Asymmetric Hydrogenation Using Monodentate Phosphoramidite Ligands

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ABSTRACT

Monodentate phosphoramidites are excellent ligands for Rh-catalyzed asymmetric hydrogenations of substituted olefins. Enantioselectivities between 95 and 99% were obtained in the asymmetric hydrogenation of protected α- and β-dehydroamino acids and esters, itaconic acid and esters, aromatic enamides, aromatic enol esters, aromatic and aliphatic enol carbamates, and α-substituted cinnamic acids. An iridium catalyst Ir(L*)(COD)Cl was developed that contains only a single bulky phosphoramidite based on 3,3′-disubstituted BINOL or bisphenol as a chiral ligand. With this catalyst, acetylated dehydroamino acid esters could be hydrogenated with very good enantioselectivity. Most reactions have turnover frequencies of 250–1600 h^{-1}, depending upon the hydrogen pressure. The enantioselectivity is unaffected by the pressure over a wide range. Because of their modularity and easy synthesis, parallel ligand synthesis is possible. Results obtained with these library ligands deviate only slightly from those obtained with purified ligands. Using this *instant ligand library* protocol, DSM has developed catalysts for industrial processes. These MonoPhos ligands are currently used in production for pharmaceutical intermediates by DSM. It is possible to use catalysts based on a mixture of two different monodentate ligands, such as two different monodentate phosphoramidites or one phosphoramidite and one achiral phosphine ligand. Dependent upon the substrate, the "mixed" catalyst may lead to higher enantioselectivity and rate than the "homocatalysts".

Introduction

Asymmetric hydrogenation is arguably one of the most researched areas in homogeneous catalysis.[1] After its inception through the work of Knowles,[2] Horner,[3] and Kagan,[4] the first industrial application followed soon.[5] The later work of Noyori and Takaya on the use of the ligand BINAP opened up the possibility of asymmetric ketone hydrogenation,[6] and again, this led to a number of industrial applications.[7] Since then, many synthetic groups have developed new classes of ligands. However, despite these auspicious beginnings, use of asymmetric hydrogenation for production of fine chemicals has remained rather scarce.[8] Today, the majority of enantiopure fine chemicals either stems from natural sources or is produced in racemic form and subsequently resolved. Several publications have appeared in which this paradox is explained.[9] Barriers that are quoted are (i) time-to-market pressure, (ii) costs of catalysts, (iii) lack of robustness of the process, and (iv) patent issues. The time-to-market pressure is mainly felt in the area of pharmaceuticals, where process development starts at a relatively late stage because of the high attrition rate of new drug candidates. However, it is important that the new drug is launched immediately upon approval by the regulatory authorities in view of the limited period of patent protection that is left after the long time that it took to develop the drug. This leaves a very narrow window for process improvement.

At DSM, it was decided to tackle the time-to-market issue with a high-throughput experimentation (HTE) approach. If a large library of ligands would be available, it should be possible to find a highly enantioselective hydrogenation catalyst in just a matter of weeks. At that moment in time, there was no record of a parallel synthesis of large libraries of phosphorus ligands in solution. At the outset, it was clear that it would be very difficult to devise a parallel synthesis of chiral bidentate

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Laurent Lefort (Nancy, France, 1969) received his Ph.D. degree under the guidance of Prof. Henry Amariglio at the University of Nancy (1996). After two postdoctoral stays at the University of Rochester under the guidance of Prof. W. J. Jones (NY) and at CPE-Lyon (France) under the guidance of Prof. J.-M. Basset, he joined Symyx (Santa Clara, CA), where he worked in the field of high-throughput synthesis of catalysts. In 2003, he moved to DSM (Geleen, NL), where he works as a research chemist in the homogeneous catalysis group.

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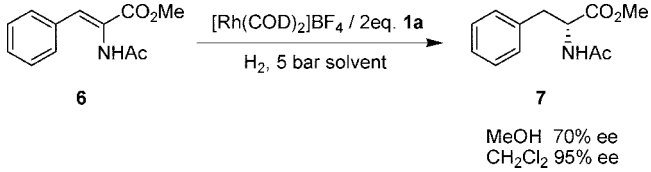
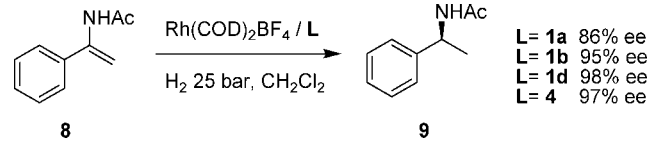
Scheme 1. Rh/MonoPhos-Catalysed Asymmetric Hydrogenation



Scheme 2. Rh/Phosphoramidite-Catalyzed Enamide Hydrogenation



phosphine libraries. Not only are these ligands made by lengthy syntheses, often including a resolution step, they are also purified by column chromatography. We thus had to scout for new ligands that could be made in a limited number of steps in high yield. This marked the beginning of a long and fruitful collaboration between the DSM and University of Groningen groups.

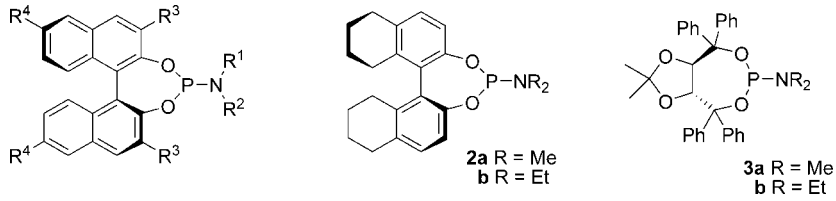
Monodentate Phosphoramidites as Ligands for Asymmetric Olefin Hydrogenation

Since the Feringa group had already developed the use of monodentate phosphoramidite ligands in the copper-catalyzed 1,4 addition of dialkylzincs to olefins,[10] it was decided to test the suitability of bidentate phosphoramidites in Rh-catalyzed asymmetric olefin hydrogenation. This resulted in some rather disappointing results. A range of bidentate phosphoramidite ligands based on BINOL or Taddol and bridged by C1–C3 diamines led to slow hydrogenations and low enantioselectivities. Surprisingly, the use of the monodentate ligand MonoPhos (**1a**) in the Rh-catalyzed asymmetric hydrogenation of methyl 2-acetamido-cinnamate led to an enantiomeric excess (ee) of 70% when MeOH was used as a solvent (Scheme 1).[11] The second breakthrough was the finding that this reaction is highly solvent dependent and that use of nonprotic solvents, such as EtOAc, led to a dramatic increase in enantioselectivity (95% ee in CH_2Cl_2). Interestingly, in that same year, the use of BINOL-based monodentate phosphonites[12] and phosphites[13] in Rh-catalyzed asymmetric hydrogenation was reported by Pringle and co-workers and Reetz and co-workers, respectively. Best results with the catalysts based on these ligands were also obtained in nonprotic solvents. After our first publications, Zhou published the use of ligand **5**, which also leads to excellent results in asymmetric hydrogenation but takes seven steps plus a resolution to prepare.[14] Reetz recently revealed nonsymmetrical BINOL-based phosphoramidites containing only a single substituent in the 3 (and not the 3′) position.[15] An overview of frequently used monodentate phosphoramidite ligands is shown in Figure 1.[16]

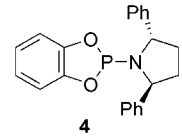
Using **1a** as a ligand, a large range of olefins, such as substituted 2-acetamido-cinnamic acids and esters (92–99% ee), 2-acetamido acrylic acid (99% ee) and methyl ester (97% ee), and itaconic acid (97% ee) and methyl ester (94% ee), were hydrogenated with excellent ee and rates [turnover frequency (TOF) of 250–500 h^{-1}].[17] The acetyl protecting group is not a prerequisite for high enantioselectivity. Hydrogenations of either formyl- or BOC-protected dehydroamino acids also proceed with excellent enantioselectivities.[18]

These hydrogenations are usually carried out at 5–10 bar. At 1 bar they are slower, because of a slow hydrogenation of the cyclooctadiene (COD) ligand of the [Rh(**1**)$_2$(COD)]BF_4 precatalyst. Interestingly, in contrast to bidentate bisphosphines, the enantioselectivity of these hydrogenations remained unchanged when the pressure was varied between 1 and 100 bar. Since the reaction is first-order in hydrogen, this allows for very fast reactions.[17]

Despite this success, we soon found that also with monodentate ligands every substrate has its own optimal ligand. A nice illustration of this stems from the Rh-



1a $R^1 = R^2$ = Me, $R^3 = R^4$ = H (MonoPhos)
b $R^1 = R^2$ = Et, $R^3 = R^4$ = H
c $R^1 = R^2$ = *i*-Pr, $R^3 = R^4$ = H
d $R^1 = R^2$ = -$(CH_2)_5$-, $R^3 = R^4$ = H (PipPhos)
e $R^1 = R^2$ = -$(CH_2)_2O(CH_2)_2$-, $R^3 = R^4$ = H (MorfPhos)
f R^1 = Me, R^2 = CH_2Ph, $R^3 = R^4$ = H
g $R^1 = R^2$ = (*R*)-$CH(CH_3)Ph$, $R^3 = R^4$ = H
h $R^1 = R^2$ = (*S*)-$CH(CH_3)Ph$, $R^3 = R^4$ = H
i R^1 = H, R^2 = (*R*)-$CH(CH_3)Ph$, $R^3 = R^4$ = H
j $R^1 = R^2$ = Me, R^3 = Me, R^4 = H
k $R^1 = R^2$ = Me, R^3 = H, R^4 = Br
l $R^1 = R^2$ = -$(CH_2)_5$-, R^3 = Me, R^4 = H
m R^1 =H, R^2 = *i*-Pr , $R^3 = R^4$ = H
n $R^1 = R^2$ = -$(CH_2)_2O(CH_2)_2$-, R^3 = Me, R^4 = H
o $R^1 = R^2$ = Me, R^3 = Ph, R^4 = H
p $R^1 = R^2$ = CH_2Ph, $R^3 = R^4$ = H



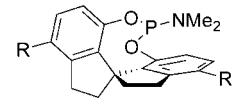
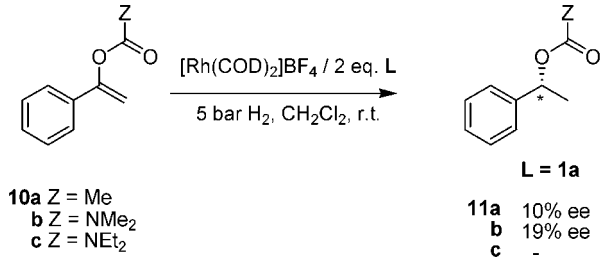
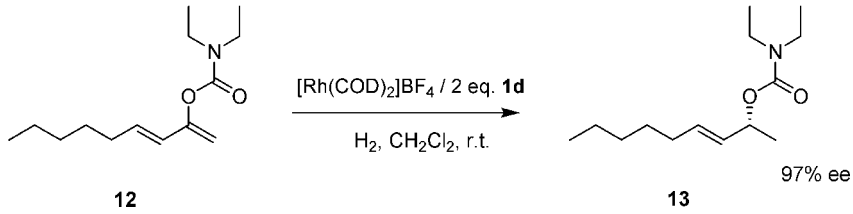


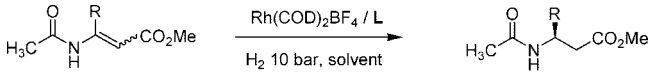
FIGURE 1. Monodentate phosphoramidite ligands.

Scheme 3. Rh-Catalyzed Asymmetric Hydrogenation of Enol Acetates and Enol Carbamates Using MonoPhos and PipPhos





Scheme 4. Asymmetric Hydrogenation of *E*- and *Z*-β-Dehydroamino Acid Esters



Substrate	*Ligand*	*Solvent*	ee
***E*-14a**	**1a**	CH_2Cl_2	95%
***E*-14a**	**1f**	CH_2Cl_2	99%
***Z*-14a**	**1i**	*i*PrOH	95%
Z-14b	**1i**	*i*PrOH	92%

catalyzed asymmetric hydrogenation of aromatic enamides. Using MonoPhos, we obtained the acetylated amine (**9**) with 86% ee (Scheme 2).[19] Much better results were obtained by Chan using the rather similar ligand **1b**.[20] In collaboration with the Reetz group, we developed the use of the ligand PipPhos (**1d**), which actually performs even better in most applications than **1a**.[21] In the present case, use of this ligand resulted in 98% ee. It is not strictly necessary to have BINOL-based ligands for good results. Ligand **4** based on catechol and a chiral amine also resulted in 97% ee.[22]

Asymmetric hydrogenation of enol acetates, such as **10a**, gives access to chiral alcohols after hydrolysis of the acetate ester (Scheme 3). Since enol acetates are structurally very similar to enamides, we also examined the asymmetric hydrogenation of this class of substrates. We were quite surprised to find out that, using **1a** as a ligand, the saturated acetate **11a** was obtained with an ee of only 10%. Reasoning that the major difference between these substrates and the enamides was in the electron density of the carbonyl group, we decided to examine the corresponding enol carbamates. Although the ee improved upon hydrogenation of **10b**, it remained at only 19%. However, replacing **1a** by PipPhos (**1d**) spectacularly improved the hydrogenation results with both the aromatic enol acetates and the enol carbamates (Scheme 3).[23]

Interestingly, asymmetric hydrogenation of aliphatic dienol carbamate **12** could be affected in 97% ee. Thus, this is an easy entrance into chiral aliphatic alcohols and allylic alcohols.

Another class of substrates that necessitated the development of new ligands was the β-dehydro-amino acid derivatives **14**. From published results with bidentate phosphines, it was clear that hydrogenation of the *E*

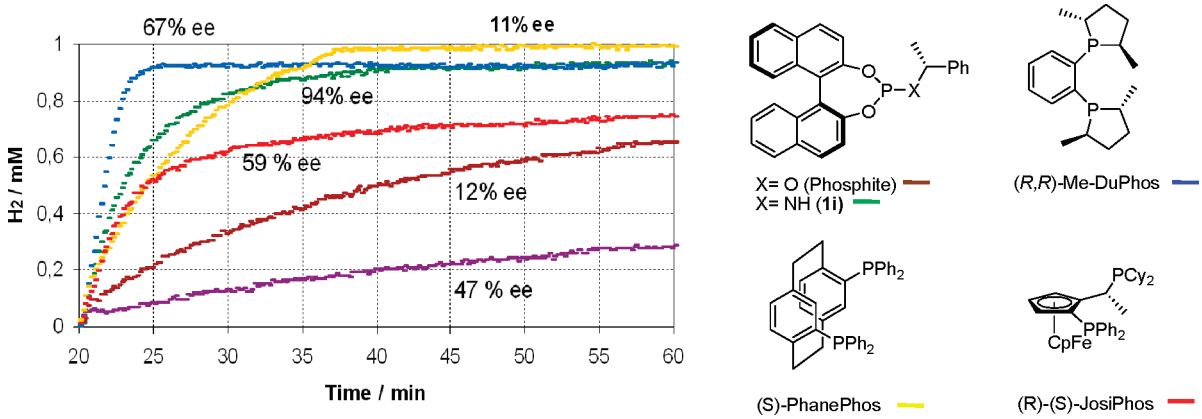
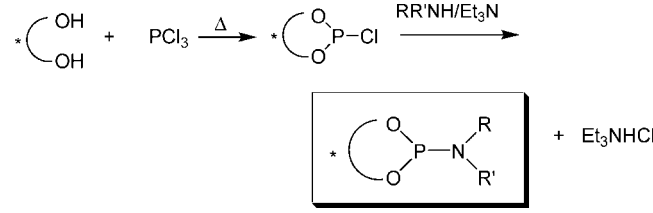


FIGURE 2. Comparison of hydrogenation rates in the asymmetric hydrogenation of *Z*-ethyl 3-*N*-acetamido-crotonate (purple = **1a**).

derivatives is rather easy, and indeed, we were able to affect the rhodium-catalyzed asymmetric hydrogenation of **14a** using MonoPhos as a ligand with 95% ee (Scheme 4). A minor change sufficed to create an excellent ligand, **1f**, that induced 99% ee in the same substrate.[24] However, the commonly used synthesis of these substrates from the acetoacetates via amination and acetylation leads mainly to the *Z* precursors.

Hydrogenation of the *Z* precursors is much more problematic. Presumably, this is related to the strong internal hydrogen bond between the ester carbonyl and the NH of the amide. Hydrogenation of *Z*-**14a** and *Z*-**14b** using Rh/**1a** was very slow, necessitating a change of ligand and conditions. For these substrates, the protic solvent *iso*-propanol works much better. This solvent is capable of breaking the hydrogen bond in the substrate, thus enabling its bidentate binding to the metal. In addition, although the rate of the hydrogenation in this solvent improved substantially, it was not yet sufficient for industrial application,[25] and, the ee obtained with **1a** remained low. Knowing from experience that the rate is in part determined by the steric bulk around nitrogen, we decided to switch to monodentate phosphoramidites based on primary amines. Our initial fears that these ligands would be too unstable turned out to be unfounded; the crystalline ligands in general have a very good shelf life. Remarkably, ligand **1i** induced a very fast reaction, and products **15a** and **15b** were obtained with excellent ee's.[24] In Figure 2, the rate of this catalyst is compared with catalysts based on a number of well-known bidentate ligands and the phosphite analogue of **1i** (NH replaced by O), showing that the catalyst is only surpassed by DUPHOS in rate but surpasses all ligands in terms of ee.[26] Particularly, the comparison between the phosphoramidite- and phosphite-based catalysts suggests that this high rate is not due to the steric factors as originally intended. Ding recently showed that primary amine-based phosphoramidites display a hydrogen-bond interaction in the Rh complex.[27] This could render the NH bond rather acidic, allowing for an ionic hydrogenation mechanism (hydride-proton transfer). This fast hydrogenation rate is not limited to this substrate class; Rh/**1i** even surpassed Rh/DUPHOS in the asymmetric hydrogenation of **6**.

Scheme 5. Synthesis of Phosphoramidite Ligands



Instant Ligand Libraries

To achieve our ambition of being able to screen large libraries of ligands in the robot, we had to develop methodology for the parallel synthesis of phosphoramidite ligands. The most frequently used phosphoramidite synthesis is shown in Scheme 5.[17] The order of the two steps can also be reversed, which is beneficial when hindered amines are used.[28] MonoPhos (**1a**) itself is made in a single step by refluxing BINOL with hexamethyl phosphorustriamide (HMPT) in toluene.[29] It is also possible to convert **1a** into another ligand in a transamination reaction.

Using stock solutions of the phosphochloridites, it should in principle be possible to make phosphoramidites in the robot as shown in Figure 3. Parallel screening, combined with fast analysis would then allow rapid evaluation of the ligands. The major bottleneck would be the purification of the ligands, which is not easily robotized. Since the synthesis of Scheme 5 yields the ligand in about 90–95% purity, it could be an option to discard the purification altogether.

Thus, we tested the crude product of a ligand synthesis (BINOL-PCl plus Et_2NH and Et_3N) in the rhodium-catalyzed asymmetric hydrogenation of methyl 2-acetamido-cinnamate (Scheme 6).

This resulted in a much lower rate of hydrogenation and also a decrease of enantioselectivity. The reason for this is clear: the inhibiting effect of chloride on these hydrogenations is well-documented.[30] Conducting the ligand synthesis in toluene and filtration of the crude ligand solution quite effectively removes the Et_3NHCl salt. Remarkably, application of this filtered ligand solution resulted in a fast hydrogenation reaction, yielding a product with only slightly lower ee than with the purified ligand (Scheme 6). This simple purification protocol allows for the preparation of libraries of phosphoramidites in solution and was named "instant ligand libraries".[31] The ligand synthesis is performed in oleophobic titer well plates using a liquid-dispensing robot in the glovebox. After vacuum filtration to remove the salts,

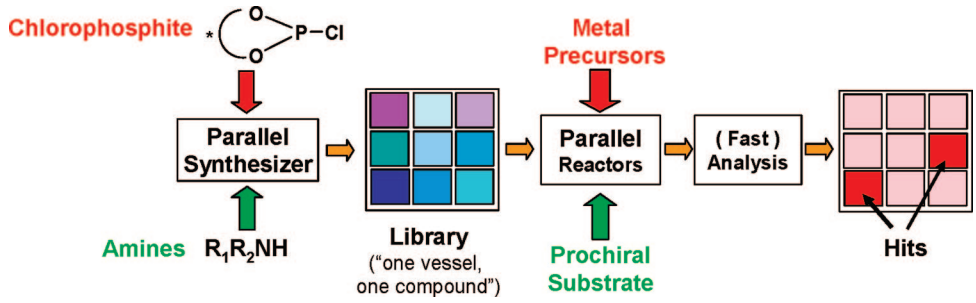
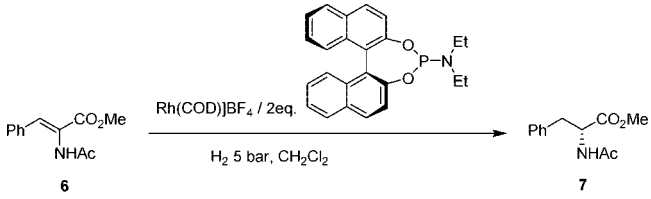


FIGURE 3. Concept for parallel synthesis and screening of phosphoramidite ligands.

Scheme 6. Effect of Phosphoramidite Purity on the Yield and Enantioselectivity in Asymmetric Hydrogenation



	Conv. (%)	*ee (%)*
Crude ligand	14	60
Filtration of salts	100	96
Purified ligand	100	99

the ligand solutions are transferred to a vial followed by a solution of the metal precursor, the substrate, and other reactants or additives. The tray with 96 vials is then transferred into a Premex-96 hydrogenation apparatus and hydrogenated overnight.

This simple protocol now allows for the preparation of a library of 96 phosphoramidite (or phosphite) ligands in a single day, followed by screening overnight and analyzing the next day. This concept has revolutionized the finding of chiral ligands for asymmetric transformations. A nice example of this is the research performed by DSM to find a cost-effective catalyst for the asymmetric hydrogenation of the α-alkylated cinnamic acid derivative **16**, which is an intermediate in the synthesis of the blood-pressure-lowering drug Aliskiren (**19**) (Scheme 7).[32]

In this research, an initial screening of $[Rh(COD)_2]BF_4$ with eight phosphoramidite ligands in the hydrogenation of **16** resulted in enantioselectivities up to 48% and a maximal TOF of 50 h^{-1}. Confident that the *instant ligand library* protocol would allow augmentation of the enantioselectivity, we first concentrated on increasing the rate of the reaction. Since the rate of the hydrogenation reaction is determined by the oxidative addition of hydrogen, increased electron density of the ligands will facilitate this process. We thus investigated the use of additives that are known to be good electron donors, such as amines, phosphines, and even bisphosphines. In a random screen of 96 additives, we identified triarylphosphines as a promising class of additives. Not only was the rate enhanced 10-fold by the addition of 1 equiv of triarylphosphine with respect to the rhodium, the enantioselectivity also improved dramatically in these reactions. In Figure 4, the effect of an added triphenylphosphine ligand on the rate and enantioselectivity of the Rh-

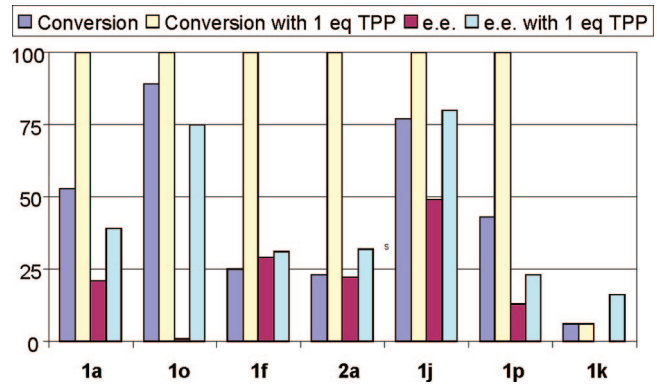


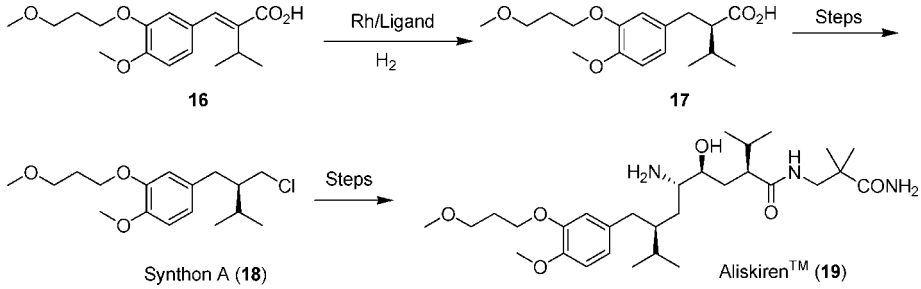
FIGURE 4. Effect of PPh_3 (TPP) on the Rh-phosphoramidite-catalyzed asymmetric hydrogenation of **16** (*x* axis shows ligand numbers; see Figure 1 for structures).

phosphoramidite-catalyzed asymmetric hydrogenation of **16** is depicted. This mixed ligand effect was independently discovered around the same time by the group of Reetz, using combinations of phosphites or phosphonites with triarylphosphines.[33] The use of a mixture of two different chiral monodentate ligands will be discussed later.

>With the rate aspect taken care of, the enantioselectivity was then tackled by a screen of 96 phosphoramidite ligands under the best conditions, using triphenylphosphine as an additive. This library was prepared from the 3,3′-dimethyl-BINOL skeleton only, since ligands derived from this structure gave the best results in the preliminary study. Indeed, most ligands perform well in this screen (Figure 5). The ligand that was finally chosen (**1l**) is a compromise of activity, enantioselectivity, and accessibility. Further screening to optimize the conditions revealed that using *i*-PrOH/H_2O (80:20) as a solvent resulted in the highest rate and enantioselectivity. The entire protocol was validated on a larger scale using ligand **1l** in purified form and tri-*m*-tolylphosphine (Scheme 8). From these results, the enormous acceleration in rate (TOF = 1800 h^{-1}) and increase in enantioselectivity (90% ee), that have been achieved through this parallel screening effort in search of ligands, additives and conditions become clear.

In this reaction, we used a mixture of $[Rh(COD)_2]BF_4$/**1l**/triarylphosphine in a ratio of 1:2:1. Use of the more obvious 1:1:1 mixture resulted in lower ee's. The reason for this becomes clear upon inspection of the ^{31}P nuclear magnetic resonance (NMR) spectra of the precatalysts prior to hydrogenation. In the first case, only a mixture of $[Rh(\mathbf{1l})_2(COD)]BF_4$ and $[Rh(\mathbf{1l})(Ar_3P)(COD)]BF_4$ is

Scheme 7. Asymmetric Hydrogenation Step in the Synthesis of Aliskiren



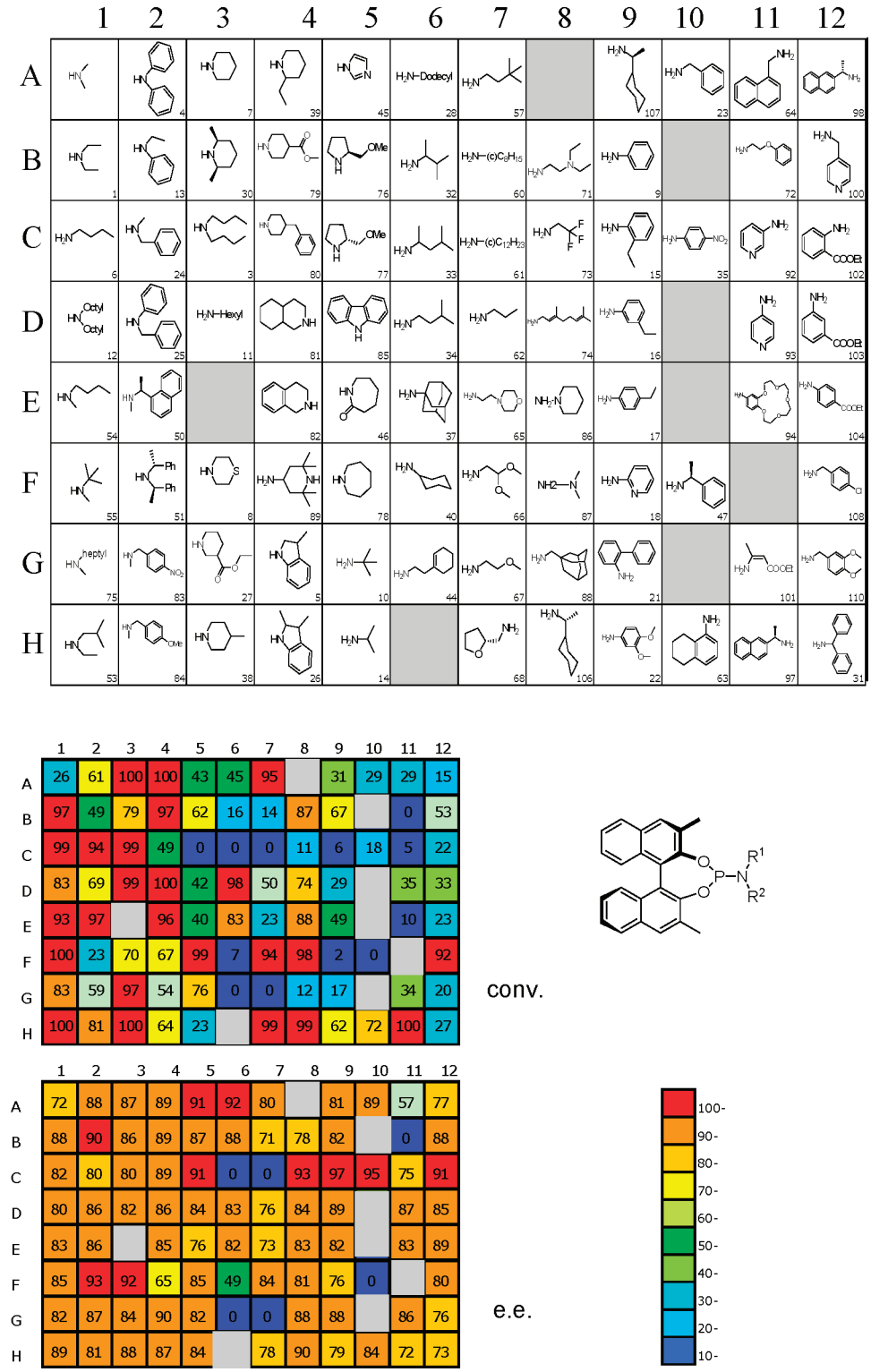


FIGURE 5. Screening of monodentate phosphoramidite ligands based on 3,3′-dimethyl-BINOL in the Rh-catalyzed hydrogenation of **16** with PPh_3 as an additive (conditions: 55 °C, 25 bar H_2, *i*-PrOH, $[Rh(COD)_2]BF_4$, **1**/Rh = 100, ligand/Rh = 2, PPh_3/Rh = 1).

found.[34] Since the first catalyst is much slower than the second, its presence is inconsequential and the rate and ee are determined only by the mixed species. The NMR of the 1:1:1 mixture shows a mixture containing the mixed catalyst and both homocatalysts. The homocatalyst derived from $[Rh(Ar_3P)_2(COD)]$ BF_4 is, of course, very fast and nonenantioselective, leading to substantial amounts of racemic product. Thus, the ratio between the two ligands needs to be tuned in every single case.[35]

Mixtures of Ligands

Next, the scope of the phosphine effect on the asymmetric hydrogenation of a range of α-alkylated cinnamic

Scheme 8. Validation of the Screening Results on a Large Scale

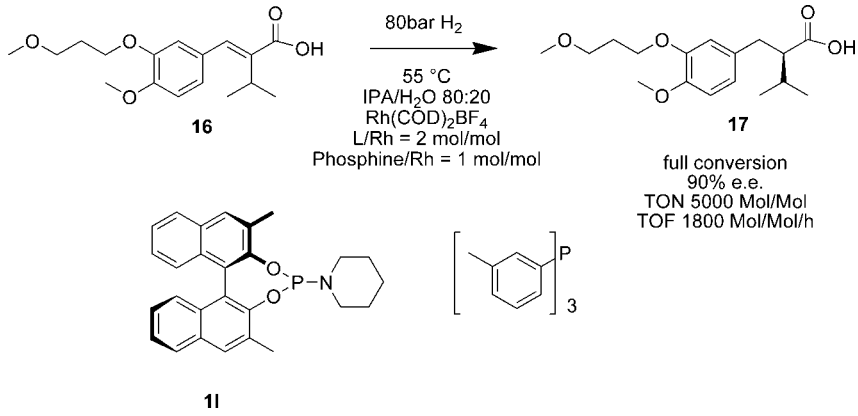
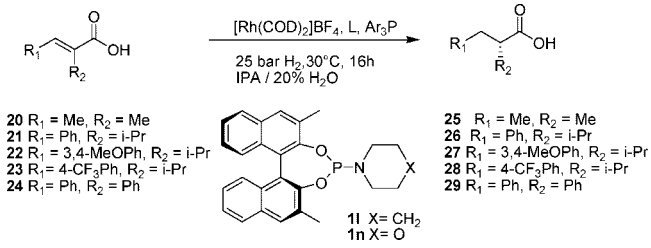


Table 1. Mixed Ligands in Rh-Catalyzed Asymmetric Hydrogenation of α-Substituted Cinnamates and Crotonate



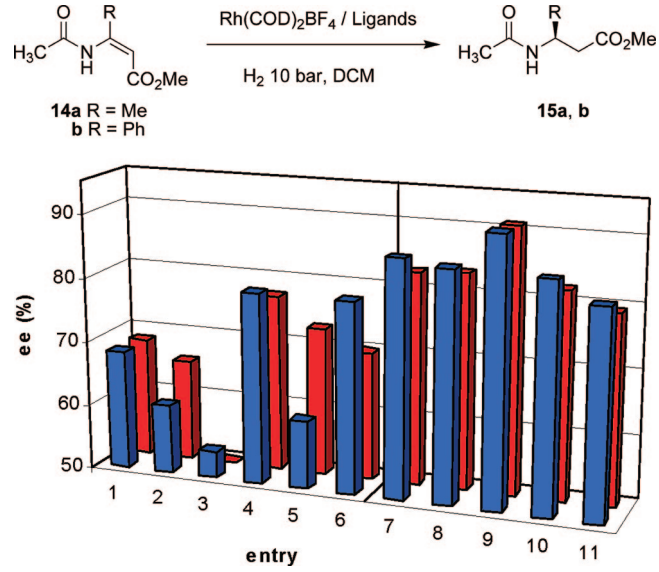
entry	substrate	product	L	Ar_3P	ee
1	**20**	**25**	**1n**	P(*m*-Tol)$_3$	87
2	**21**	**26**	**1l**	P(*o*-Tol)$_3$	99
3	**22**	**27**	**1l**	PPh_3	92
4	**23**	**28**	**1l**	P(*m*-Tol)$_3$	95
5	**24**	**29**	**1l**	P(*o*-Tol)$_3$	95

and acrylic acids was determined in Groningen. In this research, we determined that also with other substrates triarylphoshines induce the highest increase in rate and enantioselectivity. Trialkylphosphines also had a positive effect but much less pronounced than the triarylphosphines. We examined the asymmetric hydrogenation of α-methylcinnamic acid using eight different BINOL-based phosphoramidite ligands with and without added triphenylphosphine. In every single case, the added triphenylphophine improved the rate and enantioselectivity.[36]

A number of different α,β-unsaturated acids was hydrogenated using the same catalyst system. The results are shown in Table 1. Good to excellent ee's were obtained in all cases.

The use of mixtures of ligands can also be applied to two different chiral monodentate ligands. This concept was independently developed by Reetz and co-workers with mixtures of monodentate phosphinites and/or phosphites.[37] In Groningen, we tested this approach in the asymmetric hydrogenation of acetylated β^3-dehydroamino acid esters.[38] In this research, we have screened mixtures of two phosphoramidite ligands using **1a**, **1f**, **1i**, **1j**, **1k**, and **2a** in the Rh-catalyzed asymmetric hydrogenation of an aliphatic and aromatic *Z*-β^3-dehydroamino acid ester (**14a** and **14b**; Scheme 9). In Scheme 9, the results of the screening are displayed. Entries 1–6 show enantioselectivities obtained with the homocatalysts. We then started to screen mixtures of these ligands. Not surprisingly, most combinations of two different ligands induced lower enantioselectivities. However, there was one marked exception: all combinations that included the NH ligand **1i** led to better results (entries 7–11 in Scheme 9). Particularly striking is the combination of ligand **1j**, which was the worst performer in the homo series in combination with **1i** (entry 9).

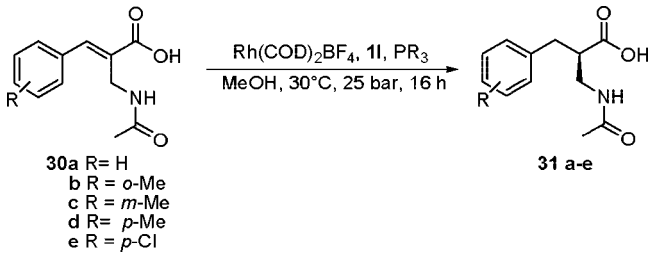
Scheme 9. Rh/Phosphoramidite-Catalysed Hydrogenations Using Homo (Entries 1–6) and Hetero (Entries 7–11) Catalysts[a]



[a] Reprinted with permission from The Royal Society of Chemistry (RSC) from ref 38. [b] Blue Bars, Results with **14a**; Red Bars, Results with **14b**; Entry 1, **1a**; Entry 2, **2a**; Entry 3, **1j**; Entry 4, **1k**; Entry 5, **1f**; Entry 6, **1i**; Entry 7, **1a** + **1i**; Entry 8, **2a** + **1i**; Entry 9, **1j** + **1i**; Entry 10, **1k** + **1i**; Entry 11, **1f** + **1i**.

After having established the enantioselective preparation of β^3-amino acids, we were interested to see if we could also find an enantioselective hydrogenation catalyst to access β^2-amino acids. The prochiral substrates were made in good yield by a Baylis–Hillman reaction between an aromatic aldehyde and methyl acrylate catalyzed by 1,4-diazabicyclo[2.2.2]octane (DABCO), followed by a Ritter reaction with acetonitrile and hydrolysis of the methyl ester. Initial screening suggested that these substrates behaved very similarly to the α-alkylated cinnamic acids.

Table 2. β^2-Amino Acids via Mixed Ligand Asymmetric Hydrogenation



		phosphines				
entry	substrate	PPh_3	P(*o*-Tol)$_3$	P(*m*-Tol)$_3$	P(*p*-Tol)$_3$	P(naphthyl)$_3$
1	**30a**	89	91	89	85	91
2	**30b**	82	90	82	77	−(<5)
3	**30c**	83	86	84	84	91
4	**30d**	78	89	81	85	91
5	**30e**	85	80 (65)[a]	79 (90)	78	56 (86)

[a] Numbers in parentheses are conversion in the case of incomplete conversion.

Thus, an *instant ligand library* containing 96 ligands was screened in the presence of 1 equiv of PPh_3. Since ligands based on 3,3′-dimethyl-BINOL gave the best results, a focused library of 16 phosphoramidites × 6 triarylphosphines was screened. Ligand **1l** again emerged as the best ligand, but in this case, several triarylphosphines gave good results. In Table 2, results of the asymmetric hydrogenation of a number of 2-acetamidomethyl-cinnamic acids using ligand **1l** in the presence of different triarylphosphines are displayed.[39] Hydrogenation of **30a** using Rh/**1l** without added triarylphosphine resulted in very low ee.

Hydrogenation with Phosphoramidite Complexes Based on Other Metals

Since most noble metals catalyze hydrogenation reactions, we were interested in expanding the possibilities of the *instant ligand library* by using other metal precursors than rhodium. Iridium complexes as homogeneous hydrogenation catalysts were first explored by Crabtree, who developed the catalyst that bears his name: [Ir(COD)(PCy$_3$)(Py)]BF$_4$.[40] Recently, Pfaltz and co-workers have developed the use of chiral Crabtree catalysts based on P–N ligands as a catalyst for the asymmetric hydrogenation of unfunctionalized alkenes.[41] We were interested to explore the catalytic activity of complexes [Ir(L^1)(L^2)(COD)]BF$_4$, where L^1 = phosphoramidite and L^2 = L^1, PR_3, or pyridine. Although we screened several phosphoramidites in combination with different ligands and counteranions, we did not find an efficient hydrogenation catalyst. The breakthrough came upon the observation that, with bulky phosphoramidites based on BINOL carrying substituents in the 3,3′ positions, an active but also enantioselective catalyst was obtained without abstraction of the chloride ligand, i.e., from the noncationic catalyst precursor [Ir(COD)(L)Cl] containing only one phosphoramidite ligand per metal. Interestingly, both rate and enantioselectivity of this catalyst increased upon increasing the bulk of the substituents in the 3,3′ positions (Figure 6). In particular, the catalyst based on ligand **32** was relatively fast (TOF = 150 h^{-1}) and induced high enantioselectivity in the product **7**.[42] An X-ray structure unequivocally showed the presence of a single phosphoramidite ligand in the complex (Figure 7).

We also developed catalysts based on ruthenium for the asymmetric hydrogenation of ketones with very high

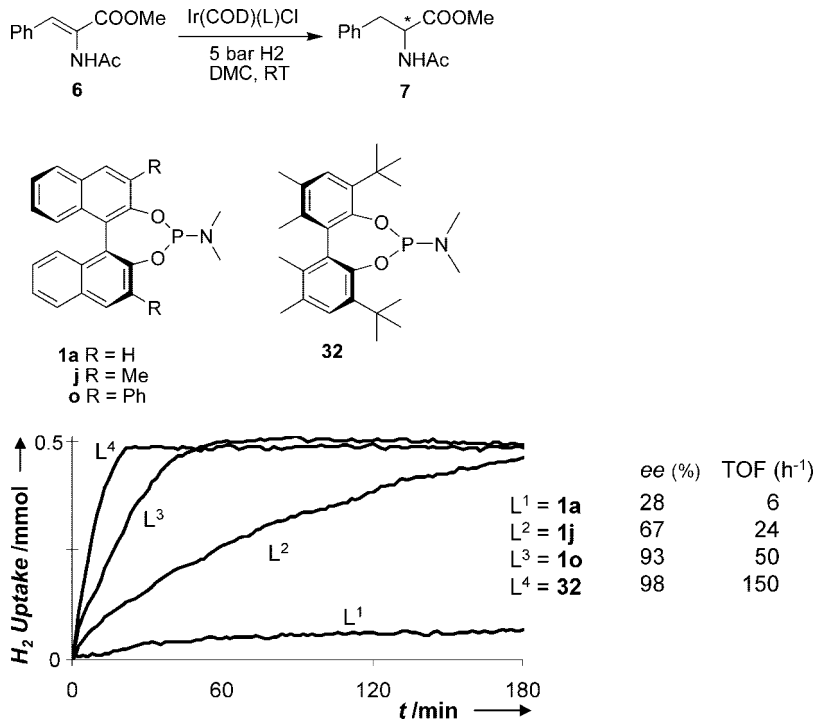


FIGURE 6. Rate and enantioselectivity of Ir(COD)(L)Cl depend upon 3,3′ substituents in L.

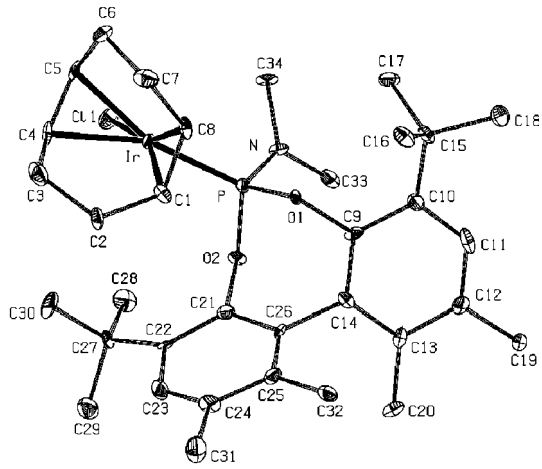


FIGURE 7. X-ray structure of Ir(**32**)(COD)Cl.

enantioselectivity. This work will be communicated in the near future.[43]

Mechanistic Aspects

Most of the mechanistic work that we have performed thus far was based on the combination of $[Rh(COD)_2]BF_4$ and MonoPhos (**1a**). Upon slow addition of a solution of the ligand to the catalyst precursor, $[Rh(\mathbf{1a})_2(COD)]BF_4$ is formed in good yield. If the ligand is added too fast, substantial amounts of $[Rh(\mathbf{1a})_4]BF_4$ are formed. An X-ray could be obtained from this latter complex.[17] ^{31}P NMR shows that $[Rh(\mathbf{1a})_2(COD)]BF_4$ is present in solution as two isomers that differ in the relative position of the two phosphoramidite ligands (NMe_2 on the same or different hemisphere of the square planar complex). There has been some controversy in the literature concerning the nature of the active catalyst.[44] Although we had shown that the enantioselectivity of the product changed in a nonlinear fashion with the ee of the ligand, which strongly suggests a catalyst containing two ligands (or a dimer), experiments in which the ligand/metal ratio was varied from 1 to 3 threw an entirely new light on the discussion.[17] In the asymmetric hydrogenation of **6**, we found that a **1a**/Rh ratio of 3 leads to an inactive catalyst, although with other substrates, this ratio may lead to an active catalyst. Strangely enough, upon lowering the **1a**/Rh ratio from 2 to 1 the catalyst became faster, whereas the enantioselectivity remains exactly the same. This suggested the possibility that a complex containing a single ligand could be the active catalyst. At the time, this seemed a strange notion; with iridium, we have now shown that this is indeed possible. However, our later work with rhodium catalysts based on mixtures of different chiral phosphoramidites shows beyond a doubt that the active hydrogenation catalyst contains two ligands. High-pressure ^{31}P NMR experiments with $[Rh(\mathbf{1a})_2(COD)]BF_4$ showed complex mixtures after exposure to hydrogen. The addition of **6** led to changes in parts of the NMR. Electrospray ionization mass spectrometry (ES–MS) showed that during hydrogenation a number of different complexes are formed that may have one, two, three, or four MonoPhos ligands attached to rhodium (Table 3). In addition, the complexes may carry norbornadiene (nbd) or one molecule of the substrate (**6**). [17]

Table 3. Rhodium Species Observed with ES–MS in the Hydrogenation of 6 with $[Rh(nbd)_2]BF4$/1a (2 equiv) at 1 Bar

time (min)	species
30	RhL(substrate),[a] RhL_2(nbd), RhL_2(substrate),[a] RhL_3, RhL_3(substrate)
60	RhL(substrate),[a] RhL_2(nbd), RhL_2(substrate),[a] RhL_3, RhL_4
120	RhL(substrate),[a] RhL_2(substrate),[a] RhL_3, RhL_4

[a] Small peaks.

Thus, it seems that the higher rate at lower ligand/metal ratios is best explained by the assumption that the relative amount of $[RhL_2(substrate)]^+$ is maximized with respect to the inactive RhL_3 and RhL_4 at L/Rh ratios <2. Preliminary kinetics show that the reaction is first-order in hydrogen and the substrate.[45]

Conclusion

Monodentate phosphoramidites are a highly versatile class of ligands not only for asymmetric hydrogenation but also in many other reactions. The ligands are highly modular and easy to synthesize, enabling their robotic parallel synthesis. DSM developed and routinely applies this *instant ligand library* to find catalysts that induce high enantioselectivity in substrates of commercial interest. This has led to robust, scalable processes up to the ton scale.

The possibility to use catalysts based on two different monodentate ligands, which was independently discovered by Reetz and us, has greatly expanded their scope. New applications also in asymmetric hydrogenation are continuously being found.

We are deeply indebted to our past and present co-workers for their enormous contributions to this research.

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