : 4	8	100	13
22	**71**	**18**	5	100 : 2 : 4	4	100	86 (*R*)
23	**71**	**1**	5	100 : 2 : 4	4	94	47 (*R*)
24	**71**	**65**	5	100 : 2 : 4	4	50	40 (*S*)
25	**71**	**47**	25	100 : 2 : 4	8	100	97 (*R*)
26	**71**	**48**	25	100 : 2 : 4	8	100	85 (*R*)
27	**71**	**49**	25	100 : 2 : 4	8	100	90 (*R*)
28	**71**	**55**	25	100 : 2 : 4	8	100	62 (*R*)
29	**71**	**58**	25	100 : 2 : 4	8	100	10 (*R*)
30	**71**	**59**	25	100 : 2 : 4	8	75	25 (*R*)
31	**71**	**60**	25	100 : 2 : 4	8	94	11 (*R*)
32	**71**	**61**	25	100 : 2 : 4	8	100	40
33	**71**	**62**	25	100 : 2 : 4	8	94	34
34	**72**	**65**	1.3	100 : 1 : 1.2	12	5	78 (*R*)
35	**73**	**16**	10	100 : 1 : 2.2	—	—	—
36	**74**	**16**	10	100 : 1 : 2.2	—	100	90 (*S*)
37	**74**	**17**	10	100 : 1 : 2.2	—	100	91 (*S*)
38	**74**	**6**	10	100 : 1 : 2.2	—	100	84 (*S*)
39	**74**	**9**	10	100 : 1 : 2.2	—	100	90 (*S*)
40	**75**	**65**	1	100 : 1 : 2	12	43	71 (*S*)
41	**75**	**1**	1	100 : 1 : 2	12	63	55 (*R*)

General conditions: T = rt, solvent = CH_2Cl_2.[a] T = 0 °C. [b] T = −20 °C.



70 (MorfPhos)



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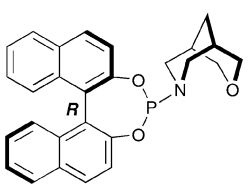

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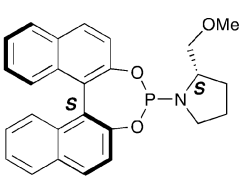

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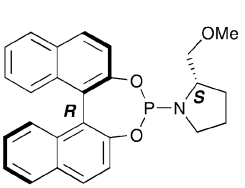

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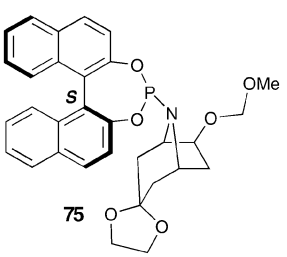

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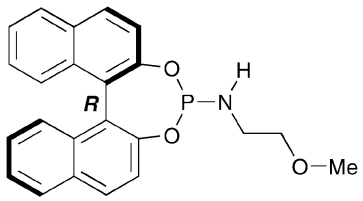

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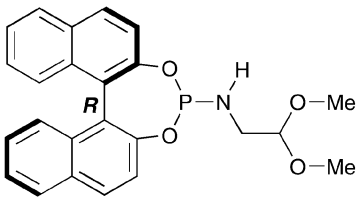

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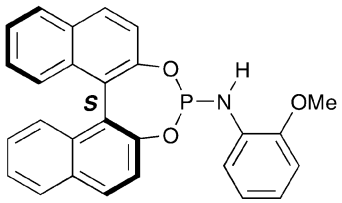
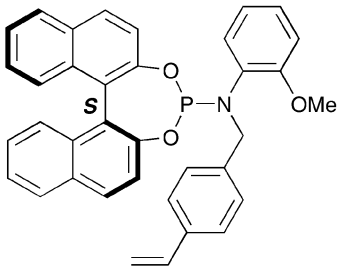


78



79

to be difficult, and not selective at all when operating under 25 bar (Table 1, entry 6).[29]

The behaviour of the thiomorpholine derivative **71** strongly contrasts with that of **70**. Thus, drastic drops in the ee's and in the hydrogenation rates were observed during the reduction of the olefins **1** and **15**, and dimethyl itaconate **65** (Table 1, entries 22–24). Bernsmann *et al*. put forth the hypothesis that the catalyst is inhibited by sulfur–rhodium interactions during the catalytic process.[48] The same effect seems to take place in the reduction of enamides (**47–62**), a marked decrease of the ee's relative to those obtained with **70** being observed here again. (Table 1, entries 25–33). Only with the enamides **47** and **49** do the selectivities and conversions approach those obtained with **70** (Table 1, entries 26 and 28).

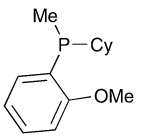
The phosphoramidite **72**, which may act as a hemilabile *P,O* ligand, was only tested in the hydrogenation of dimethyl itaconate **65**. This experiment gave 78% ee (*vs*. 98% for **70**) and a poor conversion (see entries 34 and 5, respectively, in Table 1).[51]

The three phosphoramidites **73–75**, each containing a five-membered N-heterocyclic moiety substituted by an ether arm, were used in the hydrogenation of some α-dehydroamino esters (**1**, **6**, **9**, **16**, and **17**) and of dimethyl itaconate (**65**). Surprisingly, the L-proline-derived phosphoramidite **73** showed no catalytic activity (Table 1, entry 35). In contrast, diastereomer **74** fully hydrogenated the selected α-dehydroamino esters with ee's up to 91% (Table 1, entries 36–39). Zeng *et al*. attributed these unexpected results to the match and mismatch of the central chirality (*i.e*. of the proline moiety) and the axial chirality of the binaphthyl moiety, the ether function playing a minor role.[52] Possible transient binding of the ether function (which would make this atom a centre of chirality) during catalysis was not considered.

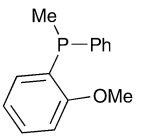
Ligand **75** was tested with the substrates **1** and **65**, but both the activity and the ee's were mediocre (Table 1, entries 40 and 41).[53]

In the mixed phosphoramidite-ether ligands **76–82**, the nitrogen atom is no longer part of a ring. The phosphoramidites **76** and **77** displayed good activities in the hydrogenation of the α-dehydroamino ester **1**, but led to selectivities not higher than 82% (Table 2, entries 1 and 3). Hydrogenation with these two ligands of the β-dehydroamino ester **33** was less easy. Furthermore, in this case the ee's dropped to *ca*. 65% (Table 2, entries 2 and 4).[54]

Doherty *et al*. prepared ligands **78** and **79** with the expectation that the *P,O* part would behave as a hemilabile six-membered chelate, as was observed in complexes with the anisyl phosphines CAMP and PAMP.[55] Should O-binding occur, this would then probably result in the formation of diastereomers. In fact, reductions of the α-dehydroamino acid and esters **1**, **15**, **18**, and **19** using ligand **78**, led to lower ee's (up to 30%) than using binoPNMe$_2$ (Table 2, entries 5–8). This was also the case when the ligand was employed in the reduction of dimethyl itaconate **65** (91% *vs*. 94%; see Table 2, entry 9).



CAMP



PAMP

Substitution of the N-bonded hydrogen of **78** by a *p*-vinylbenzyl group (leading to ligand **79**), resulted in all cases in a dramatic drop of enantioselectivity (Table 2, entries 10–14). Doherty *et al*. attributed these results to the steric bulk at nitrogen but without demonstrating that this creates an unfavourable interaction with the substrate. Interestingly, the configuration of the products obtained after hydrogenation with **79** of olefins **15**, **18** and **65** (Table 2: entries 13, 10 and 14, respectively) is opposite to the one obtained when using binoPNMe$_2$.[27] In contrast, the less bulky ligand **78** results in the expected configurations (*cf*. Table 2, entries 8, 5 and 9).

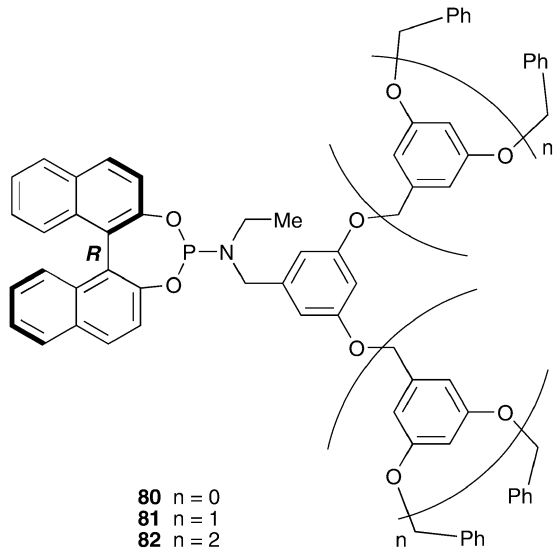
Tang *et al*.[56] refuted this interpretation by using the bulky, dendritic phosphoramidites **80–82** as ligands for the asymmetric hydrogenation of some α-dehydroamino esters (**1–3**, **5–9**, **11** and **12**) and dimethyl itaconate (**65**) (Table 3, entries 1–42). The highest activities were obtained by

Table 2 Olefin hydrogenation using the mixed phosphoramidite–ether ligands **76–79**

Entry	Ligand	Olefin	$P(H_2)$ (bar)	S : Rh : L	Time (h)	Conv (%)	Ee (%) (*config*)
1	**76**	**1**	1	100 : 1 : 2	6	100	79 (*S*)
2	**76**[a]	**33**	1	100 : 1 : 2	6	13	66 (*S*)
3	**77**	**1**	1	100 : 1 : 2	6	100	82 (*S*)
4	**77**[a]	**33**	1	100 : 1 : 2	6	30	64 (*S*)
5	**78**	**18**	1	100 : 5 : 10	20	100	76 (*R*)
6	**78**	**19**	1	100 : 5 : 10	20	100	67 (*R*)
7	**78**	**1**	1	100 : 5 : 10	20	100	82 (*R*)
8	**78**	**15**	1	100 : 5 : 10	20	100	63 (*R*)
9	**78**	**65**	1	100 : 5 : 10	20	100	91 (*S*)
10	**79**	**18**	1	100 : 5 : 10	20	100	37 (*S*)
11	**79**	**19**	1	100 : 5 : 10	20	100	46 (*R*)
12	**79**	**1**	1	100 : 5 : 10	20	100	33 (*R*)
13	**79**	**15**	1	100 : 5 : 10	20	100	39 (*S*)
14	**79**	**65**	1	100 : 5 : 10	20	100	29 (*R*)

General conditions: T = rt, solvent = CH_2Cl_2.[a] Solvent = *i*-PrOH.

applying standard conditions, namely with a ligand : metal ratio of 2 : 1.



80 n = 0
81 n = 1
82 n = 2

All runs led to better or comparable selectivities (ee's > 95%) and activities than the reference ligand (Table 3, entries 1–32). It should be mentioned here that there is only a limited number of instances where a monophosphoramidite has given higher ee's than MonoPhos. Tang *et al*. attributed the good selectivities to a partial encapsulation of the catalytic centre within the high generation dendritic wedges, in other terms, to the selectivity being controlled by the second coordination sphere. Furthermore, the steric protection about the metal centre led to a catalyst with a better lifetime. Increasing the ligand : metal ratio induced, in most cases, a drastic drop in the enantioselectivity and the TOF as well (see for example, Table 3, entries 36–39 and 41). These latter findings are in agreement with those reported by van den Berg *et al*. when using MonoPhos in excess.[31] In one instance, however, an excess of ligand **82** (4.2 equiv.) led to an excellent selectivity, ee = 97%, and a good activity (Table 3, entry 40). Possibly, in this case, the dendritic wedges prevent the formation of a complex bearing more than two phosphorus ligands. Thus, in the resulting complex, the bulky metal environment may lead to higher chiral induction.[56] These assumptions were confirmed by adding free metal precursor during an hydrogenation run carried out with an initial ligand : metal ratio close to 4 (Table 3, entry 42), so as to obtain a L : M ratio of 2, and incidentally achieving a performance comparable to experiments done under standard conditions.

4.2 Amino groups containing ester functions

Monodentate phosphoramidites containing an auxiliary ester function were independently reported by de Vries (**83–86**)[48,54] and Matt (**87** and **88**)[38] (note, the stereochemistry of the CCO_2 carbon atom of **83** was not given in the original paper).

de Vries *et al*. found that ligands **83–86**, when combined with rhodium(I), led to efficient catalysts for the hydrogenation of α-dehydroamino esters **1** and **18** and dimethyl itaconate (**65**) (Table 4, entries 1, 3 and 5–10). The observed selectivities were, however, all lower than the ones obtained with MonoPhos. Using ligands **83** and **84** for the reduction, in *iso*-propanol, of the β-dehydroamino ester **33** (Table 4, entries 2 and 4) gave poor conversions (less than 8%) and weak ee's (between 26 and 29%).

The alanine- and phenylalanine-derived phosphoramidites **87** and **88** were tested in the hydrogenation of olefins **1**, **5**, and **6**. As a general trend, these ligands displayed slightly lower hydrogenation rates than those observed with **83–86**. The reaction occurred *ca*. 1.5 times faster with the alanine derivative **87** than with the more crowded ligand **88**. The highest ee's (92%) were obtained with **88** (hydrogenation of substrate **1**).

4.3 Olefin hydrogenation using phosphoramidites incorporating an amide

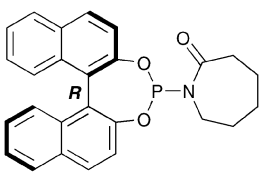
Only one publication deals with the synthesis of a phosphoramidite containing an amido group, namely **89**. This ligand was used for the hydrogenation of substrates **1** and **33**. As already observed with ligands **83** and **84**, the selectivity for the reduction of **1** (ee = 68%) with **89** was significantly higher than for **33** (ee = 22%). The same observation holds for the reaction rate (Table 5, entries 1 and 2).[54]

Overall, the performance of this ligand is far from that of the reference ligand.

Table 3 Olefin hydrogenation with the dendritic phosphoramidites **80–82**

Entry	Ligand	Olefin	$P(H_2)$ (bar)	Olefin : Rh : L	Time (h)	Conv (%)	Ee (%) (*config*)
1	**80**	**1**	20	100 : 1 : 2	10	100	97.5 (*S*)
2	**81**	**1**	20	100 : 1 : 2	10	100	97.4 (*S*)
3	**82**	**1**	20	100 : 1 : 2	10	100	97.9 (*S*)
4	**81**	**1**	1	100 : 1 : 2	1	100	97.8 (*S*)
5	**80**	**1**	15	1000 : 1 : 2	15	100	97.7 (*S*)
6	**82**	**1**	15	1000 : 1 : 2	15	100	97.8 (*S*)
7	**80**	**1**	10	1000 : 1 : 2	0.2	95.8	97.3 (*S*)
8	**81**	**1**	10	1000 : 1 : 2	0.2	97.0	97.5 (*S*)
9	**82**	**1**	10	1000 : 1 : 2	0.2	74	97.3 (*S*)
10	**80**[a]	**1**	20	100 : 1 : 2	0.2	95.8	97.3 (*S*)
11	**81**[b]	**1**	20	100 : 1 : 2	0.2	97.0	97.5 (*S*)
12	**80**	**2**	20	100 : 1 : 2	—	100	97.8 (*S*)
13	**81**	**2**	20	100 : 1 : 2	—	100	97.6 (*S*)
14	**80**	**6**	20	100 : 1 : 2	—	100	96.0 (*S*)
15	**81**	**6**	20	100 : 1 : 2	—	100	97.3 (*S*)
16	**80**	**5**	20	100 : 1 : 2	—	100	97.4 (*S*)
17	**81**	**5**	20	100 : 1 : 2	—	100	97.1 (*S*)
18	**80**	**3**	20	100 : 1 : 2	—	100	97.5 (*S*)
19	**81**	**3**	20	100 : 1 : 2	—	100	97.0 (*S*)
20	**80**	**9**	20	100 : 1 : 2	—	100	97.7 (*S*)
21	**81**	**9**	20	100 : 1 : 2	—	100	97.7 (*S*)
22	**80**	**11**	20	100 : 1 : 2	—	100	96.2 (*S*)
23	**81**	**11**	20	100 : 1 : 2	—	100	97.0 (*S*)
24	**80**	**12**	20	100 : 1 : 2	—	100	96.3 (*S*)
25	**81**	**12**	20	100 : 1 : 2	—	100	96.2 (*S*)
26	**82**	**12**	20	100 : 1 : 2	—	100	97.3 (*S*)
27	**80**	**8**	20	100 : 1 : 2	—	100	95.6 (*S*)
28	**81**	**8**	20	100 : 1 : 2	—	100	95.0 (*S*)
29	**80**	**7**	20	100 : 1 : 2	—	100	95.6 (*S*)
30	**81**	**7**	20	100 : 1 : 2	—	100	94.6 (*S*)
31	**80**	**65**	20	100 : 1 : 2	—	100	97.7 (*S*)
32	**81**	**65**	20	100 : 1 : 2	—	100	97.0 (*S*)
33	**81**	**1**	1	100 : 1 : 2.1	3	88	97.9 (*S*)
34	**81**	**1**	1	100 : 1 : 1	3	98.7	97.8 (*S*)
35	**81**	**1**	1	100 : 2 : 1	3	100	94.5 (*S*)
36	**81**	**1**	1	100 : 1 : 3	3	4.4	—
37	**81**	**1**	1	100 : 1 : 4	3	1.4	—
38	**81**	**1**	20	100 : 1 : 4.2	5	5.7	—
39	**80**	**1**	20	100 : 1 : 4.2	5	4.0	—
40	**82**	**1**	20	100 : 1 : 4.2	5	46.6	97.0 (*S*)
41	**81**	**1**	1	100 : 1 : 3.5	4	4.0	—
42	**81**[c]	**1**	1	100 : 1 : 3.5	4	97.6	97.2 (*R*)

General conditions: T = rt, solvent = CH_2Cl_2.[a] Solvent: CH_2Cl_2/MeOH = 2 : 1 (v/v). [b] Solvent: CH_2Cl_2/MeOH = 1 : 1 (v/v). [c] Olefin : rhodium : Ligand = 100 : 1 : 3.5 to 100 : 1 : 2.



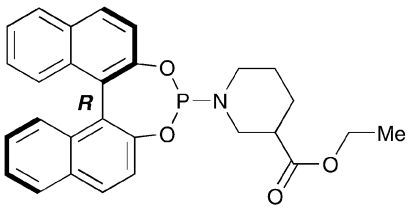
89

4.4 Olefin hydrogenation with phosphoramidites containing a pyridinic fragment

Phosphoramidites containing a pyridine moiety (**90–94**) have been employed for the hydrogenation of different dehydroamino esters and dimethyl itaconate (Table 6, entries 1–19).[48,54,55]

Doherty *et al.*[55] synthesized the quinoline derivative **90**. Adding this ligand to $[Rh(COD)_2]BF_4$ in a 2 : 1 stoichiometry provided no catalysis (Table 6, entry 1), apparently due to the formation of the inactive bis-*P,N*-chelate complex $[Rh(\mathbf{90})_2]BF_4$. Inactive, cationic rhodium bis-chelate complexes had already been reported by other authors.[57] Reducing the metal : ligand ratio to 1 : 1 resulted in an active catalyst, but the ee's did not exceed 69% (Table 6, entry 2). Careful examination of the reaction mixture revealed that beside the expected $[Rh(\mathbf{90})(COD)]BF_4$ complex, the bis-chelate $[Rh(\mathbf{90})_2]BF_4$ had formed as the major compound (ratio 2 : 3). The mono-chelate complex could be isolated and was used in several hydrogenation experiments (substrates used: **1**, **15**, **18** and **65**; see Table 6, entries 3–6) but the selectivities were all below those of the reference ligand. The highest ee, 95%, was obtained with dimethyl itaconate (**65**). Results for substrate **19** were the least satisfactory, as ligand **90** induced only weak selectivities (ee's up to 63%) and low conversions (Table 6, entries 7 and 8).

In order to generate functionalised resins suitable for the preparation of supported catalysts, Doherty *et al.*[55] synthesised the polyphosphoramidite **91**, which is a co-polymer of **90a** and styrene. The polymeric ligand was used for the catalytic reduction of the substrates **1**, **15**, **18**, **19** and **65** (Table 6, entries



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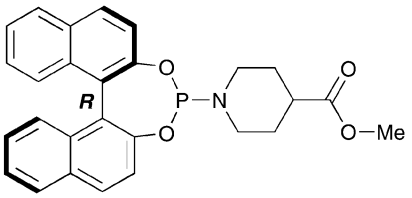

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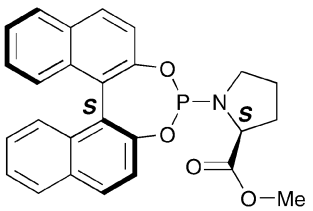

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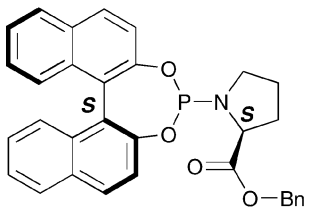

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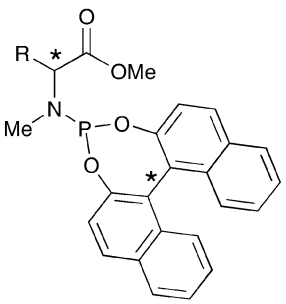


(S_{Bn},S_{bin})-**87a** (R = benzyl)
(R_{Bn},R_{bin})-**87b** (R = benzyl)
(R_{Bn},S_{bin})-**87c** (R = benzyl)
(S_{Bn},R_{bin})-**87d** (R = benzyl)
(S_{Me},R_{bin})-**88a** (R = methyl)
(S_{Me},S_{bin})-**88b** (R = methyl)

9–13). The rhodium loading in the catalyst was 0.26 wt%. The investigations revealed that [Rh(**90**)(COD)]BF_4 outperforms the supported versions of this complex. The worst result was obtained in the hydrogenation of dimethyl itaconate (**65**), for which both the selectivity (ee = 49%) and the activity were low (Table 6, compare entries 4 and 9).

The phosphoramidites **92–94**, which are sterically less demanding than ligands **90** and **91**, were the basis of automated screening experiments conducted by Lefort *et al.*[54] on the catalytic asymmetric reduction of substrates **1** and **33** (Table 6, entries 14–19) (*the ligands were not purified during the automated steps; in some ligand syntheses, several phosphorus containing products were formed*). Only **92** catalysed the hydrogenation of these dehydroamino esters, but again the selectivities (ee 75% for **1**; 1% for **33**) were lower than when using the reference ligand (Table 6, entries 14 and 15). The authors attributed the apparent absence of reaction with ligands **93** and **94** to the fact that these ligands were not actually formed under the conditions used. It is likely that the pyridinic nitrogen atom of **92** has but a slight influence on the catalytic outcome. Indeed, replacement of the pyridinyl group by the *p*-NO_2-aryl group (*i.e.* using ligand **95**) led to similar selectivity and activity (Table 6, entries 20 and 21).

4.5 Using phosphoramidites in which the amino part bears a tertiary amine

de Vries *et al.* studied the phosphoramidites **96–98**, in which the P-bonded amino group contains a tertiary amine.[54] As for the mixed phosphoramidite–pyridinyl ligands described above, the ligands were obtained through an automated procedure. The screening tests concerned the asymmetric hydrogenation of the α- and β-dehydroamino esters **1** and **33**. The hydrogenations with **96** were unsuccessful (Table 7, entries 1 and 2). In contrast, catalysts based on phosphoramidites **97** or **98** led to fast hydrogenation of **1**. The corresponding selectivities (ee = 73% for **97**, 88% for **98**) were again poorer than when using MonoPhos (Table 7, entries 3 and 5). Both ligands gave mediocre results in the hydrogenation of β-dehydroamino ester **33**, the ee being only 39% with ligand **98**, and 13% with **97** (Table 7, entries 4 and 6). Note that the latter test was performed in iso-propanol.

Table 4 Olefin hydrogenation using the mixed phosphoramidite–ester ligands **83–88**

Entry	Ligand	Olefin	$P(H_2)$ (bar)	S : Rh : L	Time (h)	Conv (%)	Ee (%) (*config*)
1	**83**	**1**	1	100 : 1 : 2	6	100	87 (*S*)
2	**83**[a]	**33**	1	100 : 1 : 2	6	2	29 (*S*)
3	**84**	**1**	1	100 : 1 : 2	6	100	92 (*S*)
4	**84**[a]	**33**	1	100 : 1 : 2	6	8	26 (*S*)
5	**85**	**18**	5	100 : 2 : 4	4	100	88 (*R*)
6	**85**	**1**	5	100 : 2 : 4	4	100	52 (*R*)
7	**85**	**65**	5	100 : 2 : 4	4	100	15 (*S*)
8	**86**	**18**	5	100 : 2 : 4	4	100	84 (*R*)
9	**86**	**1**	5	100 : 2 : 4	4	100	68 (*R*)
10	**86**	**65**	5	100 : 2 : 4	4	100	68 (*S*)
11	**87a**	**1**	5	100 : 1 : 2.2	24	90	85 (*R*)
12	**87a**[b]	**5**	5	100 : 1 : 2.2	16	100	47 (*R*)
13	**87a**[c]	**5**	5	100 : 1 : 2.2	16	100	37 (*R*)
14	**87a**[d]	**5**	5	100 : 1 : 2.2	16	100	35 (*R*)
15	**87a**	**5**	5	100 : 1 : 2.2	16	75	86 (*R*)
16	**87a**	**5**	5	100 : 1 : 2.2	24	100	90 (*R*)
17	**87a**	**6**	5	100 : 1 : 2.2	24	98	89 (*R*)
18	**87b**	**1**	5	100 : 1 : 2.2	24	100	92 (*S*)
19	**87b**	**1**	5	100 : 1 : 1	24	100	69 (*S*)
20	**87b**	**1**	5	100 : 1 : 1.5	24	100	83 (*S*)
21	**87b**	**1**	5	100 : 1 : 2.5	24	100	90 (*S*)
22	**87b**	**5**	5	100 : 1 : 2.2	24	94	88 (*S*)
23	**87b**	**6**	5	100 : 1 : 2.2	24	99	92 (*S*)
24	**87c**	**1**	5	100 : 1 : 2.2	24	93	87 (*R*)
25	**87c**	**1**	5	100 : 1 : 1	24	86	79 (*R*)
26	**87c**	**1**	5	100 : 1 : 1.5	24	85	81 (*R*)
27	**87c**	**1**	5	100 : 1 : 2.2	24	86	85 (*R*)
28	**87c**	**5**	5	100 : 1 : 2.2	24	12	67 (*R*)
29	**87d**	**1**	5	100 : 1 : 2.2	24	93	90 (*S*)
30	**87d**	**5**	5	100 : 1 : 2.2	24	14	68 (*S*)
31	**88a**	**1**	5	100 : 1 : 2.2	18	100	81 (*S*)
32	**88a**	**5**	5	100 : 1 : 2.2	18	100	78 (*S*)
33	**88b**	**1**	5	100 : 1 : 2.2	18	100	78 (*R*)
34	**88b**	**5**	5	100 : 1 : 2.2	18	100	76 (*R*)

General conditions: T = rt, solvent = CH_2Cl_2; [Rh] = 1–2 mol%.[a] Solvent = *i*-PrOH. [b] Solvent = THF. [c] Solvent = MeOH. [d] Solvent = EtOAc.

Table 5 Hydrogenation of olefins **1** and **33** with the phosphoramidite–ketone **89**

Entry	Ligand	Olefin	$P(H_2)$ (bar)	S : Rh : L	Time (h)	Conv (%)	Ee (%) (*config*)
1	**89**	**1**	1	100 : 1 : 2	6	100	68 (*S*)
2	**89**[a]	**33**	1	100 : 1 : 2	6	4	22 (*S*)

General conditions: T = rt, solvent = CH_2Cl_2.[a] Solvent = *i*-PrOH.

Unlike **96–98**, phosphoramidite **99** was prepared as a pure product.[48] When used in the hydrogenation of α-dehydroamino esters **1** and **18** and of dimethyl itaconate **65**, it gave results close to those obtained with MonoPhos (full conversions and ee's up to 97%) (Table 7, entries 7–9). In the reduction of enamides **47–49**, **55**, **56** and **59–62**, phosphoramidite **99** led to higher ee's (up to 99%) than MonoPhos (Table 7, entries 10–14 and 17–20). Other enamides, such as **57** and **58**, gave low enantioselectivities (4% for 57; 21% for 58; *cf*. 49% for MonoPhos) (Table 7, entries 15 and 16), thus clearly showing that **99** is only well suited to certain substrates.

4.6 Using phosphoramidites in which the phosphorus atom is connected to a sulfoximinyl group

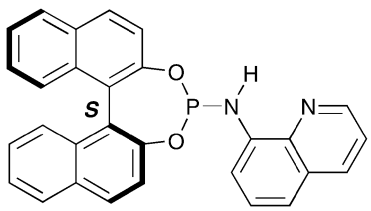
Reetz, Gais *et al*. have prepared and characterised a series of phosphoramidites that incorporate a chiral (**100** and **101**) or an achiral (**102** and **103**) sulfoximine moiety. These compounds were tested in the asymmetric hydrogenation of α-dehydroamino esters **1** and **18**, the enamide **47** and dimethyl itaconate (**65**).[58] All four ligands showed good activities for these substrates (see Table 8). Using chiral sulfoximines **100** and **101** with substrates **1**, **18** and **65** led to excellent selectivities (ee's up to 99%), significantly higher than those obtained with the reference ligand. Interestingly, for the latter three olefins, the configuration at sulfur had no impact on the enantioselectivities, the diastereomeric phosphoramidites **100** and **101** inducing identical selectivities (same absolute ee value) (Table 8, entries 1–3 and 5–7). This is no longer the case when using enamide **47** as substrate. In this case, the ee drops from 87.5% when using ligand **100** (matched case) to 76% with ligand **101** (mismatched case) (Table 8, entries 4 and 8).

Phosphoramidites **102** and **103** having achiral sulfoximinyl moieties gave high ee's (all higher than 94%) in the hydrogenation of **1**, **18** and **65** (Table 8, entries 9–11 and 13–15). Their performance was, however, considerably poorer in the reduction of **47** (Table 8, entries 12 and 16). The question of whether these phosphoramidites behave in a monodentate manner or as *P*,*O*-chelates remains open.

Table 6 Olefin hydrogenation using phosphoramidites containing a pyridinic substituent

Entry	Ligand	Olefin	$P(H_2)$ (bar)	S : Rh : L	Time (h)	Conv (%)	Ee (%) (*config*)
1	**90**	**18**	1	100 : 5 : 10	20	0	—
2	**90**	**18**	1	100 : 5 : 5	20	100	69 (*R*)
3	**90**[a]	**18**	1	100 : 5 : 5	20	100	84 (*R*)
4	**90**[a]	**65**	1	100 : 5 : 5	20	100	95 (*S*)
5	**90**[a]	**1**	1	100 : 5 : 5	4	100	78 (*R*)
6	**90**[a]	**15**	1	100 : 5 : 5	20	98	75 (*R*)
7	**90**[a]	**19**	1	100 : 5 : 5	20	49	63 (*R*)
8	**90**[ac]	**19**	1	100 : 5 : 5	20	74	54 (*R*)
9	**91**[a]	**65**	1	100 : 5 : 5	20	57	49 (*S*)
10	**91**[a]	**18**	1	100 : 5 : 5	20	96	65 (*R*)
11	**91**[a]	**19**	1	100 : 5 : 5	20	23	57 (*R*)
12	**91**[a]	**1**	1	100 : 5 : 5	20	100	64 (*R*)
13	**91**[a]	**15**	1	100 : 5 : 5	20	100	49 (*R*)
14	**92**	**1**	6	100 : 1 : 2	1	100	75 (*S*)
15	**92**[b]	**33**	6	100 : 1 : 2	1	59	1 (*S*)
16	**93**	**1**	6	100 : 1 : 2	1	0	—
17	**93**[b]	**33**	6	100 : 1 : 2	1	0	—
18	**94**	**1**	6	100 : 1 : 2	1	0	—
19	**94**[b]	**33**	6	100 : 1 : 2	1	0	—
20	**95**	**1**	6	100 : 1 : 2	1	100	73 (*S*)
21	**95**[b]	**33**	6	100 : 1 : 2	1	2	21 (*S*)

General conditions: T = rt, solvent = CH_2Cl_2.[a] Isolated complex; [b] solvent = *i*-PrOH. [c] T = 30 °C.



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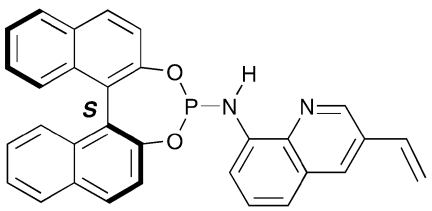

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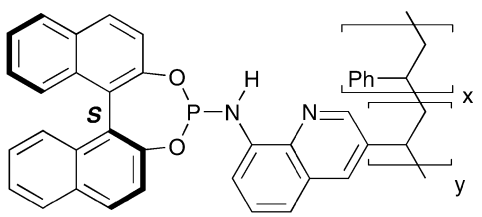
4.7 Phosphoramidites with amino groups containing at least one stereogenic centre

The idea of introducing chirality into the substituents of the amino group of phosphoramidites was developed by several research groups with the expectation that this would improve the (dominant) efficiency of the "binoP" part. In the following, we will only consider phosphoramidites having a stereogenic centre as the sole functionality present in the amino group.

Each of the three diastereomers **104–106** contains a chiral methylbenzylamino group.

Ligand *S*,*R*-**104** was used for the reduction of β-dehydroamino esters (*Z*)-**32**, (*Z*)-**33**, (*Z*)-**35**, (*Z*)-**36**, and (*Z*)-**39**, (*Z*)-**40** and (*E*)-**41**.[59] Peña *et al*. first examined the hydrogenation of



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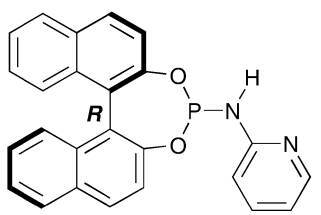

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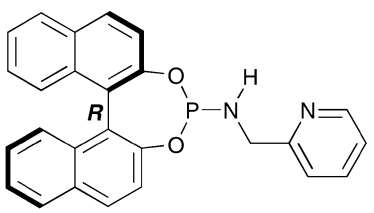

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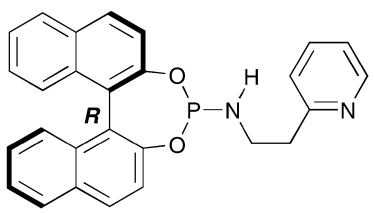

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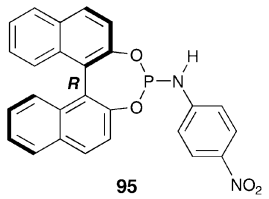

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the *Z*-olefins and found that carrying out the catalysis in a protic solvent such as *i*-PrOH gave the best enantioselectivities (Table 9, see entries 1 and 2). This kind of solvent possibly induces breaking of any intramolecular hydrogen bond in the substrate. The enantioselectivity also improved with an increase in the hydrogen pressure (Table 9, entries 3 and 4). The authors further found it advantageous to preform the catalyst in dichloromethane, rather than mixing the ligand, the precursor metal complex and the olefin in *i*-PrOH (Table 9, entries 4 and 5). By applying these optimised conditions, the authors were able to hydrogenate quantitatively (*Z*)-**32** and (*Z*)-**40** in *i*-PrOH with ee's of 94% and 92%, respectively (Table 9, entries 13 and 12). These results are the highest reported so far in the Rh-catalysed hydrogenation of β-aryl-β-(acylamino)acrylates.[60] Regarding the *E* isomer **41**, ee's were much higher and hydrogenation occurred much faster when operating in a *non protic* solvent. Thus, while the hydrogenation of (*E*)-**41** gave 83% ee in CH_2Cl_2 (conv. 100%), only 52% ee was reached in *i*-PrOH (conv. 52%) (Table 9, entry 15 *vs.* 14). In comparison, use of MonoPhos for the hydrogenation of **41** in CH_2Cl_2 provided an ee of 95%, *vs.* 64% in *i*-PrOH. The observation that CH_2Cl_2 is the better solvent for hydrogenations carried out with MonoPhos was also verified when reducing α-dehydroamino ester **1** (ee 95% *vs.* 89% with *S*,*R*-**104**) (Table 9, entry 16).[44]

Using *S*,*R*-**104** for the reduction of **63** in *i*-PrOH resulted in fast hydrogenation, but no chiral induction was observed (Table 9, entry 17).[29] The reduction of the dehydroamino ester **45** with this ligand was unsuccessful (Table 9, entries 18 and 19).[30]

Ligand **105**, which is the enantiomer of **104**, was only used in the hydrogenation of substrates **1** and **33**.[54] These runs were carried out in CH_2Cl_2 instead of *i*-PrOH (Table 9, entries 20 and 21). They led to lower ee's than the tests performed with **104** in *i*-PrOH (ee's up to 88% with **105** *vs.* 95% with **104**).

Compound *S*,*S*-**106**, a diastereomer of the two previous phosphoramidites was tested by Panella *et al.* in the catalytic reduction of 2-(formamido)acrylic acid **20**.[47] This reaction gave only 54% ee and a low conversion rate (21%; see Table 9, entry 22).

In a patent published in 2003, van den Berg *et al.* described the phosphoramidite *S*,*S*,*S*-**107**, containing two stereogenic centres within the amino group.[28] Only one catalytic run was described with this ligand, namely the reduction of the α-dehydroamino ester **1** under standard conditions.

Combining this phosphoramidite with rhodium(I) resulted in a moderate enantioselectivity (ee = 42% *vs.* 95% for MonoPhos) (Table 10, entry 1).

Eberhardt *et al.* recently synthesized the phosphoramidites **108**, all containing a chiral dinaphtho-azepinyl moiety, and found that rhodium complexes of the latter led to high hydrogenations rates with olefins **1**, **5** and **6**.[39] The highest enantioselectivities, up to 99% (!), were achieved for those stereomers of **108** having two chiral binaphthyl groups with opposite configurations. Thus, these results unambiguously showed that the performance of phosphoramidites with two binaphthyl units may significantly surpass those of MonoPhos.

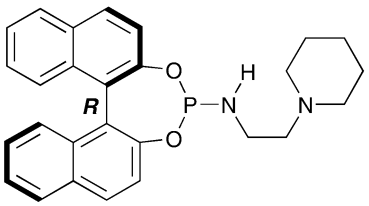
5. Bidentate P(III)/P(III)-ligands containing at least one phosphoramidite unit

While in the last decade many new BINOL-derived monophosphoramidite ligands have been described, a large library of bidentate phosphorus ligands containing the binoP–NRR′ unit has also been created. These bidentates, which differ from

Table 7 Olefin hydrogenation using phosphoramidites containing a auxiliary amine

Entry	Ligand	Olefin	$P(H_2)$ (bar)	S : Rh : L	Time (h)	Conv (%)	Ee (%) (*config*)
1	**96**	**1**	6	100 : 1 : 2	1	5	70 (*S*)
2	**96**[a]	**33**	6	100 : 1 : 2	1	0	—
3	**97**	**1**	6	100 : 1 : 2	1	100	73 (*S*)
4	**97**[a]	**33**	6	100 : 1 : 2	1	5	13 (*S*)
5	**98**	**1**	6	100 : 1 : 2	1	100	88 (*S*)
6	**98**[a]	**33**	6	100 : 1 : 2	1	22	39 (*S*)
7	**99**	**18**	5	100 : 2 : 4	4	100	96 (*R*)
8	**99**	**1**	5	100 : 2 : 4	4	100	97 (*R*)
9	**99**	**65**	5	100 : 2 : 4	4	100	91 (*S*)
10	**99**	**47**	25	100 : 2 : 4	8	100	99 (*R*)
11	**99**	**48**	25	100 : 2 : 4	8	100	99 (*R*)
12	**99**	**49**	25	100 : 2 : 4	8	100	98 (*R*)
13	**99**	**55**	25	100 : 2 : 4	8	100	98 (*R*)
14	**99**	**56**	25	100 : 2 : 4	8	100	17 (*R*)
15	**99**	**57**	25	100 : 2 : 4	8	39	4
16	**99**	**58**	25	100 : 2 : 4	8	100	21 (*S*)
17	**99**	**59**	25	100 : 2 : 4	8	100	87 (*R*)
18	**99**	**60**	25	100 : 2 : 4	8	95	82 (*R*)
19	**99**	**61**	25	100 : 2 : 4	8	100	>99
20	**99**	**62**	25	100 : 2 : 4	8	65	8

General conditions: T = rt, solvent = CH_2Cl_2.[a] Solvent = *i*-PrOH.



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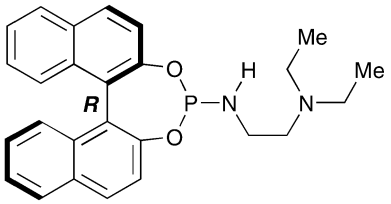

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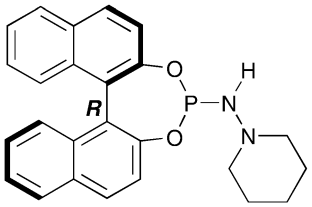

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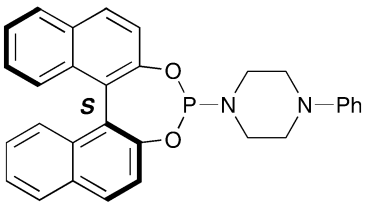

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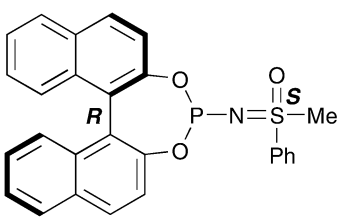
Table 8 Olefin hydrogenation using phosphoramidites derived from a sulfoximine

Entry	Ligand	Olefin	$P(H_2)$ (bar)	S : Rh : L	Time (h)	Conv (%)	Ee (%) (*config*)
1	**100**	**65**	1.3	1000 : 1 : 2	20	100	>99 (*R*)
2	**100**	**18**	1.3	1000 : 1 : 2	20	100	98.8 (*S*)
3	**100**	**1**	1.3	1000 : 1 : 2	20	100	97.0 (*S*)
4	**100**	**47**	1.3	1000 : 1 : 2	20	100	87.5 (*S*)
5	**101**	**65**	1.3	1000 : 1 : 2	20	100	99.0 (*S*)
6	**101**	**18**	1.3	1000 : 1 : 2	20	100	98.0 (*R*)
7	**101**	**1**	1.3	1000 : 1 : 2	20	100	94.0 (*R*)
8	**101**	**47**	1.3	1000 : 1 : 2	20	100	76.0 (*R*)
9	**102**	**65**	1.3	1000 : 1 : 2	20	100	>99.0 (*R*)
10	**102**	**18**	1.3	1000 : 1 : 2	20	100	98.2 (*S*)
11	**102**	**1**	1.3	1000 : 1 : 2	20	100	95.2 (*S*)
12	**102**	**47**	1.3	1000 : 1 : 2	20	100	84.5 (*S*)
13	**103**	**65**	1.3	500 : 1 : 2	20	100	98.0 (*R*)
14	**103**	**18**	1.3	500 : 1 : 2	20	100	98.2 (*S*)
15	**103**	**1**	1.3	500 : 1 : 2	20	100	94.0 (*S*)
16	**103**	**47**	1.3	500 : 1 : 2	20	100	64.0 (*S*)

General conditions: T = rt, Solvent = CH_2Cl_2.



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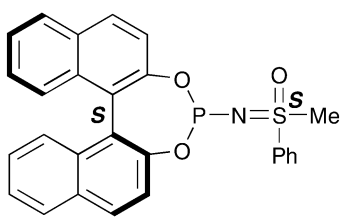

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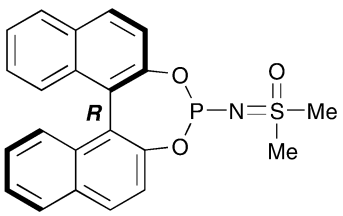

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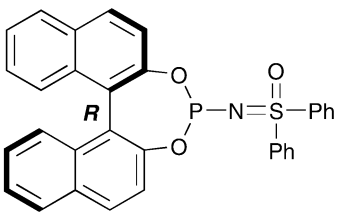

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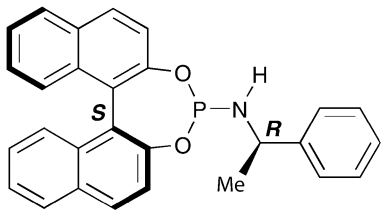
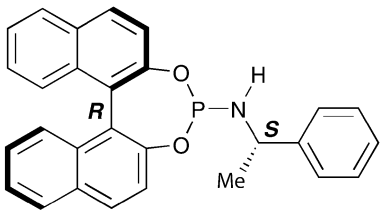
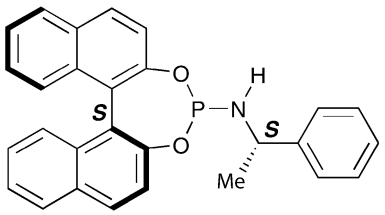


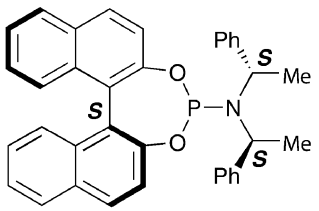
(S,R)-**104**



(R,S)-**105**



(S,S)-**106**



(S,S,S)-**107**

the previous ones in that they may form chelate complexes can be divided into three main groups:

(*i*) phosphoramidite-phosphines (X = C and R′ = aryl in **A**); (*ii*) phosphoramidite- phosphinites (or phosphites) (X = O, R′ = aryl or oxyaryl); (*iii*) diphosphoramidites bearing two "binoPN" units (X = N, R′ = bino).

5.1 Phosphoramidite-phosphines

Ferrocene was used as a framework for the synthesis of the mixed bidentates **109–115**. All these ligands contain, beside a binoP moiety, a diphenylphosphinyl end. Note that one of the cyclopentadienyl rings was hetero-1,2-disubstituted, rendering the ferrocenyl unit inherently chiral.

In 2004, Chan *et al*., using $[Rh(COD)_2]BF_4$ as the catalyst precursor, tested S_{Fe},R_C,S_{bino}-**109** in the reduction of α-dehydroamino esters **1**, **3**, **4**, **11**, **13**, and **14** and of enamide **47**.[61] Significantly higher ee's were obtained in THF *vs*. CH_2Cl_2 or MeOH (Table 11, entries 1, 2 and 3). The authors also observed that the hydrogen pressure had no influence on enantiodiscrimination (Table 11, entries 3–5). Under optimum conditions, excellent selectivities (ee's > 98%) were obtained for all the α-dehydroamino esters tested (Table 11, entries 4–10). In contrast, reduction of enamide **47** gave only moderate to good enantioselectivities (Table 11, entries 11–14), whatever the solvent used. One year later, Boaz from Eastman Chemical Company employed the same ligand for the hydrogenation of the substrates **1**, **10**, **15**, **19**, **23**, and **64**, but used

Table 9 Olefin hydrogenation using phosphoramidites **104–106**

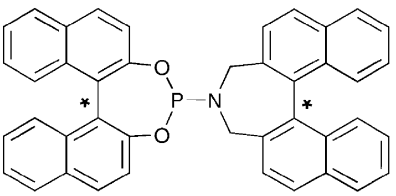
Entry	Ligand	Olefin	$P(H_2)$ (bar)	S : Rh : L	Time (h)	Conv (%)	Ee (%) (*config*)
1	*S*,*R*-**104**[ab]	**33**	1	100 : 1 : 2	24	88	3 (*R*)
2	*S*,*R*-**104**[bc]	**33**	1	100 : 1 : 2	24	98	20 (*R*)
3	*S*,*R*-**104**[bc]	**33**	1	100 : 1 : 2	3	40	47 (*R*)
4	*S*,*R*-**104**[bc]	**33**	10	100 : 1 : 2	16	100	77 (*R*)
5	*S*,*R*-**104**[c]	**33**	10	100 : 1 : 2	1	100	94 (*R*)
6	*S*,*R*-**104**[c]	**33**	10	100 : 2 : 4	0.3	100	95 (*R*)
7	*S*,*R*-**104**[c]	**36**	10	100 : 2 : 4	0.3	100	94 (*R*)
8	*S*,*R*-**104**[c]	**35**	10	100 : 2 : 4	0.3	100	94 (*R*)
9	*S*,*R*-**104**[c]	**35**	10	200 : 1 : 2	1	100	94 (*R*)
10	*S*,*R*-**104**[c]	**39**	10	100 : 2 : 4	0.3	100	92 (*R*)
11	*S*,*R*-**104**[c]	**39**	25	100 : 2 : 4	0.05	100	92 (*R*)
12	*S*,*R*-**104**[c]	**40**	10	100 : 2 : 4	0.3	100	92 (*S*)
13	*S*,*R*-**104**[c]	**32**	10	100 : 2 : 4	0.3	100	94 (*S*)
14	*S*,*R*-**104**[c]	**41**	10	100 : 1 : 2	18	52	52 (*S*)
15	*S*,*R*-**104**	**41**	10	100 : 1 : 2	18	100	83 (*S*)
16	*S*,*R*-**104**[a]	**1**	2	200 : 1 : 2	3	100	89 (*R*)
17	*S*,*R*-**104**[c]	**63**	25	100 : 1 : 2	5	91	0
18	*S*,*R*-**104**	**45**	25	100 : 1 : 2	16	0	—
19	*S*,*R*-**104**[c]	**45**	25	100 : 1 : 2	16	<10	—
20	*R*,*S*-**105**	**1**	6	100 : 1 : 2	1	100	70 (*S*)
21	*R*,*S*-**105**	**33**	6	100 : 1 : 2	1	51	88 (*S*)
22	*S*,*S*-**106**	**20**	5	100 : 1 : 2	—	21	54 (*R*)

General conditions: *T* = rt, solvent = CH_2Cl_2.[a] Solvent = EtOAc.[b] Olefin, $[Rh(COD)_2]BF_4$ and ligand dissolved in the suitable solvent.[c] Solvent = *i*-PrOH.

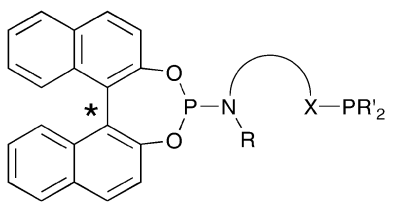
Table 10 Hydrogenation of olefin **1** with *S,S,S*-**107** and **108a–d**

Entry	Ligand	Olefin	$P(H_2)$ (bar)	S : Rh : L	Time (h)	Conv (%)	Ee (%) (*config*)
1	*S,S,S*-**107**	**1**	1	20 : 1 : 2.2	4	100	42 (*R*)
2	*S,S*-**108a**	**1**	5	20 : 1 : 2.2	1	100	82 (*R*)
3	*S,S*-**108a**	**5**	5	20 : 1 : 2.2	1	100	85 (*R*)
4	*S,S*-**108a**	**6**	5	20 : 1 : 2.2	1	100	81 (*R*)
5	*R,R*-**108b**	**1**	5	20 : 1 : 2.2	1	100	83 (*S*)
6	*R,R*-**108b**	**5**	5	20 : 1 : 2.2	1	100	86 (*S*)
7	*R,R*-**108b**	**6**	5	20 : 1 : 2.2	1	100	81 (*S*)
8	*S,R*-**108c**	**1**	5	20 : 1 : 2.2	1	100	96 (*S*)
9	*S,R*-**108c**	**5**	5	20 : 1 : 2.2	1	100	97 (*S*)
10	*S,R*-**108c**	**6**	5	20 : 1 : 2.2	1	100	98 (*S*)
11	*R,S*-**108d**[a]	**1**	5	20 : 1 : 2.2	1	100	74 (*R*)
12	*R,S*-**108d**[b]	**1**	5	20 : 1 : 2.2	1	100	57 (*R*)
13	*R,S*-**108d**[c]	**1**	5	20 : 1 : 2.2	1	100	72 (*R*)
14	*R,S*-**108d**	**1**	5	1000 : 1 : 2.2	4	100	99 (*R*)
15	*R,S*-**108d**[d]	**1**	5	20 : 1 : 2.2	4	89	96 (*R*)
16	*R,S*-**108d**	**1**	5	100 : 1 : 2.2	1	100	99 (*R*)
17	*R,S*-**108d**	**5**	5	100 : 1 : 2.2	1	100	99 (*R*)
18	*R,S*-**108d**	**6**	5	100 : 1 : 2.2	1	100	99 (*R*)

General conditions: T = rt, solvent = CH_2Cl_2.[a] Solvent = THF. [b] Solvent = MeOH. [c] Solvent = AcOEt. [d] T = 0 °C.



(S_{bin},S_{aze})-**108a**
(R_{bin},R_{aze})-**108b**
(S_{bin},R_{aze})-**108c**
(R_{bin},S_{aze})-**108d**



A X = C, O, or, N, R = H, alkyl, or aryl, R' = aryl or oxyaryl

$[Rh(COD)_2](CF_3SO_3)$ as the catalyst precursor.[62] Surprisingly, in this case the ee's did not exceed 92.6% (Table 11, entries 15–20), suggesting a negative influence of the counteranion. Interestingly, however, upon changing the chirality of the binoP moiety, that is on going from S_{Fe},R_C,S_{bino}-**109** to the diastereomer S_{Fe},R_C,R_{bino}-**110**, important changes were observed for the enantioselectivity, the latter either increasing (Table 11, compare, for example, entry 15 with 21 and 16 with 22 (99.9% ee !)) or diminishing (Table 11, compare, *e.g.* entry 17 with 23 and 18 with 24). These match–mismatch effects were observed for all the substrates that were hydrogenated under rhodium catalysis.

Using the same diastereomeric ligands for the ruthenium-catalysed hydrogenation of β-ketoesters **66–69** afforded poorer enantioselectivities (ee's < 38.2%) (Table 11, entries 27–34).[63] No match–mismatch effect could be identified here.

Zheng *et al*. synthesised the related ligands **111–114**. These were used in the hydrogenation of enamides, α-dehydroamino esters and dimethyl itaconate.[64] With R_{Fe},S_C,S_{bino}-**111**, excellent enantioselectivities (ee's > 97%) and high catalytic activities were observed for most substrates (Table 12, entries 1–18). Only the hydrogenation of the β-dehydroamino esters **33**, **34**, and **41** gave mediocre selectivities (ee's < 65%) (Table 12, entries 19–21).[65]

The diastereomer R_{Fe},S_C,R_{bino}-**112** was only tested in the hydrogenation of enamide **47**. The results were disappointing (ee = 10.6%; see Table 12, entry 22). Again, the authors invoked a match–mismatch effect to explain the low performance of **112** *vs*. **111** (99.6% ee). A similar difference was also observed for the same substrate with the diastereomers S_{Fe},S_C,S_{bino}-**113** and S_{Fe},S_C,R_{bino}-**114**, although not to such an extent (Table 12, see entries 23 and 24).

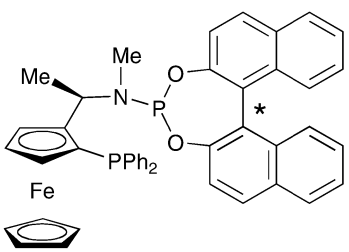
As the couple S_{Fe},S_C,S_{bino}-**113**/R_{Fe},S_C,S_{bino}-**111** led to hydrogenated substrates with an *R* configuration (Table 12, entries 23 and 1), and the couple S_{Fe},S_C,R_{bino}-**114**/R_{Fe},S_C,R_{bino}-**112** to products with the *S* configuration (Table 12, entries 24 and 23), Zheng *et al*. concluded that the binaphthyl fragment alone controls the chirality of the hydrogenation products.

Zheng surmised that because of potential interactions with the substrate, an N–H proton on the amino fragment could be crucial to achieving efficient stereocontrol in the hydrogenation of β-(acylamino)acrylates.[65] As anticipated, R_{Fe},S_C,S_{bino}-**115**, which contains an N–H bond, showed a better selectivity (ee = 98%) in the hydrogenation of olefin **34** (Table 13, entry 1) than the related aminomethylated ligand R_{Fe},S_C,S_{bino}-**111** (Table 12, entry 19). Performing the reduction of **34** and similar olefins at a lower temperature (T = 5 °C) had a beneficial effect on the enantioselectivities (Table 13, entries 2–26). In all cases, the reduction of the *E*-isomers exhibited higher enantioselectivities than the corresponding *Z*-isomers (Table 13, entries 16, 18, 20, 23, and 25 *vs*., respectively, entries 15, 17, 19, 22, and 24). Remarkably, the sense of enantioselection for (*E*)-β-dehydroamino esters was opposite to that observed for *Z*-isomers.

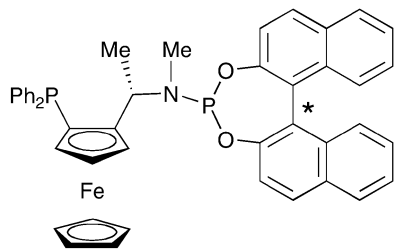
Table 11 Hydrogenation of olefins with the ferrocenyl-derived bidentate ligands **106** and **107**

Entry	Ligand	Olefin	$P(H_2)$ (bar)	S : Rh : L	Time (h)	Conv (%)	Ee (%) (*config*)
1	S_{Fe},R_C,S_{bino}-**109**	**1**	20.7	100 : 1 : 1	—	100	96 (*S*)
2	S_{Fe},R_C,S_{bino}-**109**[a]	**1**	20.7	100 : 1 : 1	—	100	87 (*S*)
3	S_{Fe},R_C,S_{bino}-**109**[b]	**1**	13.8	100 : 1 : 1	—	100	98 (*S*)
4	S_{Fe},R_C,S_{bino}-**109**[b]	**1**	20.7	100 : 1 : 1	—	100	99 (*S*)
5	S_{Fe},R_C,S_{bino}-**109**[b]	**1**	34.5	100 : 1 : 1	—	100	99 (*S*)
6	S_{Fe},R_C,S_{bino}-**109**[b]	**11**	20.7	100 : 1 : 1	—	100	99.6 (*S*)
7	S_{Fe},R_C,S_{bino}-**109**[b]	**4**	20.7	100 : 1 : 1	—	100	97.4 (*S*)
8	S_{Fe},R_C,S_{bino}-**109**[b]	**13**	20.7	100 : 1 : 1	—	100	99 (*S*)
9	S_{Fe},R_C,S_{bino}-**109**[b]	**3**	20.7	100 : 1 : 1	—	100	99 (*S*)
10	S_{Fe},R_C,S_{bino}-**109**[b]	**14**	20.7	100 : 1 : 1	—	100	99 (*S*)
11	S_{Fe},R_C,S_{bino}-**109**	**47**	20.7	100 : 1 : 1	—	100	73 (*S*)
12	S_{Fe},R_C,S_{bino}-**109**[b]	**47**	20.7	100 : 1 : 1	—	100	77 (*S*)
13	S_{Fe},R_C,S_{bino}-**109**[c]	**47**	20.7	100 : 1 : 1	—	100	76 (*S*)
14	S_{Fe},R_C,S_{bino}-**109**[bd]	**47**	20.7	100 : 1 : 1	—	100	87.5 (*S*)
15	S_{Fe},R_C,S_{bino}-**109**[be]	**1**	1	100 : 1 : 1	6	—	17.5 (−)
16	S_{Fe},R_C,S_{bino}-**109**[be]	**15**	1	100 : 1 : 1	6	—	54.1 (−)
17	S_{Fe},R_C,S_{bino}-**109**[be]	**19**	1	100 : 1 : 1	6	—	85.6 (−)
18	S_{Fe},R_C,S_{bino}-**109**[be]	**10**	1	100 : 1 : 1	6	—	81.2 (−)
19	S_{Fe},R_C,S_{bino}-**109**[be]	**23**	1	100 : 1 : 1	6	—	5.0 (−)
20	S_{Fe},R_C,S_{bino}-**109**[be]	**64**	1	100 : 1 : 1	6	—	92.6 (−)
21	S_{Fe},R_C,R_{bino}-**110**[be]	**1**	1	100 : 1 : 1	6	—	99.1 (−)
22	S_{Fe},R_C,R_{bino}-**110**[be]	**15**	1	100 : 1 : 1	6	—	99.9 (−)
23	S_{Fe},R_C,R_{bino}-**110**[be]	**19**	1	100 : 1 : 1	6	—	67.1 (−)
24	S_{Fe},R_C,R_{bino}-**110**[be]	**10**	1	100 : 1 : 1	6	—	—
25	S_{Fe},R_C,R_{bino}-**110**[be]	**23**	1	100 : 1 : 1	6	—	35.6 (−)
26	S_{Fe},R_C,R_{bino}-**110**[be]	**64**	1	100 : 1 : 1	6	—	95.7 (−)
27	S_{Fe},R_C,S_{bino}-**109**	**66**	20.7	200 : 1 : 1	6	100	3.5
28	S_{Fe},R_C,S_{bino}-**109**	**69**	20.7	200 : 1 : 1	6	68	2.7
29	S_{Fe},R_C,S_{bino}-**109**	**68**	20.7	200 : 1 : 1	6	96	1.7
30	S_{Fe},R_C,S_{bino}-**109**	**67**	20.7	200 : 1 : 1	6	5	1.2
31	S_{Fe},R_C,R_{bino}-**110**	**66**	20.7	200 : 1 : 1	6	80	0.4
32	S_{Fe},R_C,R_{bino}-**110**	**69**	20.7	200 : 1 : 1	6	55	2.3
33	S_{Fe},R_C,R_{bino}-**110**	**68**	20.7	200 : 1 : 1	6	91	1.1
34	S_{Fe},R_C,R_{bino}-**110**	**67**	20.7	200 : 1 : 1	6	15	38.2

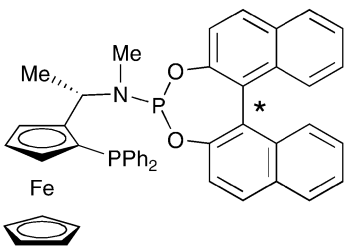
General conditions: T = rt, solvent = CH_2Cl_2.[a] Solvent = MeOH. [b] Solvent = THF. [c] Solvent = *i*-PrOH. [d] T = 0 °C. [e] With [{ligand}-Rh(COD)](CF_3SO_3) as catalyst.



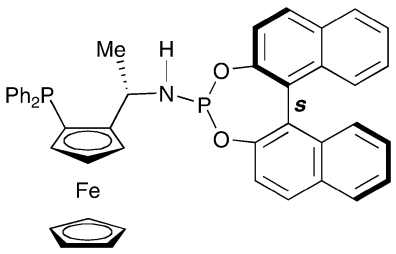
S_{Fe},R_C,S_{bino}-**109**
S_{Fe},R_C,R_{bino}-**110**



R_{Fe},S_C,S_{bino}-**111**
R_{Fe},S_C,R_{bino}-**112**



S_{Fe},S_C,S_{bino}-**113**
S_{Fe},S_C,R_{bino}-**114**



R_{Fe},S_C,S_{bino}-**115**

Table 12 Hydrogenation of olefins with the ferrocenyl-derived bidentate ligands **111–114**

Entry	Ligand	Olefin	$P(H_2)$ (bar)	S : Rh : L	Time (h)	Conv (%)	Ee (%) (*config*)
1	R_{Fe},S_C,S_{bino}-**111**	**47**	10	100 : 1 : 1.1	1	100	99.6 (*R*)
2	R_{Fe},S_C,S_{bino}-**111**	**47**	10	1000 : 1 : 1.1	1	100	99.6 (*R*)
3	R_{Fe},S_C,S_{bino}-**111**	**47**	10	5000 : 1 : 1.1	1	100	99.3 (*R*)
4	R_{Fe},S_C,S_{bino}-**111**	**54**	10	1000 : 1 : 1.1	1	100	98.7 (*R*)
5	R_{Fe},S_C,S_{bino}-**111**	**48**	10	1000 : 1 : 1.1	1	100	98.8 (*R*)
6	R_{Fe},S_C,S_{bino}-**111**	**52**	10	1000 : 1 : 1.1	1	100	99.0 (*R*)
7	R_{Fe},S_C,S_{bino}-**111**	**51**	10	1000 : 1 : 1.1	1	100	99.2 (*R*)
8	R_{Fe},S_C,S_{bino}-**111**	**47**	10	100 : 1 : 1.1	1	100	99.6 (*R*)
9	R_{Fe},S_C,S_{bino}-**111**[a]	**65**	10	100 : 1 : 1.1	0.5	100	99.9 (*S*)
10	R_{Fe},S_C,S_{bino}-**111**[b]	**65**	10	100 : 1 : 1.1	0.5	100	99.9 (*S*)
11	R_{Fe},S_C,S_{bino}-**111**[c]	**65**	10	100 : 1 : 1.1	0.5	100	99.9 (*S*)
12	R_{Fe},S_C,S_{bino}-**111**	**65**	10	100 : 1 : 1.1	0.5	100	99.6 (*S*)
13	R_{Fe},S_C,S_{bino}-**111**	**65**	10	1000 : 1 : 1.1	0.5	100	99.9 (*S*)
14	R_{Fe},S_C,S_{bino}-**111**	**65**	10	10000 : 1 : 1.1	0.5	100	99.1 (*S*)
15	R_{Fe},S_C,S_{bino}-**111**	**1**	10	100 : 1 : 1.1	24	100	97.6 (*R*)
16	R_{Fe},S_C,S_{bino}-**111**	**1**	10	100 : 1 : 2.2	24	100	99.0 (*R*)
17	R_{Fe},S_C,S_{bino}-**111**	**65**	10	100 : 1 : 1.1	24	100	99.9 (*S*)
18	R_{Fe},S_C,S_{bino}-**111**	**47**	10	100 : 1 : 1.1	24	100	99.6 (*R*)
19	R_{Fe},S_C,S_{bino}-**111**	**34**	10	100 : 1 : 1.1	12	100	65 (−)
20	R_{Fe},S_C,S_{bino}-**111**	**41**	10	100 : 1 : 1.1	12	100	24 (−)
21	R_{Fe},S_C,S_{bino}-**111**	**33**	10	100 : 1 : 1.1	12	100	50 (−)
22	R_{Fe},S_C,R_{bino}-**112**	**47**	10	100 : 1 : 1.1	1	100	10.6 (*S*)
23	S_{Fe},S_C,S_{bino}-**113**	**47**	10	100 : 1 : 1.1	1	100	82.6 (*R*)
24	S_{Fe},S_C,R_{bino}-**114**	**47**	10	100 : 1 : 1.1	1	100	99.6 (*S*)

General conditions: T = rt, solvent = CH_2Cl_2.[a] Solvent = MeOH. [b] Solvent = THF. [c] Solvent = PhMe.

Some mixed phosphoramidite-phosphine ligands not derived from ferrocene (**116–122**) have been prepared by three independent groups[66–68] The diastereomeric ligands **116** and **117** were used by Leitner in the rhodium-catalyzed hydrogenation of dimethyl itaconate (**65**) and α-dehydroamino ester **18**. When using a M : L ratio of 1, the latter ligands showed high catalytic activities and stabilities (Table 14, entries 1–4 and 6). The authors further showed that starting from the dehydroamino ester **18** and increasing the M : L ratio for ligand **117** from 1.0 to 2.2 led to a dramatic drop in the catalytic activity (Table 14, entry 5).

The diastereomer R_{bino},R_C-**117** gave significantly higher enantioselectivities than its diastereomer R_{bino},S_C-**116** in the reduction of dimethylitaconate (ee's up to 97.8%), thus revealing a clear match–mismatch effect (Table 14, entries 1 and 2 *vs*. entries 3–6).

Table 13 Olefin hydrogenation with R_{Fe},S_C,S_{bino}-**115**

Entry	Ligand	Olefin	$P(H_2)$ (bar)	S : Rh : L	Time (h)	Conv (%)	Ee (%) (*config*)
1	R_{Fe},S_C,S_{bino}-**115**	**34**	10	100 : 1 : 1.1	12	100	98 (*R*)
2	R_{Fe},S_C,S_{bino}-**115**[a]	**34**	10	100 : 1 : 1.1	12	100	>99 (*R*)
3	R_{Fe},S_C,S_{bino}-**115**[a]	**31**	10	100 : 1 : 1.1	12	100	98 (*R*)
4	R_{Fe},S_C,S_{bino}-**115**[a]	**30**	10	100 : 1 : 1.1	12	100	97 (*R*)
5	R_{Fe},S_C,S_{bino}-**115**[a]	**29**	10	100 : 1 : 1.1	12	100	99 (*R*)
6	R_{Fe},S_C,S_{bino}-**115**[a]	**28**	10	100 : 1 : 1.1	12	100	98 (*R*)
7	R_{Fe},S_C,S_{bino}-**115**[a]	**25**	10	100 : 1 : 1.1	12	100	>99 (*R*)
8	R_{Fe},S_C,S_{bino}-**115**[a]	**24**	10	100 : 1 : 1.1	12	100	98 (*R*)
9	R_{Fe},S_C,S_{bino}-**115**[a]	**32**	10	100 : 1 : 1.1	12	100	98 (*R*)
10	R_{Fe},S_C,S_{bino}-**115**[a]	**27**	10	100 : 1 : 1.1	12	100	98 (*R*)
11	R_{Fe},S_C,S_{bino}-**115**[a]	**34**	10	1000 : 1 : 1.1	1	100	98 (*R*)
12	R_{Fe},S_C,S_{bino}-**115**[a]	**25**	10	1000 : 1 : 1.1	1	100	98 (*R*)
13	R_{Fe},S_C,S_{bino}-**115**[a]	**34**	10	5000 : 1 : 1.1	1	100	97 (*R*)
14	R_{Fe},S_C,S_{bino}-**115**[a]	**25**	10	5000 : 1 : 1.1	1	100	96 (*R*)
15	R_{Fe},S_C,S_{bino}-**115**	**35**	10	100 : 1 : 1.1	1	100	92 (*S*)
16	R_{Fe},S_C,S_{bino}-**115**	**42**	10	100 : 1 : 1.1	1	100	92 (*R*)
17	R_{Fe},S_C,S_{bino}-**115**[a]	**35**	10	100 : 1 : 1.1	1	100	93 (*S*)
18	R_{Fe},S_C,S_{bino}-**115**[a]	**42**	10	100 : 1 : 1.1	1	100	97 (*R*)
19	R_{Fe},S_C,S_{bino}-**115**[a]	**33**	10	100 : 1 : 1.1	1	100	92 (*S*)
20	R_{Fe},S_C,S_{bino}-**115**[a]	**41**	10	100 : 1 : 1.1	1	100	98 (*R*)
21	R_{Fe},S_C,S_{bino}-**115**[a]	**37**	10	100 : 1 : 1.1	1	100	93 (*S*)
22	R_{Fe},S_C,S_{bino}-**115**[a]	**36**	10	100 : 1 : 1.1	1	100	93 (*S*)
23	R_{Fe},S_C,S_{bino}-**115**[a]	**43**	10	100 : 1 : 1.1	1	100	99 (*R*)
24	R_{Fe},S_C,S_{bino}-**115**[a]	**38**	10	100 : 1 : 1.1	1	100	92 (*R*)
25	R_{Fe},S_C,S_{bino}-**115**[a]	**44**	10	100 : 1 : 1.1	1	100	98 (*S*)
26	R_{Fe},S_C,S_{bino}-**115**[a]	**43**	10	1000 : 1 : 1.1	1	100	95 (*R*)

General conditions: solvent = CH_2Cl_2.[a] T = 5 °C.

Table 14 Hydrogenation of olefins with mixed phosphoramidite-phosphines **116–126**

Entry	Ligand	Olefin	$P(H_2)$ (bar)	S : Rh : L	Time (h)	Conv (%)	Ee (%) (*config*)
1	*S*,*R*-**116**	**65**	30	1000 : 1 : 1.1	24	>99	64.2 (*R*)
2	*S*,*R*-**116**	**65**	30	1000 : 1 : 2.2	24	>99	78.8 (*R*)
3	*R*,*R*-**117**	**65**	30	1000 : 1 : 1.1	24	>99	95.6 (*R*)
4	*R*,*R*-**117**	**65**	30	1000 : 1 : 2.2	24	>99	98.8 (*R*)
5	*R*,*R*-**117**	**18**	30	1000 : 1 : 2.2	24	8.0	12.4 (*S*)
6	*R*,*R*-**117**[a]	**18**	30	1000 : 1 : 1.0	24	>99	97.8 (*S*)
7	*S*,*S*-**118**	**1**	10	100 : 1 : 1.1	12	100	98.1 (*R*)
8	*S*,*S*-**118**	**47**	10	100 : 1 : 1.1	12	100	98.6 (*R*)
9	*S*,*R*-**119**	**47**	10	100 : 1 : 1.1	12	100	95.9 (*R*)
10	*S*,*R*-**119**	**1**	10	100 : 1 : 1.1	12	100	17.3 (*R*)
11	*S*,*S*-**120**	**1**	10	100 : 1 : 1.1	12	100	99.1 (*R*)
12	*S*,*S*-**120**	**1**	10	5000 : 1 : 1.1	12	100	99.0 (*R*)
13	*S*,*S*-**120**	**1**	10	10000 : 1 : 1.1	12	100	98.8 (*R*)
14	*S*,*S*-**120**[b]	**1**	10	100 : 1 : 1.1	12	100	80.1 (*R*)
15	*S*,*S*-**120**[c]	**1**	10	100 : 1 : 1.1	12	100	93.5 (*R*)
16	*S*,*S*-**120**[d]	**1**	10	100 : 1 : 1.1	12	100	92.3 (*R*)
17	*S*,*S*-**120**	**7**	10	100 : 1 : 1.1	12	100	99.6 (*R*)
18	*S*,*S*-**120**	**6**	10	100 : 1 : 1.1	12	100	99.0 (*R*)
19	*S*,*S*-**120**	**8**	10	100 : 1 : 1.1	12	100	>99.9 (*R*)
20	*S*,*S*-**120**	**9**	10	100 : 1 : 1.1	12	100	99.7 (*R*)
21	*S*,*S*-**120**	**65**	10	100 : 1 : 1.1	12	100	99.9 (*R*)
22	*S*,*S*-**120**	**47**	10	100 : 1 : 1.1	12	100	99.5 (*R*)
23	*S*,*S*-**120**	**50**	10	100 : 1 : 1.1	12	100	99.1 (*R*)
24	*S*,*S*-**120**	**51**	10	100 : 1 : 1.1	12	100	99.0 (*R*)
25	*S*,*S*-**120**	**52**	10	100 : 1 : 1.1	12	100	98.8 (*R*)
26	*S*,*S*-**120**	**48**	10	100 : 1 : 1.1	12	100	98.5 (*R*)
27	*S*,*S*-**120**	**49**	10	100 : 1 : 1.1	12	100	99.8 (*R*)
28	*S*,*S*-**120**	**53**	10	100 : 1 : 1.1	12	100	99.9 (*R*)
29	*S*,*R*-**121**	**47**	10	100 : 1 : 1.1	12	100	73.9 (*R*)
30	*S*,*R*-**121**	**1**	10	100 : 1 : 1.1	12	100	48.5 (*R*)
31	*R*-**122**	**1**	1	100 : 1 : 1	1/6	100	97.9 (*S*)
32	*R*-**122**	**1**	1	100 : 1 : 1	0.1	100	96.1 (*S*)
33	*R*-**122**[c]	**1**	1	100 : 1 : 1	23	85	19.5 (*S*)
34	*R*-**122**	**65**	1	100 : 1 : 1	0.5	100	96.2 (*R*)
35	*R*-**122**[c]	**65**	1	100 : 1 : 1	6.5	100	7.3 (*R*)
36	*R*-**123**	**1**	5	100 : 1 : 1.1	2	100	89 (*S*)
37	*R*-**123**	**5**	5	100 : 1 : 1.1	2	100	89 (*S*)
38	*R*-**123**	**6**	5	100 : 1 : 1.1	2	100	89 (*S*)
39	*S*-**124**	**1**	5	100 : 1 : 1.1	2	100	88 (*R*)
40	*S*-**124**	**5**	5	100 : 1 : 1.1	2	100	88 (*R*)
41	*S*-**124**	**6**	5	100 : 1 : 1.1	2	100	88 (*R*)
42	*R*-**125**	**1**	5	100 : 1 : 1.1	8	100	9 (*S*)
43	*R*-**125**	**5**	5	100 : 1 : 1.1	8	100	15 (*S*)
44	*R*-**125**	**6**	5	100 : 1 : 1.1	8	100	10 (*S*)
45	*S*-**126**	**1**	5	100 : 1 : 1.1	8	100	7 (*R*)
46	*S*-**126**	**5**	5	100 : 1 : 1.1	8	100	16 (*R*)
47	*S*-**126**	**6**	5	100 : 1 : 1.1	8	100	9 (*R*)

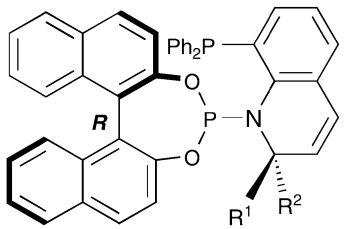
General conditions: T = rt, solvent = CH_2Cl_2.[a] With [Rh{*R*,*R*-**117**}(COD)](BF_4) as catalyst. [b] Solvent = PhMe. [c] Solvent = MeOH. [d] Solvent = EtOAc.

Zheng *et al*. used *N*-substituted (*S*)-α-phenylethylamine as a building block for the synthesis of bidentate phosphine-phosphoramidites **118–121**.[67] Dimethyl itaconate, α-dehydroamino esters (**1**, **6–9**), and enamides (**47–53**) were hydrogenated with rhodium-catalysts based on these ligands. Phosphine-phosphoramidites **119** and **121** showed low enantiodiscrimination in the reduction of dehydroamino ester **1** (Table 14, entries 10 and 30), but gave moderate to good results with enamide **47** (Table 14, entries 9 and 29). In sharp contrast with these results, their respective diastereomers **118** and **120** led to excellent enantioselectivities (ee's up to 99.5%) with these two substrates (Table 14, compare entries 7 and 11; compare entries 8 and 22). The observed match between the *S* configurations of the chiral center and the binaphtholate moiety, led Zheng *et al*. to use ligand **120** for the hydrogenation of various other substrates.[67]

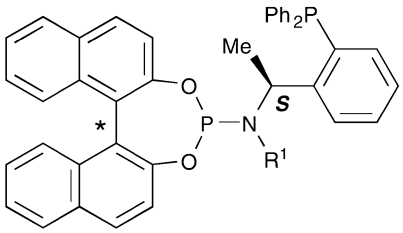
Different solvents were tested with **120** for the hydrogenation of olefin **1** (Table 14, entries 11 and 14–16). Dichloromethane proved to be the best in terms of enantioselectivity (ee's up to 99.1%). The runs carried out in CH_2Cl_2 with **120** on other α-dehydroamino esters as well as enamides led to ee's higher than 98.5% (Table 14, entries 17–28).

Interestingly, Zheng *et al*. observed that hydrogenating enamide **47** in the presence of ligand **119**, which turned out to be a mismatched ligand in the reduction of **1** (see above), induced here a very good selectivity (ee = 95.9%). However, the authors could not rationalise this result (Table 14, entry 9).

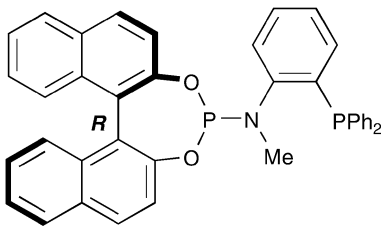
Recently, Vallianatou *et al*. synthesized phosphine-phosphoramidite **122**, a ligand which bears only the chiral binaphthyl group as stereogenic unit.[68] They tested this ligand in the rhodium-catalyzed hydrogenation of α-dehydroamino



R_{bino},S_C-**116** $R^1 = H, R^2 = Bu$,
R_{bino},R_C-**117** $R^1 = Bu, R^2 = H$



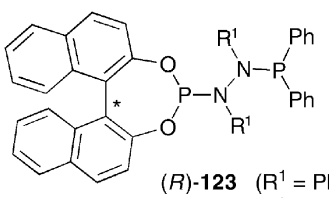
S_{bino},S_C-**118** $R^1 = H$,
R_{bino},S_C-**119** $R^1 = H$,
S_{bino},S_C-**120** $R^1 = Me$,
R_{bino},S_C-**121** $R^1 = Me$



R_{bino}-**122**

ester **1** and dimethyl itaconate **65**. Rhodium complexes containing **122** proved to be excellent catalysts (ee's > 96.1% and full conversion) for the reduction under mild conditions of these substrates in non-protic solvents (Table 14, entries 31, 32 and 34). Using a protic solvent led to lower selectivities (ee's < 19.5%) and activities, as the complex decomposed in MeOH (Table 14, entries 33 and 35).

The hydrazine derived aminophosphine ligands **123–126**, which also contain a binaphthyl group as the sole chiral unit, were assessed in the hydrogenation of olefins **1**, **5** and **6**.[69] While the *o*-tolyl containing ligands **125** and **126** gave rather low ee's (9–15%), good enantioselectivities (88–89%) were achieved with **123** and **124**.



(*R*)-**123** (R^1 = Ph)
(*S*)-**124** (R^1 = Ph)
(*R*)-**125** (R^1 = *o*-tolyl)
(*S*)-**126** (R^1 = *o*-tolyl))

5.2 Phosphoramidite-phosphinites and phosphoramidite-phosphites

In 2003, Cesarotti *et al*. synthesized the two diastereomeric phosphinites **127** and **128** from the chiral precursor (*R*)-2-ethylamino-1-butanol.[70] The two ligands were used in the rhodium-catalyzed hydrogenation of substrates **1** and **15** (in THF; counteranion: ClO_4). As a general trend, reduction of dehydroamino ester **1** gave better results (ee's up to 44%) than those for the acid derivative **15** (ee's up to 24%; see Table 15, entries 1–4).

Thus, identical configurations of the amino-alcohol backbone and the binaphthyl moiety showed a match effect (Table 15, entries 1 and 2). The authors did not give any evidence for the formation of a chelate complex, but this seems likely.

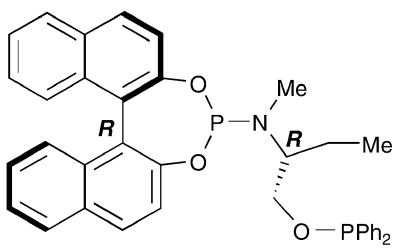
Cesarotti *et al*. further synthesised the phosphites **129** and **130** from (*S*)-2-pyrrolidinemethanol.[70] In combination with rhodium, these diastereomeric compounds showed good hydrogenation rates for substrates **1** and **15** (full conversion within 5 h), but led to moderate or low selectivities (ee's not exceeding 67%) (Table 16, entries 1–5). In this case, a match effect was found with opposite configurations of the binoP and the amino-alcohol parts (Table 16, entries 1–3).

Recently, Cramer *et al*. synthesized another two diastereomeric phosphoramidite-phosphites, namely **131** and **132**,

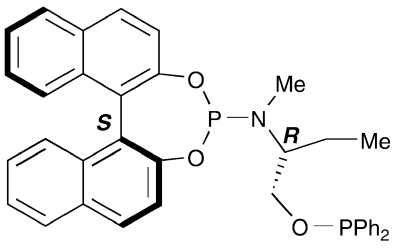
Table 15 Olefin hydrogenation with the phosphoramidite-phosphinites **127** and **128**

Entry	Ligand	Olefin	$P(H_2)$ (bar)	S : Rh : L	Time (h)	Conv (%)	Ee (%) (*config*)
1	**127**	**1**	100	100 : 1 : 1.2	0.05	100	44 (*S*)
2	**127**	**15**	1	100 : 1 : 1.2	3.5	100	24 (*S*)
3	**128**	**1**	10	100 : 1 : 1.2	2/3	100	17 (*R*)
4	**128**	**15**	1	100 : 1 : 1.2	5	100	7 (*R*)

General conditions: T = rt, solvent = THF.



R_{bino},R_C-**127**



S_{bino},R_C-**128**

Table 16 Olefin hydrogenation with the mixed phosphoramidite-phosphites **129–133**

Entry	Ligand	Olefin	$P(H_2)$ (bar)	S : Rh : L	Time (h)	Conv (%)	Ee (%) (*config*)
1	**129**[a]	**15**	10	100 : 1 : 1.2	1.5	100	63 (*R*)
2	**129**[ab]	**15**	100	100 : 1 : 1.2	1	100	67 (*R*)
3	**129**[a]	**1**	1	100 : 1 : 1.2	6	100	59 (*R*)
4	**130**[a]	**15**	10	100 : 1 : 1.2	0.5	100	12 (*S*)
5	**130**[a]	**1**	1	100 : 1 : 1.2	5	100	24 (*S*)
6	**131**	**65**	1	100 : 1 : 1	12	100	85 (*S*)
7	**131**	**1**	1	100 : 1 : 1	12	100	95 (*R*)
8	**132**	**65**	1	100 : 1 : 1	12	100	62 (*R*)
9	**132**	**1**	1	100 : 1 : 1	12	100	85 (*S*)
10	**133**	**65**	1.3	1000 : 1 : 1	20	100	96 (*S*)
11	**133**	**18**	1.3	1000 : 1 : 1	20	100	95 (*R*)

General conditions: T = rt, solvent = CH_2Cl_2.[a] In THF. [b] T = 0 °C.

based on the tropane skeleton.[53] A matched cased was seen with **131** when hydrogenating dehydroamino ester **1** (95% ee *vs*. 85% with **132**) and dimethyl itaconate (**65**) (85% ee *vs*. 62% with **132**) (Table 16, entries 6–9).

Reetz *et al*. prepared the phosphoramidite-phosphite **133** starting from the cheap, achiral 4-hydroxypiperidine.[71] This ligand was only tested in the hydrogenation of dimethyl itaconate and dehydroamino ester **18**. In both cases, the catalytic system based on **133** gave high enantioselectivities (ee's > 95%) (Table 16, entries 10 and 11). Overall the results reported for **129–132** show that the introduction of an asymmetric carbon atom into the backbone of phosphoramidite-phosphites is not a guarantee of improved selectivity.

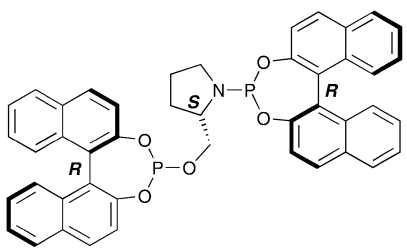
5.3 Diphosphoramidites

The first binol-derived diphosphoramidites (**134–138**) were synthesized by van den Berg *et al*. and tested in the hydrogenation of cinnamic ester **1**.[27,28] Compared to the reference ligand, the enantioselectivities were moderate (ee = 80% for **135**) and the reaction rates low (Table 17, entries 1–14). The authors showed that using methanol as solvent resulted in a drastic drop of selectivity (see *e.g*. Table 17, entries 2, 4, 6, 9, 10, and 13), and that using a ligand : M ratio of 2.2 instead of 1.1 gave no hydrogenation (Table 17, entry 3).

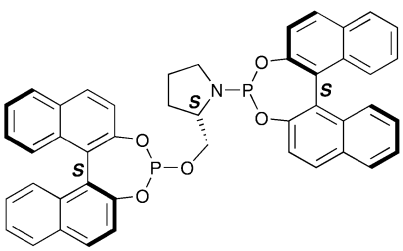
Waldmann *et al*. prepared the related ligands **139** and **140**, based on bicyclic backbones.[51] These ligands were assessed in the catalytic hydrogenation of dimethyl itaconate (**65**) and methyl acetamidoacrylate (**18**). In general, these ligands gave better selectivities and activities than the diphosphoramidites **134–138** (Table 17, entries 15–19). Thus, for example, ee's of 90% were obtained with **140** in the hydrogenation of itaconate **65**.

More recently, Reetz *et al*. have studied the catalytic properties of diphosphoramidites having linear spacers between the two P atoms (**141–143**).[71] The authors concluded that longer backbones, which are in principle more flexible, are needed for achieving higher enantioselectivities (Table 17, entries 20–25). For instance, while **143** gave 90% ee with dimethyl itaconate, the shorter ligand **141** gave only 33% ee with the same substrate.

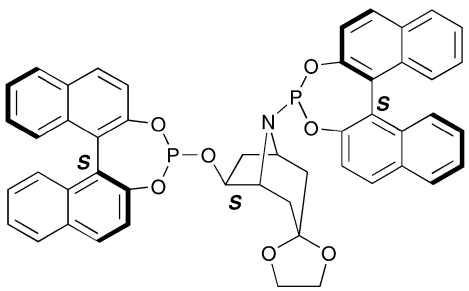
The trend of shorter diphosphoramidites giving poorer enantioselectivities does, in fact, not apply to "very short" diphosphoramidites, such as **144–147**.[69] For example, ligand **145** gave ee's comprised between 91 and 95% when used in the hydrogenation of **5**. It turned out that the enantioselectivity of



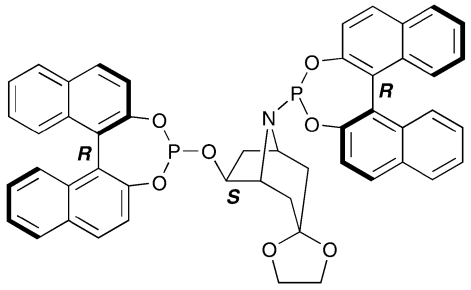
R_{bino},S_C,R_{bino}-**129**



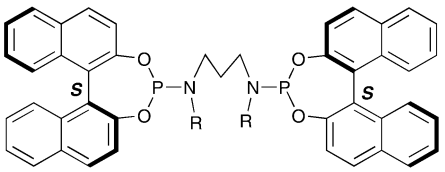
S_{bino},S_C,S_{bino}-**130**



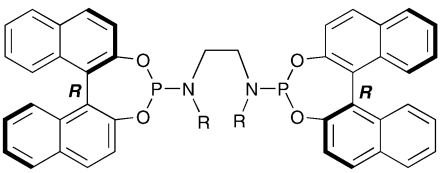
S_{bino},S_C,S_{bino}-**131**



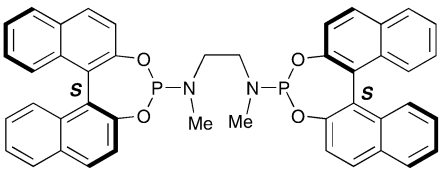
R_{bino},S_C,R_{bino}-**132**



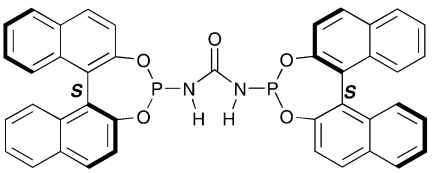
134 R = *i*-Pr
135 R = (*S*)-Methylbenzyl



136 R = (*S*)-Methylbenzyl



137



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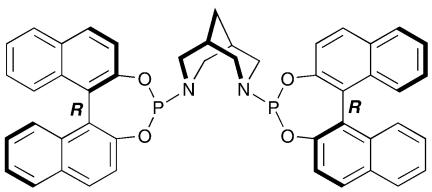
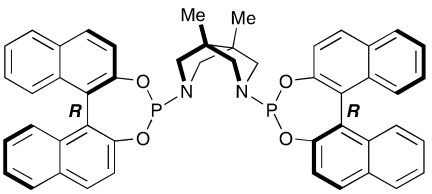


139



140

these hydrazine derivatives were shown to be markedly influenced by the nature of the two NR substituents, symmetrical but bulky R groups leading to the best results. It is worth mentioning that the ability of such short diphosphoramidites to form 5-membered chelate complexes was unambiguously shown by carrying out a crystallographic study on the complex [$PtCl_2$\{(*S*,*S*)-**144b**\}] (Fig. 4).[69]

Other results that contradict somewhat the conclusions drawn by Reetz were those obtained with the relatively short diphosphoramidites **148** and **149**, in which the nitrogen atoms are part of 6 and 7-membered rings, respectively. These led to remarkably high ee's (96% for **148** and 99% for **149**) (Table 17, entries 53–56) in the hydrogenation of **65**.[71]

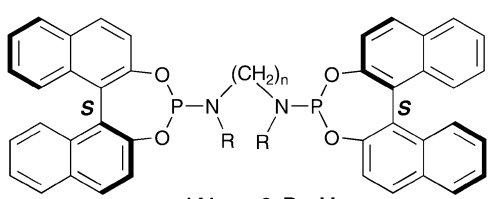
6. Remarks about the efficiency of monophosphoramidites

The difficulties inherent in obtaining efficient asymmetric catalysis are evident when it is considered that a product ratio of 99 : 1, *i.e.* an enantiomeric excess of 98%, corresponds to a difference in effective activation energies for the alternative reaction pathways of approximately 10 kJ mol^{-1}. This is an energy typical of weak chemical interactions, so that subtle structural and functional group changes in a catalyst can be associated with dramatic changes, not necessarily in the desired direction, in selectivity. Thus, though commonly guided by various principles, such as variation in the bite angle of a chelating ligand or in the conformation of a chirality-inducing element of structure, research on catalyst design has a large empirical component based on systematic syntheses of homologous and analogous species.[4] The assessment of any catalyst, in particular the metal-based catalysts which are the subject of the present article, is greatly complicated by the fact that the reactions are multistep processes in which the rate-determining step can be changed by modification of the conditions and in which selectivity can be involved at numerous different stages. In this respect, it is interesting to mention that, according to recent calculations by Reetz *et al.* on particular hydrogenation reactions with Rh(bis-monodentate phosphites) complexes, the major diastereomeric

Table 17 Olefin hydrogenation with diphosphoramidites

Entry	Ligand	Olefin	$P(H_2)$ (bar)	S : Rh : L	Time (h)	Conv (%)	Ee (%) (*config*)
1	**134**[a]	**1**	1	20 : 1 : 1.1	23	—	—
2	**134**[a]	**1**	1	20 : 1 : 2.2	23	—	—
3	**134**	**1**	1	20 : 1 : 1.1	24	100	25 (*S*)
4	**135**[a]	**1**	1	20 : 1 : 1.1	21	40	6 (*R*)
5	**135**	**1**	1	20 : 1 : 1.1	24	100	80 (*R*)
6	**136**[a]	**1**	1	20 : 1 : 1.1	21	18	12 (*S*)
7	**136**	**1**	1	20 : 1 : 1.1	24	7	28 (*S*)
8	**137**	**1**	1	20 : 1 : 1.1	24	56	72 (*R*)
9	**137**[a]	**1**	1	20 : 1 : 1.1	23	6	52 (*R*)
10	**137**[a]	**1**	1	20 : 1 : 2.2	23	—	—
11	**137**	**65**	1.3	1000 : 1 : 1	20	100	89 (*S*)
12	**137**	**18**	1.3	1000 : 1 : 1	20	100	80 (*R*)
13	**138**[a]	**1**	1	20 : 1 : 1.1	19	100	22 (*R*)
14	**138**	**1**	1	20 : 1 : 1.1	19	100	42 (*R*)
15	**139**	**65**	1.3	100 : 1 : 1.2	12	>99	54 (*R*)
16	**140**	**65**	1.3	100 : 1 : 1.2	12	>99	90 (*R*)
17	**140**	**65**	20	100 : 1 : 1.2	12	>99	90 (*R*)
18	**140**	**18**	1.3	100 : 1 : 1.2	12	98	80 (−)
19	**140**	**18**	20	100 : 1 : 1.2	12	97	86 (−)
20	**141**	**65**	1.3	1000 : 1 : 1	20	100	33 (*S*)
21	**141**	**18**	1.3	1000 : 1 : 1	20	100	50 (*R*)
22	**142**	**65**	1.3	1000 : 1 : 1	20	100	93 (*S*)
23	**142**	**18**	1.3	1000 : 1 : 1	20	100	96 (*R*)
24	**143**	**65**	1.3	1000 : 1 : 1	20	100	90 (*S*)
25	**143**	**18**	1.3	1000 : 1 : 1	20	100	98 (*R*)
26	**144a**	**1**	5	100 : 1 : 1.1	1	100	85 (*S*)
27	**144a**	**5**	5	100 : 1 : 1.1	1	100	81 (*S*)
28	**144a**	**6**	5	100 : 1 : 1.1	1	100	83 (*S*)
29	**144b**	**1**	5	100 : 1 : 1.1	1	100	85 (*R*)
30	**144b**	**5**	5	100 : 1 : 1.1	1	100	82 (*R*)
31	**144b**	**6**	5	100 : 1 : 1.1	1	100	83 (*R*)
32	**145a**	**1**	5	100 : 1 : 1.1	0.25	100	91 (*S*)
33	**145a**	**5**	5	100 : 1 : 1.1	0.25	100	92 (*S*)
34	**145a**[b]	**5**	5	100 : 1 : 1.1	0.5	100	92 (*S*)
35	**145a**	**5**	1	100 : 1 : 1.1	2	100	95 (*S*)
36	**145a**[b]	**5**	1	100 : 1 : 1.1	4	100	93 (*S*)
37	**145a**	**6**	5	100 : 1 : 1.1	0.25	100	92 (*S*)
38	**145b**	**1**	1	100 : 1 : 1.1	2	100	93 (*R*)
39	**145b**	**5**	1	100 : 1 : 1.1	2	100	94 (*R*)
40	**145b**	**6**	1	100 : 1 : 1.1	2	100	93 (*R*)
41	**146a**	**1**	5	100 : 1 : 1.1	2	100	86 (*S*)
42	**146a**	**5**	5	100 : 1 : 1.1	2	100	91 (*S*)
43	**146a**	**6**	5	100 : 1 : 1.1	2	100	90 (*S*)
44	**146b**	**1**	5	100 : 1 : 1.1	2	100	84 (*R*)
45	**146b**	**5**	5	100 : 1 : 1.1	2	100	93 (*R*)
46	**146b**	**6**	5	100 : 1 : 1.1	2	100	91 (*R*)
47	**147a**	**1**	5	100 : 1 : 1.1	4	100	60 (*S*)
48	**147a**	**5**	5	100 : 1 : 1.1	4	100	58 (*S*)
49	**147a**	**6**	5	100 : 1 : 1.1	4	100	50 (*S*)
50	**147b**	**1**	5	100 : 1 : 1.1	4	100	59 (*R*)
51	**147b**	**5**	5	100 : 1 : 1.1	4	100	58 (*R*)
52	**147b**	**6**	5	100 : 1 : 1.1	4	100	50 (*R*)
53	**148**	**65**	1.3	1000 : 1 : 1	20	100	96 (*S*)
54	**148**	**18**	1.3	1000 : 1 : 1	20	100	99 (*R*)
55	**149**	**65**	1.3	1000 : 1 : 1	20	100	99 (*S*)
56	**149**	**18**	1.3	1000 : 1 : 1	20	100	99 (*R*)

General conditions: T = rt, solvent = CH_2Cl_2.[a] Solvent = MeOH. [b] T = 0 °C.



141 n = 3, R = Me
142 n = 6, R = Me
143 n = 8, R = Me

intermediate leads to the favored enantiomeric product, which is opposite to the conventional mechanism (anti lock-and-key mechanism) as proposed by Halpern.[72]

A spectacular performance improvement over MonoPhos was recently achieved in the hydrogenation of the α-isopropylcinnamic acid derivative **150** (Fig. 5), a precursor of the blood pressure-lowering agent aliskiren,[43] by mixing chiral phosphoramidites, *e.g.* **151**, with *achiral* triaryl phosphines (Note that the phosphoramidite used, **151**, has a 3,3′-

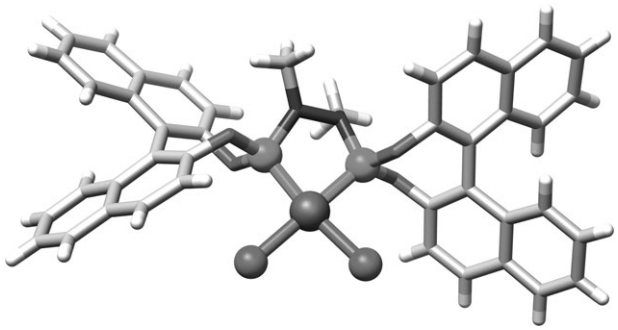
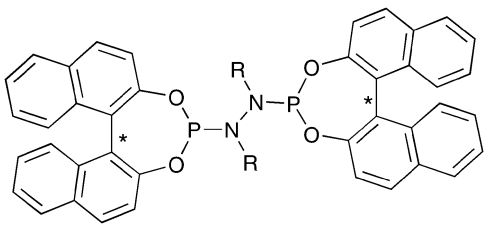


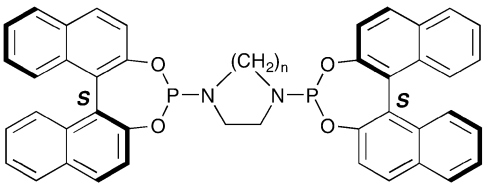
Fig. 4 X-ray structure of [$PtCl_2$\{(*S,S*)-**144b**\}] showing the formation of a chelate complex with a short diphosphoramidite.



(*R,R*)-**144a** (R = Me)
(*S,S*)-**144b** (R = Me)
(*R,R*)-**145a** (R = ^{t}Bu)
(*S,S*)-**145b** (R = ^{t}Bu)
(*R,R*)-**146a** (R = Ph)
(*S,S*)-**146b** (R = Ph)
(*R,R*)-**147a** (R = *o*-tolyl)
(*S,S*)-**147b** (R = *o*-tolyl)

substituted binoP unit which leads to higher ee's as well as higher reaction rates than the corresponding binoP-phosphoramidite).[36,41] The highest enantioselectivities were obtained when using a Rh/phosphoramidite/phosphine ratio of 1 : 2 : 1. These observations, which are in accord with related results obtained by Reetz with Rh/phosphinites systems, have been interpreted in terms of equilibria between homoligand complexes and a mixed [Rh(solvent)(phosphoramidite)(triarylphosphine)] + intermediate, which are responsible for both the enantioselectivity and activity increase.

A thorough study undertaken by Monti *et al*. has shown, that when hetero ligand combinations are used in hydrogenation reactions (and result in improved selectivities and reaction rates) the optimal stoichiometry may be far from 2 : 1 or 1 : 1, the latter depending in fact on the values of the equilibrium constants between the two homo-complexes and the hetero-complex.[73]

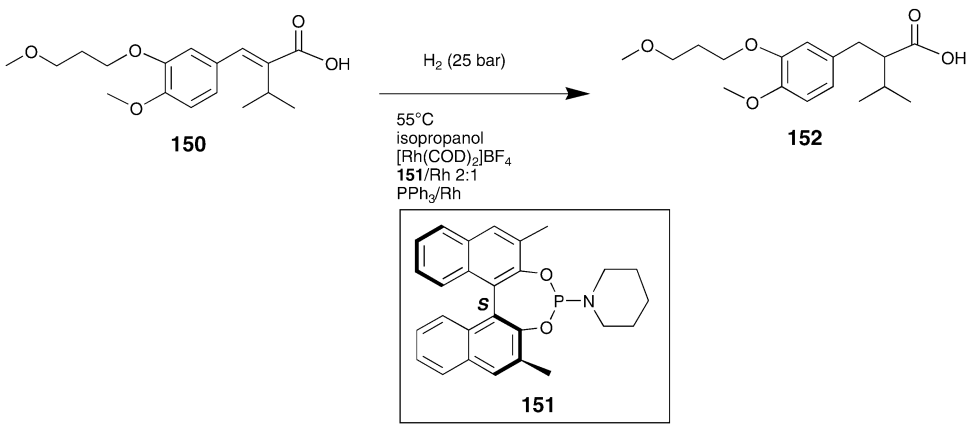


148 n = 2,
149 n = 3

Finally, it is worth mentioning that most of the amino-functionalised, BINOL-derived phosphoramidites, *e.g*. **70**, **99**, **100**, **101**, **102**, **103**, which turned out to give better results than MonoPhos in selected hydrogenations may form chelate rings of limited stability. However, to date there is no report showing that such a phenomenon occurs.

7. Conclusion

BINOL-derived monophosphoramidites are now recognised as excellent ligands for the enantioselective hydrogenation of prochiral olefins. As they can be prepared easily from binoPCl and cheap primary or secondary amines, a wide variety of new chiral monodentates have recently become accessible, each of them being adapted to a particular olefin. The results presently reviewed show that introduction of functional units into the amino group may significantly improve the catalytic outcomes for particular olefins with respect to the ones obtained with MonoPhos ligand. In some rare cases the functional group gives a product in a configuration opposite to that obtained with the reference ligand. BINOL-derived phosphoramidites containing a functional amino substituent which give strikingly better results than the latter include, for example, the morpholine derivative **70**, the piperazine derivative **99**, the sulfoximines **98** and **100**, and the azepinyl-phosphoramidite **108d**. At the present stage, the only reported bidentate ligands containing a phosphoramidite unit that lead to performances comparable to those of MonoPhos are some ferrocene-derived phosphoramidite-phosphines, which because of their



150 **152**

151

Fig. 5 Rhodium-catalysed asymmetric hydrogenation of an α-isopropylcinnamic acid. In this example, in which PPh_3 was used, an ee of 87% was obtained, *vs*. 72% with MonoPhos.

complicated syntheses cannot compete with monophosphoramidites. Surprisingly, the structural reasons for the high enantioselectivity obtained with many MonoPhos-analogues are still not understood. Analysis of possible reaction mechanisms is rendered exceptionally complicated for systems where mixed ligand intermediates result in improved selectivities because of the greater range of stereoisomeric intermediates. Clearly, further investigations, including solid state studies, are needed for a better understanding of these ligands.

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References

1 J. F. Young, J. A. Osborn, F. A. Jardine and G. Wilkinson, *Chem. Commun*., 1965, 131.
2 L. Horner, H. Büthe and H. Siegel, *Tetrahedron Lett*., 1968, **37**, 4023.
3 W. S. Knowles and M. J. Sabacky, *Chem. Commun*., 1968, 1445.
4 W. S. Knowles, *Angew. Chem., Int. Ed*., 2002, **41**, 1998.
5 L. Horner, H. Winkler, A. Rapp, A. Mentrup, H. Hoffmann and P. Beck, *Tetrahedron Lett*., 1961, **5**, 161.
6 T. P. Dang and H. B. Kagan, *J. Chem. Soc. D*, 1971, 481.
7 W. Tang and X. Zhang, *Chem. Rev*., 2003, **103**, 3029.
8 B. D. Vineyard, W. S. Knowles, M. J. Sabacky, G. L. Bachman and D. J. Weinkauff, *J. Am. Chem. Soc*., 1977, **99**, 5946.
9 M. J. Burk, Y. M. Wang and J. R. Lee, *J. Am. Chem. Soc*., 1996, **118**, 5142.
10 M. D. Fryzuk and B. Bosnich, *J. Am. Chem. Soc*., 1977, **99**, 6262.
11 H. Brunner and W. Pieronczyk, *Angew. Chem., Int. Ed. Engl*., 1979, **18**, 620.
12 A. Togni, C. Breutel, A. Schnyder, F. Spindler, H. Landert and A. Tijani, *J. Am. Chem. Soc*., 1994, **116**, 4062.
13 A. Miyashita, A. Yasuda, H. Takaya, K. Toriumi, T. Ito, T. Souchi and R. Noyori, *J. Am. Chem. Soc*., 1980, **102**, 7932.
14 R. Selke and H. Pracejus, *J. Mol. Catal*., 1986, **37**, 213.
15 F. Robin, F. Mercier, L. Ricard, F. Mathey and M. Spagnol, *Chem.–Eur. J*., 1997, **3**, 1365.
16 T. Saito, T. Yokozawa, T. Ishizaki, T. Moroi, N. Sayo, T. Miura and H. Kumobayashi, *Adv. Synth. Catal*., 2001, **343**, 264.
17 Z. Zhang, H. Quian, J. Longmire and X. Zhang, *J. Org. Chem*., 2000, **65**, 6223.
18 S. Duprat de Paule, S. Jeulin, V. Ratovelomanana-Vidal, J.-P. Genêt, N. Champion and P. Dellis, *Tetrahedron Lett*., 2003, **44**, 823.
19 D. J. Ager and S. A. Laneman, in *Asymmetric Catalysis on Industrial Scales*, ed. H.-U. Blaser and E. Schmidt, Wiley-VCH, Weinheim, 2004, pp. 259–268.
20 C. Claver, E. Fernandez, A. Gillon, K. Heslop, D. J. Hyett, A. Martorell, G. Orpen and P. G. Pringle, *Chem. Commun*., 2000, 961.
21 M. T. Reetz and T. Sell, *Tetrahedron Lett*., 2000, **41**, 6333.
22 This research was performed in collaboration between the Dutch company DSM and the University of Groningen.
23 R. Hulst, N. K. de Vries and B. L. Feringa, *Tetrahedron: Asymmetry*, 1994, **5**, 699.
24 M. J. S. Dewar and T. Nakaya, *J. Am. Chem. Soc*., 1968, **90**, 7134.
25 B. L. Feringa and H. Wynberg, *Tetrahedron Lett*., 1977, **50**, 4447.
26 A. I. Meyers and K. A. Lutomski, *J. Am. Chem. Soc*., 1982, **104**, 879.
27 M. van denBerg, A. J. Minnaard, E. P. Schudde, J. van Esch, A. H. M. de Vries, J. G. de Vries and B. L. Feringa, *J. Am. Chem. Soc*., 2000, **122**, 11539.
28 M. van den Berg, A. J. Minnaard, B. L. Feringa and J. G. de Vries, *DSM IP Assets B.V, German Pat., DE 601 23 093 T2*, 2006.
29 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 and B. L. Feringa, *Angew. Chem., Int. Ed*., 2005, **44**, 4209.
30 R. Hoen, T. D. Tiemersma-Wegman, B. Procuranti, L. Lefort, J. G. de Vries, A. J. Minnaard and B. L. Feringa, *Org. Biomol. Chem*., 2007, **5**, 267.
31 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 and J. G. de Vries, *Adv. Synth. Catal*., 2003, **345**, 308.
32 D. Ager, M. van den Berg, A. J. Minnaard, B. L. Feringa, A. H. M. de Vries, C. E. Willans, J. A. F. Boogers and J. G. de Vries, *ACS Symp. Ser*., 2004, **880**, 115.
33 A. J. Minnaard, M. van den Berg, E. P. Schudde, J. van Esch, A. H. M. de Vries, J. G. de Vries and B. L. Feringa, *Chim. Oggi*, 2001March–April), 12.
34 D. J. Ager, A. H. M. de Vries and J. G. de Vries, *Platinum Met. Rev*., 2006, **50**, 54.
35 A. H. M. de Vries and L. Lefort, *Chem.–Eur. J*., 2006, **12**, 4722.
36 A. J. Minnaard, B. L. Feringa, L. Lefort and J. G. de Vries, *Acc. Chem. Res*., 2007, **40**, 1267.
37 X. Jia, X. Li, L. Xu, Q. Shi, X. Yao and A. S. C. Chan, *J. Org. Chem*., 2003, **68**, 4539.
38 L. Eberhardt, D. Armspach, D. Matt, L. Toupet and B. Oswald, *Eur. J. Inorg. Chem*., 2007, 4153.
39 L. Eberhardt, D. Armspach, D. Matt, L. Toupet and B. Oswald, *Eur. J. Org. Chem*., 2007, 5395.
40 H.-J. Drexler, J. You, S. Zhang, C. Fischer, W. Baumann, A. Spannenberg and D. Heller, *Org. Process Res. Dev*., 2003, **7**, 355.
41 J. A. F. Boogers, U. Felfer, M. Kotthaus, L. Lefort, G. Steinbaur, A. H. M. de Vries and J. G. de Vries, *Org. Process Res. Dev*., 2007, **11**, 585.
42 F. Giacomina, A. Meetsma, L. Panella, L. Lefort, A. H. M. de Vries and J. G. de Vries, *Angew. Chem., Int. Ed*., 2007, **46**, 1497.
43 J. M. Wood, J. Maibaum, J. Rahuel, M. G. Grütter, N.-C. Cohen, V. Rasetti, H. Rüger, R. Göschke, S. Stutz, W. Fuhrer, W. Schilling, P. Rigollier, Y. Yamaguchi, F. Cumin, H.-P. Baum, C.-R. Schnell, P. Herold, R. Mah, C. Jensen, E. O'Brien, A. Stanton and M. P. Bedigian, *Biochem. Biophys. Res. Commun*., 2003, **308**, 698.
44 D. Peña, A. J. Minaard, A. H. M. de Vries, J. G. de Vries and B. L. Feringa, *Org. Lett*., 2003, **5**, 475.
45 A. H. M. de Vries, A. Meetsma and B. L. Feringa, *Angew. Chem., Int. Ed. Engl*., 1996, **35**, 2372.
46 G. Francio, C. G. Arena, F. Faraone, C. Graiff, M. Lanfranchi and A. Tiripicchio, *Eur. J. Inorg. Chem*., 1999, 1219.
47 L. Panella, A. M. Aleixandre, G. J. Kruidhof, J. Robertus, B. L. Feringa, J. G. de Vries and A. J. Minnaard, *J. Org. Chem*., 2006, **71**, 2026.
48 H. Bernsmann, M. van den Berg, R. Hoen, A. J. Minnaard, G. Mehler, M. T. Reetz, J. G. de Vries and B. L. Feringa, *J. Org. Chem*., 2005, **70**, 943.
49 W. Li and X. Zhang, *J. Org. Chem*., 2000, **65**, 5871.
50 M. T. Reetz, G. Mehler, A. Meiswinkel and T. Sell, *Tetrahedron Lett*., 2002, **43**, 7941.
51 O. Huttenloch, J. Spieler and H. Waldmann, *Chem.–Eur. J*., 2000, **6**, 671.
52 Q.-H. Zeng, X.-P. Hu, X.-M. Liang and Z. Zheng, *Chin. Chem. Lett*., 2005, **16**, 1321.
53 N. Cramer, S. Laschat and A. Baro, *Organometallics*, 2006, **25**, 2284.
54 L. Lefort, J. A. F. Boogers, A. H. M. de Vries and J. G. de Vries, *Org. Lett*., 2004, **6**, 1733.
55 S. Doherty, E. G. Robins, I. Pal, C. R. Newman, C. Hardacre, D. Rooney and D. A. Mooney, *Tetrahedron: Asymmetry*, 2003, **14**, 1517.
56 W.-J. Tang, Y.-Y. Huang, Y.-M. He and Q.-H. Fan, *Tetrahedron: Asymmetry*, 2006, **17**, 536.
57 A. D. Burrows, R. W. Harrington, M. F. Mahon, M. T. Palmer, F. Senia and M. Varrone, *Dalton Trans*., 2003, 3717.
58 M. T. Reetz, O. G. Bondarev, H.-J. Gais and C. Bolm, *Tetrahedron Lett*., 2005, **46**, 5643.
59 D. Peña, A. J. Minnaard, J. G. de Vries and B. L. Feringa, *J. Am. Chem. Soc*., 2002, **124**, 14552.
60 S.-g. Lee and Y. J. Zhang, *Org. Lett*., 2002, **4**, 2429.

61 X. Jia, X. Li, W. S. Lam, S. H. L. Kok, L. Xu, G. Lu, C.-H. Yeung and A. S. C. Chan, *Tetrahedron: Asymmetry*, 2004, **15**, 2273.
62 N. W. Boaz, J. A. Ponasik and S. E. Large, *Tetrahedron: Asymmetry*, 2005, **16**, 2063.
63 N. W. Boaz, J. A. Ponasik and S. E. Large, *Tetrahedron Lett*., 2006, **47**, 4033.
64 X.-P. Hu and Z. Zheng, *Org. Lett*., 2004, **6**, 3585.
65 X.-P. Hu and Z. Zheng, *Org. Lett*., 2005, **7**, 419.
66 G. Francio, F. Faraone and W. Leitner, *Angew. Chem., Int. Ed*., 2000, **39**, 1428.
67 J.-D. Huang, X.-P. Hu, Z.-C. Duan, Q.-H. Zeng, S.-B. Yu, D.-Y. Deng and Z. Zheng, *Org. Lett*., 2006, **8**, 4367.
68 K. A. Vallianatou, I. D. Kostas, J. Holz and A. Börner, *Tetrahedron Lett*., 2006, **47**, 7947.
69 L. Eberhardt, D. Armspach, D. Matt, B. Oswald and L. Toupet, *Org. Biomol. Chem*., 2007, **5**, 3340.
70 E. Cesarotti, S. Araneo, I. Rimoldi and S. Tassi, *J. Mol. Catal. A: Chem*., 2003, **204–205**, 211.
71 M. T. Reetz, G. Mehler and O. Bondarev, *Chem. Commun*., 2006, 2292.
72 M. T. Reetz, A. Meiswinkel, G. Mehler, K. Angermund, M. Graf, W. Thiel, R. Mynott and D. G. Blackmond, *J. Am. Chem. Soc*., 2005, **127**, 10305.
73 C. Monti, C. Gennari, U. Piarulli, J. G. de Vries, A. H. M. de Vries and L. Lefort, *Chem.–Eur. J*., 2005, **11**, 6701.

