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Monodentate Phosphoramidites: A Breakthrough in Rhodium-Catalysed Asymmetric Hydrogenation of Olefins

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Abstract: Monodentate phosphoramidites based on BINOL or substituted BINOL are excellent ligands for the rhodium-catalysed asymmetric hydrogenation of olefins. Very high enantioselectivities were obtained with MonoPhos (**7a**) the simplest member of this class, a ligand that is prepared in a single step from BINOL and HMPT. Turnover numbers up to 6000 have been obtained in the hydrogenation of dehydroamino acid derivatives. Enantioselectivities in the hydrogenation of dehydroamino acids are solvent dependent; in non-protic solvents they range from 95–99%. Itaconic acid and its dimethyl ester could be hydrogenated with 96 and 94% e.e., respectively. Hydrogenation of aromatic enamides gave the corresponding acylated amines in 86–94% e.e. Several analogous phosphoramidite ligands have been prepared. Surprisingly, bidentate ligands gave poorer results, both in terms of rate as well as enantioselectivity. Taddol-based phosphoramidites led to poor e.e. and slow rates. Methyl substituents at the 3,3′-position of BINOL led to a sharply reduced rate and a somewhat lower enantioselectivity. Bromo substituents at the 6,6′-position led to a slightly reduced rate but little effect was seen on enantioselectivity. Use of octahydro-MonoPhos (**11**) gave results that were very similar to those obtained with **7a**. The rate of the reaction is dependent on the hydrogen pressure, however, the enantioselectivity is not affected. The rate of the dehydroamino acid hydrogenation also increases if the ligand to rhodium ratio is reduced from 2.2 to 1.5 or even to 1.0; yet, there is no deleterious effect on the enantioselectivity. Catalytic activity ceases with L/Rh = 3 when dehydroamino acid derivatives were used as substrate. The reaction shows a positive non-linear effect, which confirms the presence of Rh-complexes with more than one ligand. Following the hydrogenation of methyl 2-acetamidocinnnamate with $Rh(nbd)_2BF_4$/**7a** by electrospray mass spectrometry showed the presence of several rhodium species. Notable are the presence of $[Rh(\mathbf{7a})]_3^+$ and $[Rh(\mathbf{7a})]_4^+$. There is at present insufficient evidence to conclude if the active catalytic species carries one or two ligands. In view of the low cost of MonoPhos this invention might well lead to a broader application of asymmetric olefin hydrogenation for the production of enantiopure amino acids and amines.

Keywords: asymmetric catalysis; dehydroamino acids; enamides; hydrogenation; monodentate phosphoramidite ligands; MonoPhos; P-ligands; rhodium

Introduction

Rhodium-catalysed asymmetric hydrogenation of olefins is a well-established technology.[1] Many classes of prochiral olefins can be hydrogenated with high enantioselectivity as long as at least one functional group, such as an amide, is present that can function as an additional ligand. The hydrogenation of unfunctionalised olefins, on the contrary, is an emerging area.[2] The technology is easy to use in the laboratory as the catalyst can conveniently be prepared *in situ* by combining a catalyst precursor such as $Rh(COD)_2BF_4$ and the ligand. Many hydrogenations can be performed with hydrogen pressures as low as 1–5 bar.

Since their first introduction by the groups of Knowles[3] and Horner[4] thousands of papers and patents have appeared describing new phosphorus-based chiral ligands.[5] However, a recent survey by Blaser et al. shows that at best a dozen processes based on asymmetric hydrogenation have been implemented

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for the production of enantiopure intermediates on a ton-scale.[6] We believe that this scant use of such a well-studied technology is caused by the following main reasons:

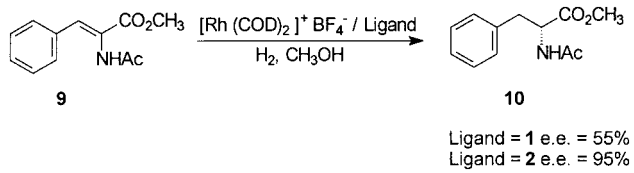
1. Time-to-market constraints often do not allow sufficient time to develop a catalytic process for new products.
2. Costs of metal and or ligand is too high.
3. Poor availability of ligands (both laboratory and production scale) on short notice.

If the targets of cost price and delivery time cannot be met, obviously, competing technologies will be used for production. In order of importance these will be classical resolution *via* crystallisation of diastereomeric salts, biocatalysis, fermentation and physical separation of racemates by chromatography or chiral simulated moving bed.

We felt that it should be possible to overcome these barriers by making available large libraries of low-cost ligands and by using high throughput experimentation for the rapid testing of their performance in a desired transformation.[7] We decided against a library of bisphosphine ligands as their synthesis entails many synthetic steps, some of which are low yielding. In addition, it is the relatively high number of synthetic steps that makes these ligands very expensive. As the Groningen group is very successful in the use of monodentate phosphoramidites as ligands in the Cu(I)-catalysed asymmetric 1,4-addition of Et_2Zn to enones[8] we were attracted to the idea of making a library of phosphoramidites[9] for testing in the rhodium-catalysed asymmetric hydrogenation.

Monodentate Ligands in Asymmetric Hydrogenation

In the first years after the discovery of the Wilkinson catalyst the search for enantioselective hydrogenations was solely focused on the development of chiral monophosphines. This was based on the assumption that the dissociation of a phosphine from the complex is essential for the initiation of the catalytic cycle. Monodentate P-chiral phosphine ligands were synthesised by the groups of Knowles[3] and Horner[4] and tested in the first attempts at asymmetric (unsubstituted) olefin hydrogenation. The reported enantioselectivities were disappointingly low but this all changed when Dang and Kagan reported the synthesis of the first chiral bisphosphine ligand (DIOP, **3**) and the remarkably high e.e.'s at that time in the hydrogenation of 2-acetamidocinnamic acid.[10] Knowles also realised that the use of bisphosphines would lead to the formation of a more rigid complex; for a long time perceived as being necessary for the achievement of high enantioselectivities. Indeed, dimerisation of the first generation ligand PAMP (**1**) to DIPAMP (**2**) (Figure 1) raised the



Scheme 1.

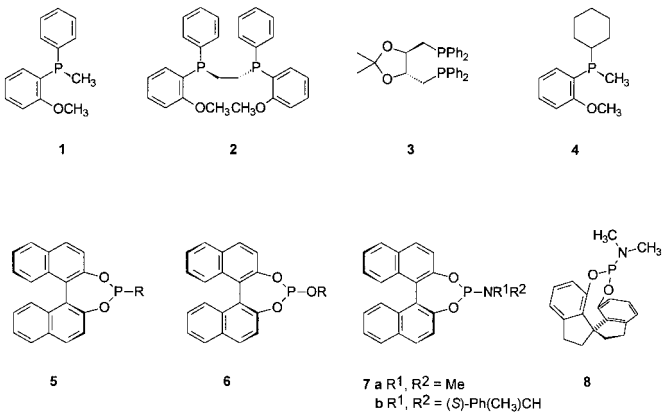


Figure 1. Chiral ligands for asymmetric hydrogenation.

enantioselectivity of the rhodium-catalysed hydrogenation of methyl 2-acetamidocinnamate (**9**) from 55% to 95% (Scheme 1).[11] The application of DIPAMP in the commercial process for L-DOPA,[3b] and the simplification of the synthesis by using non P-chiral ligands, such as DIOP (**3**), has led to the discovery of several dozens of families of chiral bisphosphines.[5] In spite of the fact that Knowles had already shown that use of monodentate CAMP (**4**) led to formation of *N*-acetylphenylalanine (**10**) in up to 88% e.e.,[12] the dogma of the superiority of bidentate phosphorus ligands was well established and remained unchallenged for many years.[13]

More recently, several other phosphorus based chiral bidentate ligands, such as bisphosphinites,[14] bisphosphonites[15] and bisphosphites[16] were developed successfully. Ligands based on amino acids were also developed but these were less successful in olefin hydrogenation.[17]

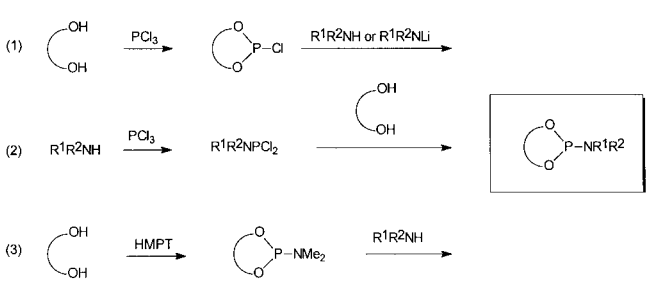
The application of these bisphosphine ligands for production of enantiopure fine chemicals was often hampered by their lengthy synthesis. Stimulated by the significant role of monodentate ligands in other transition metal-catalysed reactions,[18] we and others successfully introduced BINOL-based monodentate ligands for highly enantioselective rhodium-catalysed hydrogenations. Next to phosphoramidites (e.g., MonoPhos, **7a**),[19] publications appeared on the use of monodentate phosphonites (**5**)[20] and phosphites (**6**).[21] Later other papers appeared describing the use of chiral monodentate ligands in the asymmetric hydrogenation.[22]

Synthesis and Use of Chiral Phosphoramidites

Several methods have been developed for the preparation of phosphoramidite ligands.[23] The most frequently used procedure is the reaction of phosphorus trichloride (PCl_3) with a diol, in the presence of triethylamine as a base followed by reaction with a secondary amine or its lithiated equivalent (see Equation 1 in Scheme 2).[24] In particular for sterically demanding secondary amines, application of the lithiated amines affords higher yields and shorter reaction times. A reversed procedure, especially for bulky (chiral) phosporamidites has been reported too (see Equation 2 in Scheme 2).[23c,25]

An alternative procedure, also used for the preparation of MonoPhos (**7a**), is the phosphorylation of diols with phosphorus triamides.[26] When hexamethylphosphorous triamide (HMPT) is reacted with 1,1′-bi-2-naphthol in toluene, MonoPhos crystallises from the mixture in 90% yield. This easy and high-yielding synthesis prompted us to develop another approach to the synthesis of phosphoramidites based on the transamination of MonoPhos. In DNA and RNA solid phase synthesis, the alcoholysis of phosphoramidite nucleotides is extensively used, applying tetrazole and imidazole derivatives as catalysts.[27] By replacing alcohols with amines and with one equivalent of tetrazole, MonoPhos was converted virtually quantitatively (according to ^{31}P NMR) to the corresponding phosphoramidite (see Equation 3 in Scheme 2).[28,29]

Phosphoramidite ligands, in particularly **7b**, perform very well in the Cu(I) triflate-catalysed 1,4-addition of Et_2Zn to enones and other α,β-unsaturated systems.[30] Chiral phosphoramidites have been used as ligands in the iridium-catalysed substitution of allylic acetates mainly as part of a mechanistic study.[31] Other examples are copper-catalysed allylic alkylations,[32] palladium-catalysed intramolecular asymmetric Heck reactions,[33] palladium-catalysed asymmetric hydrosilylations[34] and nickel-catalysed asymmetric hydrovinylations.[35] Very recently, the use of a new spirobiindane-based phosphoramidite (**8**) has been described for the highly enantioselectieve hydrogenation of dehydroamino acids,[36] itaconic acid derivatives and enamides.[37] Mixed bidentate phosphine-phosphoramidite[38] and phosphite-phosphoramidite[39] ligands have been synthesised and used successfully for asymmetric olefin hydrogenation.



Scheme 2. Preparation of monodentate phosphoramidite ligands.

Results and Discussion

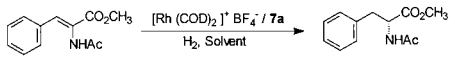
Initial Hydrogenation Results and Solvent Effect

As we had the intention to synthesise a library of monodentate phosphoramidites for use in asymmetric hydrogenation it was a matter of routine to first screen one member of the class in the rhodium-catalysed hydrogenation of methyl 2-acetamidocinnamate (**9**) to see if the catalyst would be reactive enough and show some measure of enantioselectivity. Initial hydrogenation experiments were performed at 1 bar hydrogen pressure in CH_3OH, using 5 mol % of catalyst with a L/Rh of 2.1. We were very pleased indeed to observe that using MonoPhos (**7a**) as ligand we were able to obtain a 100% yield of *N*-Ac-phenylalanine methyl ester (**10**) with an enantioselectivity of 70% after overnight reaction. This unexpectedly high e.e. invited to further optimisation. As the effect of solvent on enantioselectivity has been noted before by many authors[1] this was the first aspect we screened. This turned out to be a very rewarding enterprise as non-protic solvents, in particular CH_2Cl_2 and EtOAc led to excellent enantioselectivities in this reaction (Table 1). This solvent effect seems to be connected to the protic/non-protic nature as the protic solvent of entry 7 is very similar in polarity to CH_2Cl_2.

Asymmetric Hydrogenation of *N*-Acetyldehydroamino Acids with Rhodium/MonoPhos

The initial hydrogenation experiments were all performed in Schlenk tubes at 1 bar using a small magnetic stirring bar. Rates of these reactions were not very high.

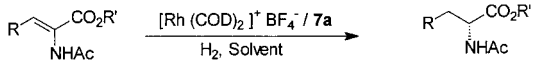
Table 1. Solvent effect on the asymmetric hydrogenation with Rh/**7a**.



Entry	Solvent	e.e.
1	CH_3OH	70%
2	CH_2Cl_2	95%
3	CH_2Cl_2	97% [a]
4	EtOAc	95%
5	THF	93%
6	Acetone	92%
7	$PrOCH_2CH_2OH$	77%

[a] Experiment at 5 °C.

Table 2. Asymmetric hydrogenation of dehydroamino acids with rhodium/**7a**.



Entry	R	R'	Mol % Rh	**7a**/Rh	Solvent	pH_2 (bar)	Time	e.e. [%]	TOF (h^{-1})[a]
1	phenyl	Me	5.0	2.2	CH_2Cl_2	1	3 h	95	6.7
2	phenyl	Me	0.5	2.2	CH_2Cl_2	5	40 min	95	300
3	phenyl	Me	0.1	2.2	CH_2Cl_2	15	2 h	95	500
4	phenyl	Me	0.015	2.0	CH_2Cl_2	5	16 h	95	337[b] (81%)
5	phenyl	Me	0.9	2.2	EtOAc	60	4 min	97	1667
6	phenyl	H	0.2	2.2	CH_2Cl_2	15	1 h	97	500
7	phenyl	H	0.1	2.2	CH_2Cl_2	5	3 h	97	333
8	phenyl	Me	5.0	1.1	EtOAc	1	2 h	96	10
9	phenyl	Me	0.015	1.0	CH_2Cl_2	5	16 h	95	375[c] (90%)
10	3-methoxyphenyl	Me	1.0	1.1	CH_2Cl_2	5	2 h	97	50
11	4-methoxyphenyl	Me	1.0	1.1	CH_2Cl_2	5	2 h	94	50
12	4-AcO-3-MeO-phenyl	Me	0.5	2.2	EtOAc	5	nd[d]	96	–
13	4-fluorophenyl	Me	1.0	1.1	CH_2Cl_2	5	25 min	96	240
14	4-fluorophenyl	H	2.0	2.2	CH_2Cl_2	27	10 min	93	300
15	3-fluorophenyl	Me	1.0	1.1	CH_2Cl_2	5	30 min	95	200
16	3-fluorophenyl	H	0.1	2.2	CH_2Cl_2	10	2 h	96	500
17	2-fluorophenyl	Me	1.0	1.1	CH_2Cl_2	5	15 min	95	400
18	4-chlorophenyl	Me	1.0	1.1	CH_2Cl_2	5	20 min	94	300
19	3,4-dichlorophenyl	H	0.1	1.1	CH_2Cl_2	5	2 h	97	500
20	3,4-dichlorophenyl	Me	1.0	1.1	CH_2Cl_2	5	30 min	99	200
21	3-nitrophenyl	Me	4.0	1.1	CH_2Cl_2	5	2 h	95	13
22	4-nitrophenyl	Me	1.0	1.1	CH_2Cl_2	5	nd	95	–
23	4-fluoro-3-nitrophenyl	Me	1.0	1.1	CH_2Cl_2	5	2 h	95	50
24	4-biphenyl	Me	1.0	1.1	CH_2Cl_2	5	25 min	95	240
25	3-fluoro-4-biphenyl	Me	1.0	1.1	CH_2Cl_2	5	25 min	93	240
26	4-acetylphenyl	Me	1.0	1.1	CH_2Cl_2	5	15 min	99	400
27	4-benzoylphenyl	Me	1.0	1.1	CH_2Cl_2	5	30 min	94	168
28	4-cyanophenyl	Me	1.0	1.1	CH_2Cl_2	5	18 h	92	4 (70%)
29	1-naphthyl	Me	1.0	1.1	CH_2Cl_2	5	10 min	93	600
30	H	Me	1.0	2.2	CH_2Cl_2	5	2 h	>99	50
31	H	H	5.0	2.2	EtOAc	1	nd	>99	–

[a] Yields are quantitative, unless noted otherwise. As reaction times are unoptimised TOFs are indicative.
[b] TON = 5400.
[c] TON = 6000.
[d] Not determined.

However, upon transferring the hydrogenation into well-stirred autoclaves, and raising the pressure to 5 bar we could raise the turnover frequency (TOF) to 300 h^{-1} (Table 2, entry 2). At high pressure (60 bar) an unoptimised TOF of 1667 h^{-1} has been achieved (entry 5). Obviously, the reaction has a positive order in hydrogen pressure. Most gratifyingly we found that, unlike with many bisphosphine ligands, *the enantioselectivity does not decrease with increasing pressure.* We can thus easily achieve the minimum substrate to catalyst ratio of 2000, which is required for economic application. In fact, we have performed successful hydrogenations at a substrate to catalyst ratio of 6500 at 5 bar (entries 4 and 9). We found that mixing catalyst precursor and ligand prior to hydrogenation, followed by stirring under N_2 for 5 min and evaporation led to faster reactions. Presumably, this is due to the loss of one equivalent of COD in this operation, which we observed by NMR. Heller has shown that the presence of COD can cause long induction periods and low reaction rates in hydrogenations with bisphosphine ligands.[40]

MonoPhos (**7a**) is stable during 48 h in methanol at room temperature even in the presence of $[Rh(COD)_2]BF_4$. However, it is well known that acids accelerate the substitution of P-N bonds with oxygen nucleophiles. Thus we were pleased to find that **7a** can be used without decomposition in the hydrogenation of dehydroamino acids: *N*-acetylphenylalanine was obtained in 97% e.e. (entries 6 and 7).

Surprisingly, the rate of the reaction was positively affected (*vide infra)* by reducing the L/Rh ratio from two to one without compromising the enantioselectivity (entries 8 and 9). A full discussion of this effect will be given later (*vide infra*). Most hydrogenations of dehy-

droamino acid derivatives were subsequently carried out using this ratio.

A variety of substituents on the phenyl group has little or no effect on the enantioselectivity of the hydrogenation, although the rate was affected significantly. The substrates for these hydrogenations were prepared from the substituted benzaldehydes *via* the Erlenmeyer synthesis[41] or by Heck reaction of the aryl bromide on methyl 2-acetamidoacrylate.[42,43] Both 3- and 4-methoxy-derivatives of *N*-acetylphenylalanine methyl ester were thus prepared in excellent enantioselectivity (entries 10 and 11). It was also possible to obtain the L-DOPA precursor in 96% e.e. (entry 12). Fluorine substitution is often used in drugs and agrochemicals as a means to manipulate the biological properties of an active substance. It was thus very gratifying that we were able to prepare *o*-, *m*- and *p*-fluoro-substituted phenylalanines with excellent enantioselectivities both as methyl esters and as free acids (entries 13 – 17). Also the 4-chloro- and 3,4-dichlorophenylalanine derivatives were prepared with excellent enantioselectivity (entries 18 – 20). The 3- and 4-nitro-substituted *N*-acetyldehydrophenylalanines could be hydrogenated with very good enantioselectivity but the rate is clearly influenced by the electron-withdrawing substituent (entries 21 – 23). The amino acid of entry 23 has been prepared before by asymmetric hydrogenation as part of a total synthesis of Teicoplanin aglycone.[44] Hydrogenation of the 4-cyano-substituted substrate was very slow; this may be due to the nitrile group functioning as a ligand for rhodium (entry 28). A number of compounds with large substituents on the 4-position could be hydrogenated with excellent enantioselectivities (entries 24, 25, 27). Although we have not yet tested dehydrophenylalanine substrates with large *ortho*-substituents the 1-naphthyldehydroalanine derivative might be considered such an example which, nonetheless, could be hydrogenated in 93% e.e. (entry 29). The hydrogenation of 2-acetamidoacrylic acid and its methyl ester gave the alanine derivatives in greater than 99% e.e. (entries 30 and 31). In all these hydrogenations use of MonoPhos with the *S* configuration gave the amino acids with the *R* configuration. Hydrogenation of β,β-disubstituted *N*-acetyldehydroamino acids is currently under study.

Ligand Variation

A number of different ligands was prepared by classical synthesis (See Experimental Section for details).[45] The backbone was varied by using different Taddol skeletons as in **14** and **15**. In addition, we probed the effect of substituents on the BINOL skeleton in the 3- and 6-positions (**13** and **12**, respectively). A number of ligands was prepared based on the BINOL skeleton, with various substituents on nitrogen (**7a – c**). Hydrogenation

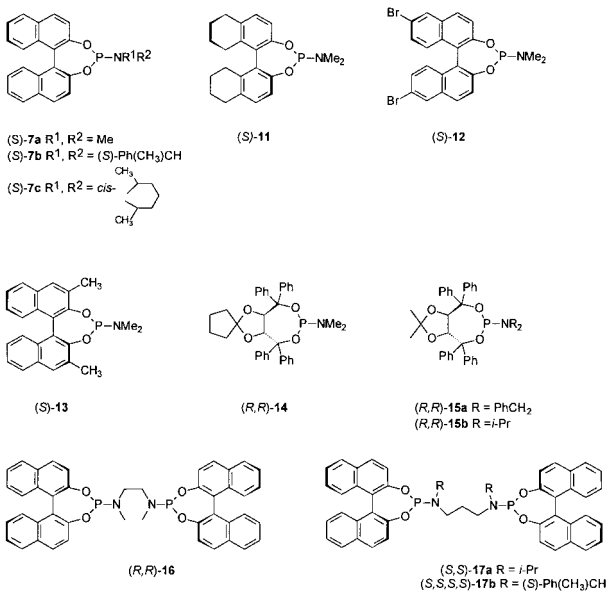


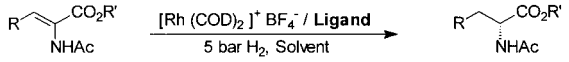
Figure 2. Phosphoramidite ligands.

of BINOL over PtO_2,[46] followed by reaction with HMPT gave **11**.

The ligands were tested in the Rh-catalysed hydrogenation of a limited number of dehydrophenylalanine derivatives; most experiments were performed on **9**. In the dehydroamino acid hydrogenations the two methyl substituents on nitrogen as in **7a** are unsurpassed up to now (Table 3, entry 14). Preliminary results with the Taddol-based ligands were not very encouraging (entries 2 – 4). The bulky skeleton is the probable reason for the much lower rate of these hydrogenations. The 6,6′-dibromo-MonoPhos **12** behaved very similar to MonoPhos in the hydrogenation of **9** (entry 7), although the rate is somewhat lower (Figure 3). The enantioselectivity did suffer when this ligand was applied for the hydrogenation of the 4-fluoro-derivative (entry 13). The effect of the 3,3-dimethyl substituents was more marked and led to a strongly reduced rate as well as a somewhat lower enantioselectivity in the hydrogenation of **9** (entry 5). Surprisingly, the configuration of the product is the same as that of the BINOL, in contrast to results with the other BINOL ligands. Hydrogenations with octahydro-MonoPhos **11** gave results that were comparable to those obtained with MonoPhos itself (entries 6, 11 and 12). This was recently confirmed by the work of Chan et al.[22c] Use of bidentate ligands such as **16** or **17a, b** was not very successful. In methanol hardly any reaction took place (not shown in the Table). However, in CH_2Cl_2 a reasonable rate could be attained, depending on bridge length. Nevertheless, enantioselectivity was much lower than with the monodentate ligands (entries 8 – 10).

A comparison of the kinetics of the hydrogenation of **9** using ligands **7a**, **11**, **12** and **13** is displayed in Figure 3. These traces represent hydrogen uptake during hydro-

Table 3. Ligand variations in the Rh-catalysed hydrogenation of dehydroamino acids and esters.



Entry	R	R'	Mol % Rh	Ligand (L/Rh)	Solvent	pH_2 (bar)	Time[a]	e.e.[b] [%]
1	phenyl	Me	5.0	**7c** (2.1)	CH_2Cl_2	1	4 h (72%)	27
2	phenyl	Me	1.0	**14** (2.2)	CH_3OH	1	44 h	2
3	phenyl	Me	5.0	**15a** (2.1)	CH_2Cl_2	1	90 h	35
4	phenyl	Me	1.0	**15b** (2.2)	CH_3OH	1	44 h	37
5	phenyl	Me	1.0	**13** (2.0)	CH_2Cl_2	5	2 h	89
6	phenyl	Me	1.0	**11** (2.0)	CH_2Cl_2	5	9 min	98
7	phenyl	Me	1.0	**12** (2.2)	CH_2Cl_2	5	28 min	94
8	phenyl	Me	5.0	**16** (1.1)	CH_2Cl_2	1	20h (22%)	72
9	phenyl	Me	5.0	**17a** (1.1)	CH_2Cl_2	1	20 h	25
10	phenyl	Me	5.0	**17b** (1.1)	CH_2Cl_2	1	20 h	80
11	3-fluorophenyl	H	2.0	**11** (2.2)	CH_2Cl_2	5	2 h	96
12	4-fluorophenyl	H	2.0	**11** (2.2)	CH_2Cl_2	5	2 h	93
13	4-fluorophenyl	H	2.0	**12** (2.2)	CH_2Cl_2	5	2 h	63
14	phenyl	Me	0.5	**7a** (2.2)	CH_2Cl_2	5	40 min	95

[a] Conversion is 100% unless noted otherwise.
[b] All products had the *R*-configuration except in entries 9 and 10; the configuration has not been determined for entry 11.

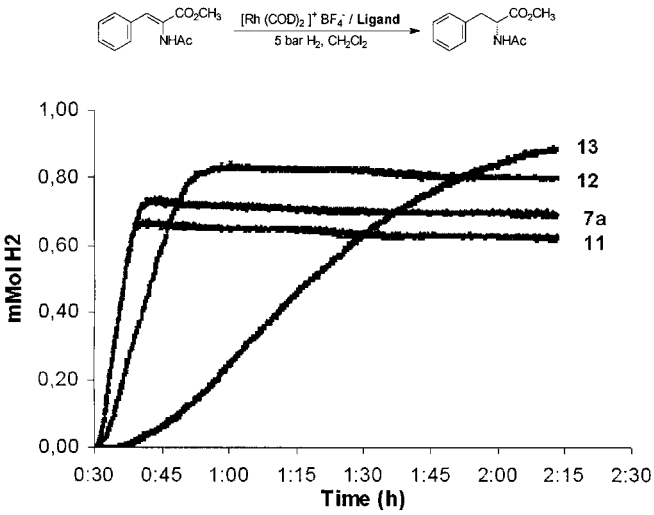


Figure 3. Hydrogen uptake in the rhodium-catalysed hydrogenation of **9** at 5 bar with different ligands.

genation at 5 bar pressure which were performed simultaneously in the Endeavor™, a semi-automated device which allows 8 parallel gas-liquid reactions with continuous monitoring of hydrogen uptake. The first 30 minutes are used for repeated purging with N_2. After the solution has been pressurised with H_2 the reaction starts almost immediately and seemingly follows zero-order kinetics with **7a** and **11**. Although hydrogenation using **12** is clearly slower the kinetic profile is very similar to those of **7a** and **11**. Quite different kinetics are observed with the 3,3′-dimethyl derivative **13**; an induction period is apparent and after a much slower reaction the rate gradually decreases which might point to some catalyst deactivation.[47] The induction period usually is related to the catalyst activation step by hydrogenation of the remaining bound COD, which can be very slow with some ligands.[40]

Enamide Hydrogenation

Asymmetric hydrogenation of enamides gives access to enantioenriched acylated amines that can be hydrolysed to the amines. We thus screened a range of enamides in the asymmetric hydrogenation with Rh/**7** and other ligands (Figure 4, Table 4).[48] The enamide substrates were prepared either by Fe/TMSCl/Ac_2O reduction of the oximes in HOAc[49,50] or *via* Grignard reaction on the nitriles followed by reaction of the magnesium imine with Ac_2O.[51]

The hydrogenation of these substrates proceeds slower than the hydrogenation of the dehydroamino acid derivatives. In addition, the enantioselectivities are somewhat lower. However, by performing the hydrogenations at $-5\,^{\circ}C$ most aromatic enamides could be hydrogenated with greater than 90% e.e. Also in this case the pressure does not effect the enantioselectivity of the reaction (entries 3 and 4). Of all the solvents screened, CH_2Cl_2 induces the highest enantioselectivities and rates. Although the reactions in EtOAc are usually somewhat slower and lead to lower e.e.'s, the temperature effect is much larger in these hydrogenations leading to good results at $-5\,^{\circ}C$. Whereas the hydrogenation of **9** is effectively blocked with L/Rh ratios of 3.0 or more, this is not the case with enamide hydrogenation (entry 12). There is only a minor effect of

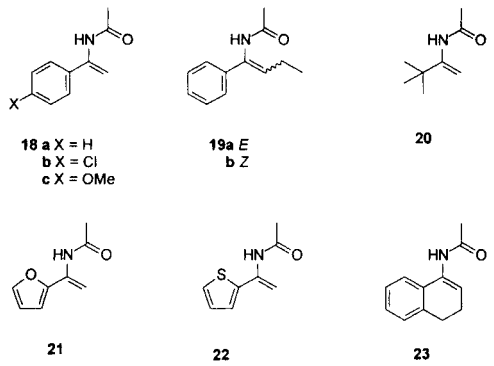


Figure 4. Enamide substrates for asymmetric hydrogenation.

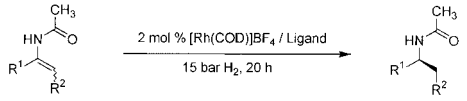
para substituents at the aromatic ring of the substrates on the enantioselectivity.

Having a third substituent on the double bond of the enamide gives rise to an *E/Z* mixture. We were able to separate this by column chromatography. The two isomers of **19** show very different hydrogenation behaviour. Whereas hydrogenation of **19b** is relatively fast and gives product in up to 89% e.e. (entries 17 and 18) the *E* isomer **19a** needed prolonged hydrogenation times and gave rise to product with low e.e. (entries 15 and 16). We also noticed that during hydrogenation **19a** isomerises to **19b** in CH_2Cl_2, although this could be prevented by carrying out the reaction in EtOAc or at lower temperature. Aliphatic enamide **20** and cyclic enamide **23** could be hydrogenated in good yield but with low enantioselectivities. Heteroaromatic enamides **21** and **22** could be hydrogenated with excellent enantioselectivities (entries 20–22).

Asymmetric Hydrogenation of Itaconic Acid and its Ester

Asymmetric hydrogenation of substituted α,β-unsaturated acids is of great current interest as several drug intermediates have structures based on α-substituted acids. We thus subjected itaconic acid and the corresponding ester to the asymmetric hydrogenation using rhodium and **7a**. As can be seen in Table 5 the

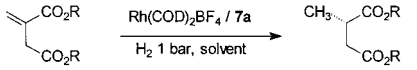
Table 4. Asymmetric hydrogenation of enamides with Rh/ligand.



Entry	Substrate	Ligand (L/Rh)	Solvent	pH_2 [bar]	Time	Conv. [%]	e.e. (RT)[a] [%]	e.e. (−5 °C) [%]
1	**18a**	**7a** (2.1)	CH_2Cl_2	15	20 h	100	86	90
2	**18a**	**7a** (2.1)	EtOAc	15	20 h	100	74	87
3	**18b**	**7a** (2.1)	CH_2Cl_2	15	20 h	100	89	92
4	**18b**	**7a** (2.2)	CH_2Cl_2	60	15 min	100	88	–
5	**18b**	**7a** (2.5)	Toluene	10	2 h	100	83	–
6	**18b**	**7a** (2.1)	EtOAc	15	20 h	100	73	93
7	**18b**	**7a** (2.5)	THF	10	1 h	100	85	–
8	**18b**	**11** (2.2)	CH_2Cl_2	15	3.5 h	100	86	–
9	**18b**	**12** (2.2)	CH_2Cl_2	15	3.5 h	100	89	–
10	**18b**	**13** (2.5)	CH_2Cl_2	10	8 h	100	44[b]	–
11	**18c**	**7a** (2.2)	CH_2Cl_2	10	<5 h	100	86	–
12	**18c**	**7a** (3.0)	CH_2Cl_2	15	6 h	100	80	–
13	**18c**	**11** (2.2)	CH_2Cl_2	15	4 h	100	62	–
14	**18c**	**12** (2.2)	CH_2Cl_2	15	4 h	100	83	–
15	**19a**	**7a** (2.1)	CH_2Cl_2	15	20 h	11	24	–
16	**19a**	**7a** (2.1)	EtOAc	15	20 h	58	15	26
17	**19b**	**7a** (2.1)	CH_2Cl_2	15	20 h	100	84	89[c]
18	**19b**	**7a** (2.1)	EtOAc	15	20 h	100	63	87[d]
19	**20**	**7a** (2.1)	CH_2Cl_2	15	20 h	80	43	–
20	**21**	**7a** (2.1)	CH_2Cl_2	15	20 h	100	85	92
21	**22**	**7a** (2.1)	CH_2Cl_2	15	20 h	100	90	94
22	**22**	**7a** (2.1)	EtOAc	15	20 h	100	81	93[e]
23	**23**	**7a** (2.1)	CH_2Cl_2	15	20 h	52	35	–

[a] The product has the same configuration as the ligand, unless stated otherwise.
[b] The product has the opposite configuration of the ligand.
[c] Conversion 47%.
[d] Conversion 52%.
[e] Conversion 22%.

Table 5. Hydrogenation of itaconic acid derivatives.[a]



Entry	R	T [°C]	Solvent	Time	Conv [%]	e.e. [%]
1	Me	0	CH_2Cl_2	20 h	>99	94
2	Me	20	EtOAc	20 h	>99	0
3	Me	0	EtOAc	20 h	>99	6
4	H	20	CH_2Cl_2	20 h	>99	96
5	H	20	EtOAc	20 h	>99	97

[a] All entries: hydrogenation with 5 mol % of catalyst.

enantioselectivities of these hydrogenations are excellent. However, there is a very strong solvent effect: hydrogenation of the ester in EtOAc led to very low enantioselectivities, even at lower temperature.[52]

Mechanistic Aspects

Many studies have appeared investigating the mechanism of rhodium-bisphosphine-catalysed asymmetric hydrogenation of dehydroamino acids.[1c] In the Halpern mechanism oxidative addition of hydrogen to the Rh-bisphosphine olefin complex is the rate-determining step.[53] Recently, Imamoto has published evidence for the formation of a Rh-bisphospine dihydride complex at low temperature, which has reopened the debate on the mechanism.[54]

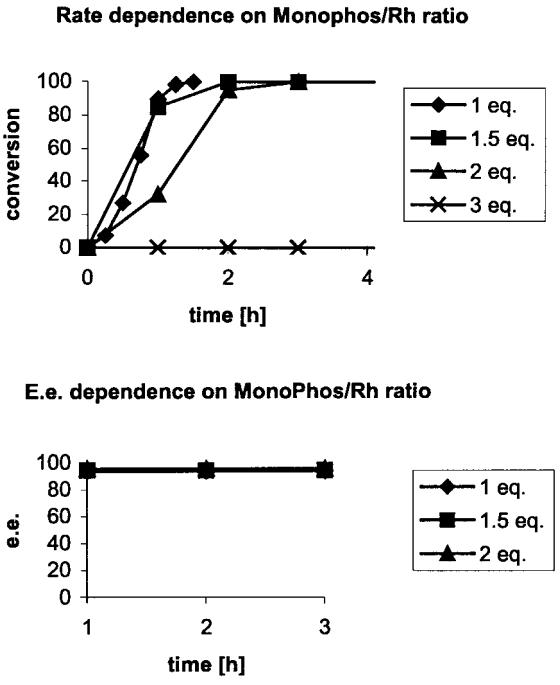


Figure 5.

One of the more surprising characteristics of the use of monodentate phosphoramidites in rhodium-catalysed hydrogenations is the effect of the ligand/rhodium ratio. Phoshoramidites bind very strongly to rhodium, in spite of their reduced sigma donating properties due to their greatly enhanced π acceptor properties as compared to phosphines. It thus did not come as a surprise that catalytic activity ceased when the L/Rh ratio was increased to 3 (Figure 5) in the hydrogenation of **9**.

However, when we lowered the ratio to 1.5 or 1 we found an unexpected increase of the rate. Even more interesting was the finding that the e.e. remained exactly the same over the whole L/Rh range from 1 to 2 (Figure 5) and remained the same throughout the hydrogenation reaction. This suggests that a single rhodium species is the active catalyst in all these hydrogenations independent of the L/Rh ratio. We have performed these experiments both at 1 bar with 5 mol % of catalyst and at 15 bar with 0.015 mol % of catalyst and found essentially the same results. Thus far we had assumed that in the entire catalytic cycle two ligands would be bound to rhodium. However, these results suggest that complexes carrying a single ligand may be responsible for the catalysis.

To shed more light on this dilemma we decided to perform a test for non-linear effects.[55] Briefly, this effect explains the non-linear dependence of the e.e. of the product on the e.e. of the ligand. It can be explained in the following manner. When a ligand with e.e. between 0 and 100% is combined in a 2:1 ratio with Rh we would expect to obtain a mixture of RhL_RL_R, RhL_RL_S and RhL_SL_S. The two catalysts that have ligands with the same configuration are kinetically equivalent but will result in products with opposite configuration. The catalyst containing one *R* and one *S* ligand is racemic and will give product with 0% e.e. Since this catalyst is diastereomeric with the other two catalysts its hydrogenation rate will also be different. If its rate is higher than the homochiral catalysts it will result in hydrogenation product with a lower e.e. than expected; this is termed a negative non-linear effect. If its rate is lower the e.e. will be higher and this is a positive non-linear effect. We performed this test using **7a** of varying degrees of enantiomeric purity in the rhodium-catalysed hydrogenation of **9**. As can be seen from Figure 6 we obtained a weak but reproducible positive non-linear effect. Although this definitely establishes the presence of complexes with two or more ligands it still does not rule out the possibility that these complexes dissociate into a mono-ligated complex, which will do the actual catalysis (Scheme 3) . It is clear that more information is necessary.

So far we have not been able to glean much information from NMR experiments as broad absorptions were observed. We thus decided to use electrospray mass spectrometry to further investigate the rhodium species that are present during hydrogenation.

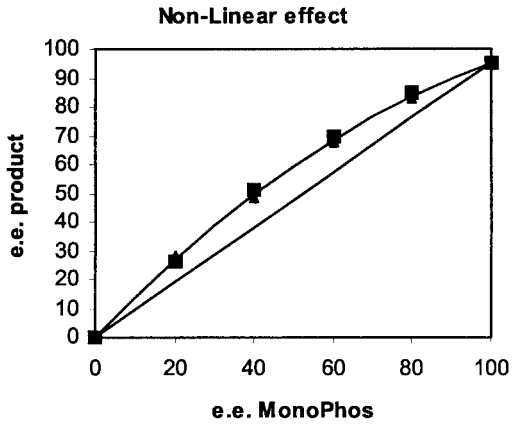
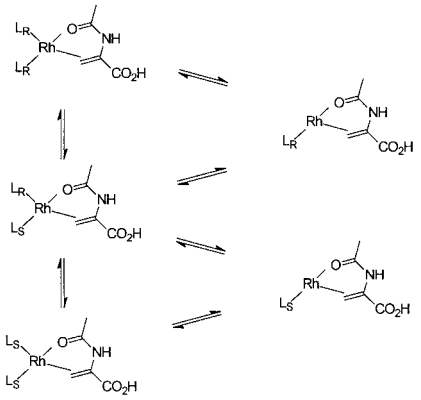


Figure 6.



Scheme 3.

Samples of a hydrogenation of **9** in CH_2Cl_2 using 5 mol % of $[Rh(nbd)_2]BF_4$/MonoPhos (1:2) as catalyst at 1 bar H_2 pressure were taken at regular intervals and examined by ES-MS. This experiment was highly revealing.

As can be seen from Table 6 the catalyst containing two ligands and 1 norbornadiene (nbd) remains present in solution for at least 60 min; after 120 min it has disappeared completely. Its persistent presence might well be due to the poor mass-transfer in these magnetically stirred solutions. We have never experienced a lag-time in the hydrogenations that were performed at higher pressures in the autoclave. We also observe

Table 6. Rhodium species observed with ES-MS in the hydrogenation of **9** with $Rh(nbd)_2BF_4$/**7a**.

Time [min]	Species
30	RhL(Substrate)*, RhL_2 (nbd), RhL_2(Substrate)*, RhL_3, RhL_3(Substrate)
60	RhL(Substrate)*, RhL_2(nbd), RhL_2(Substrate)*, RhL_3, RhL_4
120	RhL(Substrate)*, RhL_2(Substrate)*, RhL_3, RhL_4

* Small peaks

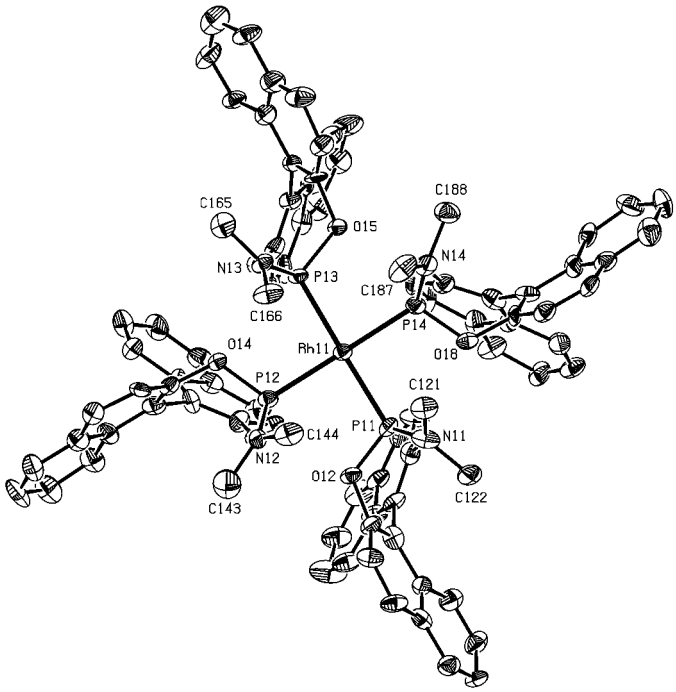


Figure 7. ORTEP representation of $[Rh(\mathbf{7a})_4]BF_4$ showing the atom numbering scheme. Ellipsoids represent 50% probability; hydrogen atoms are omitted for clarity.

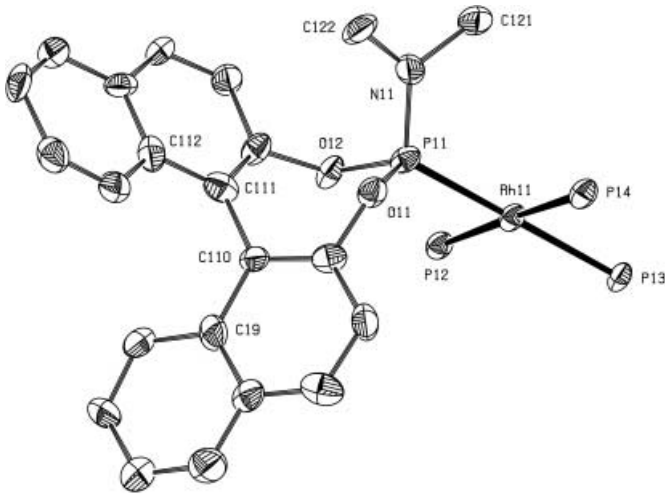


Figure 8. Detail of ORTEP representation of complex $[Rh(\mathbf{7a})_4]BF_4$ showing one of the ligands with its helical shaped diol moiety.

complexes containing 1, 2 or 3 ligands and 1 substrate molecule, however these peaks are very small. The dependence of the rate on the hydrogen pressure confirms the fact that oxidative addition of hydrogen on the RhL_n(Substrate) complex is the rate-determining step as in Halpern's original proposal.[53] The most important conclusion of this experiment is that part of the rhodium is locked up in complexes such as RhL_3 or RhL_4 that are not part of the catalytic cycle. The higher rate of hydrogenation when the L/Rh ratio is less than 2

Table 7. Selected bond lengths [Å], bond angles [°] and torsion angles [°] of [Rh(**7a**)$_4$]BF_4 with estimated standard deviations in parentheses.

Rh11-P11	2.3026(19)	P11-Rh11-P12	89.24(8)
Rh11-P12	2.311(2)	P11-Rh11-P13	178.65(8)
Rh11-P13	2.308(2)	P11-Rh11-P14	91.18(8)
Rh11-P14	2.276(3)	P12-Rh11-P13	91.84(8)
P11-O11	1.615(6)	P12-Rh11-P14	178.34(8)
P11-O12	1.612(8)	P13-Rh11-P14	87.72(8)
P12-O13	1.638(8)	P11-N11-C121	121.5(7)
P12-O14	1.652(5)	P11-N11-C122	125.0(7)
P13-O15	1.658(7)	C121-N11-C122	112.8(8)
P13-O16	1.636(6)	P12-N12-C143	126.5(7)
P14-O17	1.619(6)	P12-N12-C144	118.8(6)
P14-O18	1.644(6)	C143-N12-C144	113.9(8)
P11-N11	1.609(8)	P13-N13-C165	126.4(6)
P12-N12	1.640(8)	P13-N13-C166	119.1(6)
P13-N13	1.648(8)	C165-N13-C166	114.4(7)
P14-N14	1.604(8)	P14-N14-C187	124.0(7)
N11-C121	1.489(12)	P14-N14-C188	122.6(6)
N11-C122	1.487(12)	C187-N14-C188	110.9(8)
N12-C143	1.434(15)		
N12-C144	1.487(12)		
N13-C165	1.442(12)	C19-C110-C111-C112	61.7(13)
N13-C166	1.437(11)	C131-C132-C133-C134	59.1(12)
N14-C187	1.456(12)	C153-C154-C155-C156	58.9(13)
N14-C188	1.512(13)	C175-C176-C177-C178	58.2(13)

might well be explained by a shift in this unfavourable equilibrium towards the lower ligated species. That these higher ligated rhodium species are present in substantial amounts was proven by the isolation of [Rh(MonoPhos)$_4$]BF_4 as pentane/CH_2Cl_2 solvate crystals from one of the 1 bar hydrogenation experiments with L/Rh = 2.2. The crystal structure is displayed in Figure 7. Remarkable is the highly symmetrical structure of the square planar complex. Surprisingly, the dimethylamino groups of all 4 ligands are located in the same hemisphere.

We are currently performing kinetic experiments, which should allow us to determine the composition of the catalytic species.

Conclusion

Monodentate phosphoramidites, in particular MonoPhos and its octahydro derivative **11** are highly effective ligands for the rhodium-catalysed hydrogenation of dehydroamino acids and esters, aromatic enamides and itaconic acid derivatives. Increase of the pressure leads to increase in rate without affecting the enantioselectivity, which increases the scope of this method tremendously. MonoPhos can be prepared in a single step from readily available BINOL and HMPT, which makes it one of the cheapest chiral phosphorus ligands available. This might well have a strong positive effect on the use of asymmetric hydrogenation for the production of enantiopure intermediates. DSM Fine Chemicals is scaling this technology up for use in ton-scale production. Although the presence of several rhodium species in solution has been demonstrated by ES-MS it is as yet not possible to decide how many ligands the catalytically active species contains; it is either 1 or 2. Further kinetic studies are in progress.

Experimental Section

The following ligands were synthesised according to literature procedures: **7a**,[26] **7c**,[57] **13**,[57,58] **14**,[59] **15a, b**,[59] **16**,[57] **17a, b**.[30h] Dehydroamino acids and esters were synthesised using the Erlenmeyer azlactone or the Heck reaction.[42,43] Preparation of enamide substrates was described earlier.[48] All hydrogenation products are published compounds[14e,48,60] or will be published elsewhere.[43]

(*S*)-*O,O*′-(5,5′,6,6′,7,7′,8,8′-Octahydro-1,1′-dinaphthyl-2,2′-diyl)-*N,N*-dimethylphosphorus Amidite (11)

To a solution of (*S*)-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-dinaphthyl-2,2′-diol[46] (5 g, 17.0 mmol) in toluene (20 mL) was added tris(dimethylamino)phosphine (3.24 mL, 17.8 mmol, 1.05 mol equiv.) and the resulting reaction mixture was stirred under nitrogen at 40 °C for 16 h. After this time the reaction mixture was allowed to cool to room temperature and the solvent was removed under reduced pressure to afford a viscous yellow oil. This oil was dissolved in petroleum ether (40 – 60 °C) and purified by use of an alumina (activated, neutral) plug. Initial elution with petroleum ether (40 – 60 °C) yielded an unknown impurity, which was discarded. Subsequent elution with toluene and then dichloromethane yielded a second fraction. The solvent was removed under reduced pressure to afford (*S*)-*O,O*′-(5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-dinaphthyl-2,2′-diyl)-*N,N*-dimethylphosphorus amidite (**11**) as a white foam; yield: 3.50 g (56%). ^{31}P NMR ($CDCl_3$): δ = 143.5; ^{1}H NMR ($CDCl_3$): δ = 1.48 – 1.64 (2H, m), 1.72 – 1.88 (6H, m), 2.20 – 2.38 (2H, m), 2.49 (6H, d, $^2J_{H,P}$ = 9.2 Hz), 2.58 – 2.70 (2H, m), 2.72 – 2.88 (4H, m), 6.84 (1H, d, $^3J_{H,H}$ = 8.1 Hz), 6.99 (1H, d, $^3J_{H,H}$ = 8.8 Hz), 7.01 (1H, d, $^3J_{H,H}$ = 8.4 Hz), 7.07 (1H, d, $^3J_{H,H}$ = 7.9 Hz); ^{13}C NMR ($CDCl_3$): δ = 22.51 (t, CH_2), 22.69 (t, CH_2), 22.71 (t, CH_2), 22.77 (t, CH_2), 27.61 (t, CH_2), 27.77 (t, CH_2), 29.06 (t, CH_2), 29.18 (t, CH_2), 35.63 (q, CH_3), 35.90 (q, CH_3), 118.59 (d, 2 × CH), 129.17 (d, CH), 129.24 (d, CH), 133.00 (s, 2 × C), 134.00 (s, 2 × C), 137.43 (s, C), 137.93 (s, C), 148.32 (s, C), 148.63 (s, C); HRMS: calcd. for $C_{22}H_{26}NO_2P$: 367.170; found 367.170.

(*S*)-*O,O*′-(6,6′-Dibromo-1,1′-dinaphthyl-2,2′-diyl)-*N,N*-dimethylphosphorus Amidite (12)

To a solution of (*S*)-6,6′-dibromo-1,1′-dinaphthyl-2,2′-diol (9.31 g, 21.0 mmol) in toluene (105 mL) was added tris(dimethylamino)phosphine (5.7 mL, 31.5 mmol, 1.5 mol equiv.) and the resulting reaction mixture was stirred under nitrogen at 35 °C for 4 h. The reaction mixture was allowed to cool to room

Table 8. Crystal data and details of the structure determination of $[Rh(\mathbf{7a})_4]BF_4$.

Crystal parameters	
Moiety Formula	$2(C_{88}H_{72}N_4O_8P_4Rh^+)\cdot 2(BF_4^-)\cdot 3(C_5H_{12})\cdot 4(CH_2Cl_2)$
Formula Weight, g mol^{-1}	3810.51
Crystal system	monoclinic
Space group, no.[56]	$P2_1$, 4
a, Å	14.0048(9)
b, Å	26.505(2)
c, Å	24.981(2)
β, deg	89.960(1)
V, Å^3	9272.9(12)
θ range unit cell: min. – max., deg; reflections	2.19 – 24.72; 6812
Formula *Z*	2
SpaceGroup *Z*	2
Z' (=Formula Z/SpaceGroup *Z)*	1
ρ_{calc}, g cm^{-3}	1.365
F(000), electrons	3940
μ(Mo-K$_\alpha$), cm^{-1}	4.35
Colour, habit	yellow, block
Approx. crystal dimension, mm	$0.36\times 0.18\times 0.16$
Data Collection	
λ(Mo- K$_\alpha$), Å	0.71073
Monochromator	graphite
Measurement device type	*CCD* area-detector diffractometer
Detector area resolution (pixels/mm)	4096×4096 /62×62 (binned 512)
Temperature, K	100(1)
Measurement method	φ- and ω-scans
θ range; min. max., deg	2.19, 26.37
Index ranges	h: $-17\rightarrow 17$; k: $-27\rightarrow 33$; l: $0\rightarrow 31$
Min.- Max. absorption transmission factor	0.8896 – 0.9487
X-ray exposure time, h	13.0
Total data	32051
Unique data	32051
Data with criterion: ($F_o \geq 4.0\ \sigma(F_o)$)	25258
$R_{int} = \Sigma\ [\ \lvert F_o^2 - F_o^2\ (\text{mean})\rvert\ ]\ /\ \Sigma\ [F_o^2]$	0.0
$R_{sig} = \Sigma\sigma\ (F_o^2)/\Sigma\ [F_o^2]$	0.1094
Refinement	
Number of reflections	32051
Number of refined parameters	2098
Number of restraints	1
Final agreement factors	
$wR(F^2) = [\Sigma\ [w(F_o^2 - F_c^2)^2]\ /\ \Sigma\ [w(F_o^2)^2]]^{1/2}$	0.2214
Weighting scheme: *a, b*	0.1083, 18.6219
$w = 1/[\sigma^2(F_o^2) + (aP)^2 + bP]$	
And $P = [\max(F_o^2,0) + 2F_c^2]\ /\ 3$	
$R(F) = \Sigma\ (\lvert\lvert F_o\rvert - \lvert F_c\rvert\rvert)\ /\ \Sigma\lvert F_o\rvert$	0.0845
For $F_o > 4.0\ \sigma(F_o)$	
Absolute-Structure parameter Flack's **x**	0.08(3)
$GooF = S = [\Sigma\ [w(F_o^2 - F_c^2)^2]\ /\ (n\text{-}p)]^{1/2}$	1.067
n = number of reflections	
p = number of parameters refined	
Residual electron density in final	
Difference Fourier map, e/Å^3	− 1.3, 1.3(1)
Max. (shift/σ) final cycle	< 0.454
Average (shift/σ) final cycle	0.008

temperature and the solvent was removed under reduced pressure to afford a yellow oil. Subsequent trituration with pentane yielded (*S*)-*O,O*′-(6,6′-dibromo-1,1′-dinaphthyl-2,2′-diyl)-*N,N*-dimethylphosphorus amidite (**12**) as a yellow solid; yield: 7.5 g (69%); $[\alpha]_D^{21} = +400$ (*c* 1.0, CH_2Cl_2); ^{31}P NMR ($CDCl_3$): δ = 148.1; ^{1}H NMR ($CDCl_3$): δ = 2.46 (6H, d, $^2J_{H,P}$ = 9.2 Hz), 7.07 (1H, d, $^3J_{H,H}$ = 8.9 Hz), 7.13 (1H, d, $^3J_{H,H}$ = 9.2 Hz), 7.23 – 7.33 (3H, m), 7.43 (1H, d, $^3J_{H,H}$ = 8.8 Hz), 7.74

(1H, d, $^3J_{H,H}$ = 8.8 Hz), 7.80 (1H, d, $^3J_{H,H}$ = 8.8 Hz), 8.00 (2H, br s); ^{1}H NMR ($CDCl_3$): δ = 35.76 (q, CH_3), 36.04 (q, CH_3), 118.68 (s, C), 118.87 (d, 2 × CH), 119.09 (s, C), 128.32 (d, CH), 128.40 (d, CH), 129.26 (d, 2 × CH), 129.51 (d, CH), 129.59 (d, CH), 130.28 (d, CH), 130.32 (d, CH), 130.95 (s, C), 131.14 (s, C), 150.34 (s, C), 150.40 (s, C), 153.01 (s, 2 × C); HRMS: calcd. for $C_{22}H_{16}NO_2PBr_2$: 514.929, found 514.933.

Hydrogenations at Ambient Hydrogen Pressure

Hydrogenation reactions were performed using standard Schlenk techniques. All solvents were distilled and deoxygenated before use. Glassware was flame-dried under vacuum.

To a Schlenk tube equipped with septum and stirring bar 4.061 mg (10.00 μmol) of $Rh(COD)_2BF_4$, 7.906 mg (22.00 μmol) of ligand and 200 μmol of substrate were added. After three vacuum/nitrogen cycles followed by two vacuum/hydrogen cycles, 5 mL of solvent were added through the septum and the reaction was left stirring at room temperature under ambient H_2 pressure. Samples were taken which were filtered over a short silica column and subjected to e.e. determination. Conversions were determined by means of ^{1}H NMR.

Experiments at 5 bar Hydrogen Pressure

In a Schlenk tube equipped with a septum 8.8 μmol of (*S*)-(−)-**7a** and 4.0 μmol of $Rh(COD)_2BF_4$ were dissolved in 5 mL of dichloromethane under an inert atmosphere and added by syringe into a glass Büchi Miniclave containing a magnetic stirring bar. In the case of ethyl acetate as solvent, the dichloromethane was evaporated under vacuum and 5 mL of ethyl acetate were added. The inert atmosphere was replaced by 5 bar of hydrogen, stirring was started and 15 mL of solvent containing 800 μmol of substrate, was added. Samples were taken (1 mL) which were filtered over a short silica column and subjected to e.e. determination. Conversions were determined by means of ^{1}H NMR.

Experiments at 5–60 bar Hydrogen Pressure in Hastelloy Autoclave

To a Schlenk tube equipped with a septum and a stirring bar 4.0 mg (9.9 μmol, 0.9 mol % compared with the substrate) of $Rh(NBD)_2BF_4$ and 8.6 mg (23.93 μmol) of ligand were added in 2.5 mL of degassed dichloromethane under nitrogen atmosphere. The orange solution was stirred at room temperature for 5 min, and the solvent was evaporated under vacuum giving a yellow solid residue. In a Parr Hastelloy C autoclave of 125 ml volume were added 240 mg of methyl 2-acetomidocinnamic acid (1090 μmol). A nitrogen atmosphere was applied and 30 mL of degassed ethyl acetate were added. The yellow solid residue was dissolved in 20 ml of degassed ethyl acetate and added to the substrate solution in the autoclave and stirred by an overhead pitched blade turbine stirrer under nitrogen for 1 min. After applying 60 bar of hydrogen pressure the mixture was stirred at 680 rpm. Samples were taken after 4, 10 and 20 min. Determination of the conversion by ^{1}H NMR revealed that within 4 minutes all starting material was converted. The product had an e.e. of 97%, as determined by chiral GC on the 20 min sample.

Experiments in the Endeavor™

The Endeavor is an autoclave with eight reactors equipped with glass reaction vessels. Into these reaction vessels 1 mmol of substrate, 0.01 mmol (1 mol %) of $Rh(COD)_2BF_4$ and 0.011 mmol of ligand **7a** were weighed in. The vessels were placed in the reactors and 5 mL of dichloromethane were added. The reactors were then purged for 30 minutes with N_2 before applying a hydrogen atmosphere of 5 bars. The pressure was kept constant during the reaction and the hydrogen uptake was monitored. After completion of the reaction, the reactors were opened and samples were taken which were filtered over a short silica column and subjected to e.e. determination by GC or HPLC. Conversions were determined by means of ^{1}H NMR.

Determination of Enantiomeric Excess

The e.e.'s were determined by means of capillary GC using columns *1–4*, and by means of HPLC at ambient temperature and isocratic gradient (1 mL/min) using columns *5–7*. Carboxylic acids were transformed into there methyl ester analogues using (trimethylsilyl)diazomethane before GC analysis.

Absolute configurations were determined by comparison with reference compounds or the optical rotation was compared with the literature.

Table 9. GC and HPLC columns used:

Column No.	*Column type*
1	Supelco β-Dex 120 (30.0 m × 250 μm × 0.25 μm)
2	Chrompack Chirasil-L-Val (25.0 m × 250 μm × 0.25 μm)
3	CP Chirasil-Dex CB (25.0 m × 250 μm × 0.25 μm)
4	ASTEC G-TA (50 m × 250 μm × 0.25 μm)
5	Chiralcel-OD (250 × 4.6 mm)
6	Chiralcel OJ (250 × 4.6 mm)
7	Chiralpak-AD (250 × 4.6 mm)
8	Kromasil TBB

X-Ray Crystallographic Study of $Rh(7a)_4BF_4$

A crystal with the dimensions of 0.36 × 0.18 × 0.16 mm was mounted on top of a glass fibre, by using inert-atmosphere handling techniques, and aligned on a Bruker[61] SMART APEX CCD diffractometer (platform with full three-circle goniometer). The diffractometer was equipped with a 4K CCD detector set 60.0 mm from the crystal. The crystal was cooled to 100(1) K using the Bruker KRYOFLEX low-temperature device. Intensity measurements were performed using graphite monochromated Mo-K_α radiation from a sealed ceramic diffraction tube (Siemans). Generator settings were 50 kV/40 mA. SMART was used for preliminary determination of the unit cell constants and data collection control. The intensities of reflections of a hemisphere were collected by a combination of 3 sets of exposures (frames). Each set had a different ϕ angle

Table 10. Analysis conditions employed:

Compound	*Column No.*	*Conditions*
10	*2*	160 °C
Table 2 entry No.		
1 – 9	*2*	160 °C
10	*2*	160 °C
11	*2*	160 °C
12	*5*	heptane/*i*-PrOH, 90:10
13	*5*	hexane/*i*-PrOH, 90:10
14	*7*	hexane/EtOH/MeOH/TFA, 93:4:7:0.05
15	*5*	hexane/*i*-PrOH, 90:10
16	*7*	hexane/EtOH/MeOH/TFA, 93:4:7:0.05
17	*7*	hexane/*i*-PrOH, 90:10
18	*7*	hexane/*i*-PrOH, 90:10
19	*8*	hexane/*i*-PrOH/TFA, 90:10:0.05
20		hexane/*i*-PrOH/TFA, 90:10:0.05
21	*5*	heptane/*i*-PrOH, 90:10
22	*5*	hexane/*i*-PrOH, 90:10
23	*5*	heptane/*i*-PrOH, 90:10
24	*7*	hexane/*i*-PrOH, 90:10
25	*7*	hexane/*i*-PrOH, 90:10
26	*6*	hexane/*i*-PrOH, 80:20
27	*7*	hexane/*i*-PrOH, 70:30
28	*7*	hexane/*i*-PrOH, 90:10
29	*7*	hexane/*i*-PrOH, 90:10
30	*2*	110 °C
31	*2*	110 °C
Table 4 entry No.		
1, 2	*1*	150 °C
3 – 10	*1*	150 °C
11 – 14	*7*	hexane/*i*-PrOH, 92:8
15 – 18	*2*	150 °C
19	*3*	90 °C
20	*1*	150 °C
21, 22	*1*	150 °C
23	*3*	180 °C
Table 5 entry No.		
1 – 5	*4*	80 °C

for the crystal and each exposure covered a range of 0.3° in ω. A total of 1800 frames was collected with an exposure time of 20.0 s per frame. The overall data collection time was 13.0 h. Data integration and global cell refinement was performed with the program SAINT. The final unit cell was obtained from the *xyz* centroids of 6812 reflections after integration. Intensity data were corrected for Lorentz and polarisation effects, scale variation, for decay and absorption: a multi-scan absorption correction was applied, based on the intensities of symmetry-related reflections measured at different angular settings (SADABS),[62] and reduced to F_o^2. The program suite SHELXTL was used for space group determination (XPREP).[61] The unit cell[63] was identified as monoclinic; reduced cell calculations did not indicate any higher metric lattice symmetry.[64] The space group $P2_1$, was derived from the systematic extinctions. The *E*-statistics were indicative of a non-centrosymmetric space group.[65] Examination of the final atomic coordinates of the structure did not yield extra metric symmetry elements.[66,67] The structure was solved by Patterson methods and extension of the model was accomplished by direct methods applied to difference structure factors using the program DIRDIF.[68] The positional and anisotropic displacement parameters for the non-hydrogen atoms were refined. Refinement was complicated/frustrated by a disorder problem: from the solution it was clear that two of the four dichloromethane and two of the three pentane solvent molecule were highly disordered and partly occupied. The electron density appeared to be spread out, indicating transformational disorder. No satisfactory discrete model could be fitted in this density. The BYPASS procedure[69] was used to take into account the electron density in the potential solvent area, which resulted in an electron count of 111, within a volume of 1788.8 Å^3 in the unit cell. [The cavities are partly occupied by the dichloromethane and pentane solvent molecules; the calculated "site occupation factor for the enclosed solvent molecules" is 0.67 (=111/164).] The hydrogen atoms were included in the final refinement riding on their carrier atoms with their positions calculated by using sp^2 or sp^3 hybridisation at the C-atom as appropriate with $U_{iso} = c \times U_{equiv}$ of their parent atom, where $c = 1.2$ for the aromatic/non-methyl hydrogen atoms and $c = 1.5$ for the methyl hydrogen atoms and where values U_{equiv} are related to the atoms to which the H atoms are bonded. The methyl groups were refined as rigid groups, which were allowed to rotate freely. Final refinement on F^2 carried out by full-matrix least-squares techniques converged at $wR(F^2) = 0.2214$ for 32051 reflections and $R(F) = 0.0845$ for 25258 reflections with $F_o \geqslant 4.0\ \sigma(F_o)$ and 2098 parameters and 1 restraints. A final difference Fourier map revealed features within the range -1.3 to $+1.3(1)$ e/Å^3 located within 1.2 Å from the Rh positions, but were neglected/rejected, as being artefacts. No other significant peaks having chemical meaning above the general background were observed in the final difference Fourier syntheses. The absolute structure of the molecule actually chosen was determined by Flack's[70–73] refinement [$\mathbf{x} = 0.08(3)$]. The positional and anisotropic displacement parameters for the non-hydrogen atoms and isotropic displacement parameters for hydrogen atoms were refined on F^2 with full-matrix least-squares procedures minimising the function $Q = \Sigma_h[w(|(F_o^2) - k(F_c^2)|)^2]$, where $w = 1/[\sigma^2(F_o^2) + (aP)^2 + bP]$, $P = [\max(F_o^2,0) + 2F_c^2]/3$, F_0 and F_c are the observed and calculated structure factor amplitudes, respectively; ultimately the suggested a (=0.1083) and b (=18.6219) were used in the final refinement. Neutral atom scattering factors and anomalous dispersion corrections were taken from International Tables for Crystallography.[74] All refinement calculations and graphics were performed on a Pentium III/Debian-Linux computer at the University of Groningen with the program packages SHELXL[75] (least-square refinements), a locally modified version of the program PLUTO[76] (preparation of illustrations) and PLATON[77] package (checking the final results for missed symmetry with the MISSYM option, solvent accessible voids with the SOLV option, calculation of geometric data and the ORTEP[77] illustrations).

Crystallographic data (excluding structure factors) for the structure(s) reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 190401. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: int. code + 44(1223)336-033; E-mail: deposit@ccdc.cam.ac.uk].

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