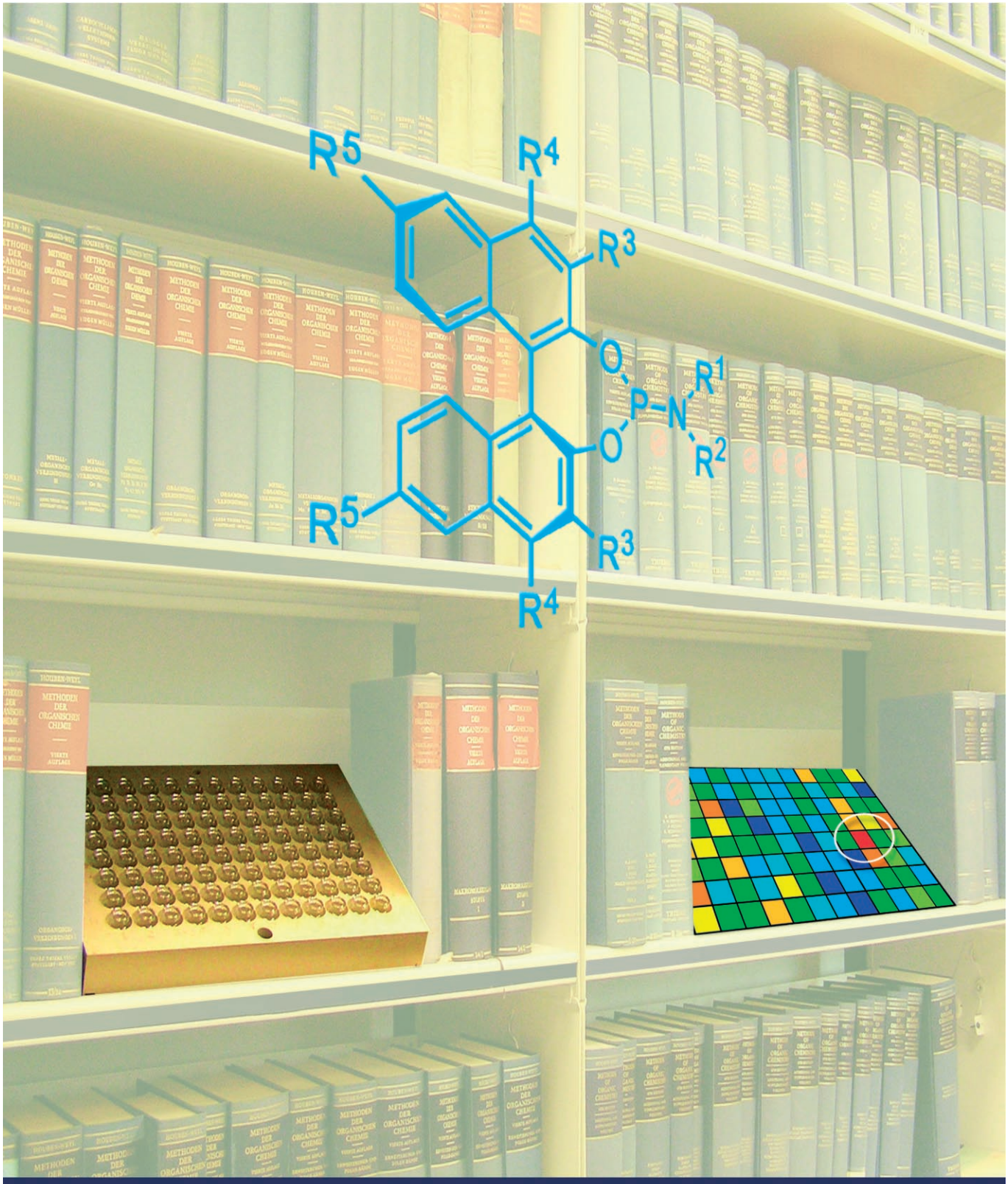

A LIBRARY OF 96 NEW LIGANDS IN 1 DAY, TESTED THE NEXT DAY

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The Combinatorial Approach to Asymmetric Hydrogenation: Phosphoramidite Libraries, Ruthenacycles, and Artificial Enzymes

Johannes G. de Vries* and Laurent Lefort[a]

Abstract: For a more general implementation of asymmetric catalysis in the production of fine chemicals, the screening for new catalysts and ligands must be dramatically accelerated. This is possible with a high-throughput experimentation (HTE) approach. However, implementation of this technology requires the rapid preparation of libraries of ligands/catalysts and consequently dictates the use of simple ligands that can be readily synthesised in a robot. In this concept article, we describe how the development of new ligands based on monodentate phosphoramidites enabled the development of an integral HTE protocol for asymmetric hydrogenation. This "instant ligand library" protocol makes it possible to synthesise 96 ligands in one day and screen them the next day. Further diversity is possible by using mixtures of monodentate ligands. This concept has already led to an industrial application. Other concepts, still under development, are based on chiral ruthenacycles as new transfer hydrogenation catalysts and the use of enzymes as ligands for transition-metal complexes.

Keywords: asymmetric catalysis · high-throughput screening · homogeneous catalysis · hydrogenation · ligand libraries

Industrial Perspective on Asymmetric Hydrogenation

Since the Nobel Prize for chemistry was awarded to W. Knowles, R. Noyori and B. K. Sharpless, asymmetric catalysis and in particular asymmetric hydrogenation can be viewed as a mature science. In addition, few people would disagree with the assessment that asymmetric catalysis is one of the most economic and environmentally friendly ways to produce enantiopure fine chemicals.[1]

Yet, a careful analysis of the number of production processes using this wonderful technology reveals a surprising paradox: the majority of chiral intermediates are still produced by using classical resolution through crystallisation of diastereomeric salts or occasionally by using hydrolytic enzymes.[2,3] A number of publications that analyse this paradox have recently appeared.[4–7] A major hurdle is caused by the time-to-market pressure. Once a new drug has finally been cleared to enter the market, there is a strong pressure to start production as soon as possible. This means that development times for these processes are measured in months rather than years. It is not surprising that given these circumstances, most development chemists choose to fall back on well-established chemistry, that is, resolution processes for the production of chiral building blocks. An additional problem is caused by the fact that existing chiral ligands often do not induce sufficiently high enantioselectivity for the substrate of interest. Developing a new ligand is usually extremely time consuming; in addition, there is no guarantee of success as there is no such thing as ligand design.[8] And this touches upon the next bottleneck: the costs of these catalysts. Not only the metals, such as rhodium, iridium, ruthenium and palladium, but also the chiral ligands that are often prepared through multistep syntheses, including chromatographic separations, can be extremely expensive.[9] Thus, it is not very surprising that until recently, asymmetric catalysis was used mostly for second-generation processes of drugs and agrochemicals.[3,4]

It is clear that asymmetric catalysis can only break through as a major production technology for new drugs and agrochemicals if something can be done about timelines and costs. We have thus embarked on a mission to solve these problems. Central to this is the use of high-throughput experimentation (HTE) as a means to substantially shorten the time necessary for catalyst screening and process development.[6,10]

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HTE is a methodology whereby a large number of chemical entities are quickly synthesised and tested in parallel. Not only the chiral ligand is an important parameter in asymmetric catalysis. Other important parameters are the metal precursor, additives, solvents and the reaction conditions. Moreover, not only the yield and (enantio)selectivity have to be analysed, but also the catalyst activity to determine if there is any prospect of industrial application. It is evident that the parameter space to be covered is huge and that HTE represents an efficient way to explore as much of it as possible, in a relatively short amount of time.

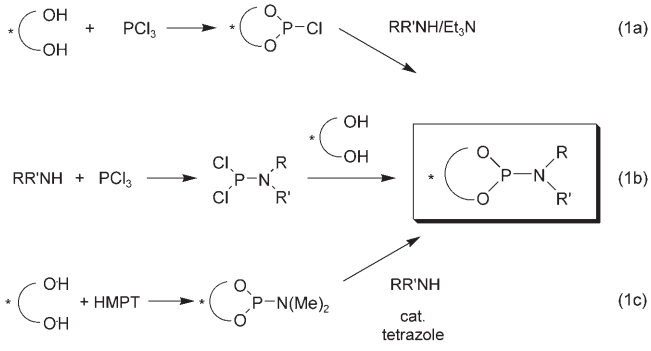
HTE requires hardware, high-throughput analysis, libraries of ligands and the right mindset. Many useful robots and synthesisers have recently come on the market and we currently use a Chemspeed ASW2000, an Endeavour (8 autoclaves), a Premex 96 (96 high-pressure reactors) and an AMTECH robot (16 autoclaves). These last two machines were developed in collaboration with DSM and are commercially available. Analysis turned out not to be a major bottleneck and conventional GC and HPLC could be used after some adaptation. In addition, we have set up a flow NMR system that can handle one sample every three minutes; this technique can be used for analysis of reaction mixtures. The mindset this approach demands is by no means trivial as most researchers are used to work with one or a few experiments at the time and build up their knowledge as they go. With the HTE approach, the available diversity space has to be assessed right from the start. In our own experience, this takes some getting used to and the discussions on what the right timing is to switch from single experiments to HTE never went away. However, the most formidable challenge we faced was the development of ligand libraries.[11]

We are aware of only three reports in the literature on the automated synthesis of phosphorus ligands (vide infra). The scarceness of reports describing ligand or catalyst libraries is related to the difficulties associated with such an endeavour. One of the most important requirements is the ease of synthesis; a prerequisite for the development of automated procedures for the preparation of large libraries. The lengthy syntheses, including chromatographic purification associated with the current state-of-the-art bisphosphines, suggests that this class is not a viable target for a library approach. To obviate the need for a parallel resolution procedure use of enantiopure starting materials is an additional requirement. For this reason, we have decided to focus on simple chiral ligands that can be prepared in 1–2 synthetic steps.

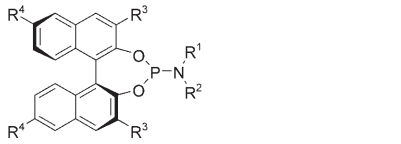
In this article, we present three concepts for catalyst or ligand libraries for use in asymmetric hydrogenation that are amenable to HTE. In our first example, concerning the use of monodentate phosphoramidites, we have completed the HTE set-up, which is now used routinely for screening catalyst libraries for new reactions stemming from our customers. This methodology has already led to the discovery of a catalyst for the ton-scale production of a drug intermediate. Our second example deals with ruthenacycles, which are new catalysts for transfer hydrogenation. Here also, we will show how we were able to prepare libraries of these catalysts. And finally, we will discuss our contribution to a new concept at the border between homogeneous catalysis and biochemistry, taking advantage of the tools of the biochemists for modifying proteins and creating extensive libraries of them which we will try to use as chiral ligands.

Monodentate Phosphoramidites as Ligands for Asymmetric Hydrogenation

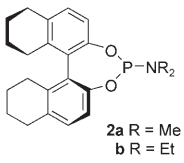
In collaboration with the group of Feringa/Minnaard from the University of Groningen, we have developed the use of monodentate phosphoramidites as ligands for asymmetric hydrogenation.[12] These ligands had previously been used for the highly enantioselective copper-catalysed 1,4-addition of diethylzinc to enones.[13] This class of ligands is admirably suitable for HTE purposes. First of all, they are modular, basically composed of two parts, a diol moiety and an amino moiety. There is a large diversity available in chiral and non-chiral diols, bisphenols and bisnaphthols; the same is true for the amines. In addition, their synthesis is simple and high yielding [Eq. (1a)–(1c)]. The method depicted in Equation (1a) is the one employed most frequently.[14] It entails refluxing the diol (or 1,1′-bis-2-naphthol (BINOL)) in pure PCl_3. This affords the chlorophosphite that, in the case of BINOL, is stable and can be stored under inert atmosphere for prolonged periods. Reaction of this compound with an amine in the presence of a base yields the phosphoramidite, which is usually 90–95% pure (based on phosphorus) and is further purified by crystallisation or column chromatography. The second method, developed by van Leeuwen et al. is well suited for more hindered amino groups [Eq. (1b)].[15] MonoPhos (**1a**) is conveniently made by refluxing enantiopure BINOL and HMPT (hexamethyl phosphorus triamide) in toluene; the product crystallises spontaneously [Eq. (1c)].[16] MonoPhos itself can serve as starting material for other ligands by catalysed exchange with primary or secondary amines [Eq. (1c)]. Initially, we used tetrazole as a catalyst.[12d] Since this material is shock-sensitive, we have discontinued its use. It seems that *N*-methylanilium trifluoroacetate (TAMA) is a very good alternative.[17]



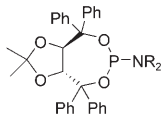
Rhodium-catalysed asymmetric hydrogenation using MonoPhos as ligand shows an extreme solvent dependency. Best results are obtained in nonprotic solvents like dichloromethane or ethyl acetate. Some of the more important MonoPhos ligands (**1**–**4**) are shown here. We have now established their use, as ligand for rhodium-catalysed hydrogenation, of *N*-acetyl-, *N*-formyl- and *N*-BOC-protected α-dehydroamino acids and esters,[12a,d,j] *N*-acetyl-β-dehydroamino acids and esters,[12b] aromatic *N*-acetyl enamides,[12c] itaconic acid and esters,[12c] Stobbe condensation products, α-alkylated cinnamates[12h] and enolacetates, enol carbamates and dienol carbamates (Scheme 1).[12i]



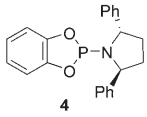
1a $R^1 = R^2 = Me$, $R^3 = R^4 = H$ (MonoPhos)
b $R^1 = R^2 = Et$, $R^3 = R^4 = H$
c $R^1 = R^2 = i\,Pr$, $R^3 = R^4 = H$
d $R^1 = R^2 = -(CH_2)_5-$, $R^3 = R^4 = H$ (PipPhos)
e $R^1 = R^2 = -(CH_2)_2O(CH_2)_2-$, $R^3 = R^4 = H$ (Morfphos)
f $R^1 = Me$, $R^2 = CH_2Ph$, $R^3 = R^4 = H$
g $R^1 = R^2 = (R)$-$CH(CH_3)Ph$, $R^3 = R^4 = H$
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 $R^1 = R^2 = -(CH_2)_2O(CH_2)_2-$, $R^3 = Me$, $R^4 = H$



2a R = Me
b R = Et



3a R = Me
b R = Et



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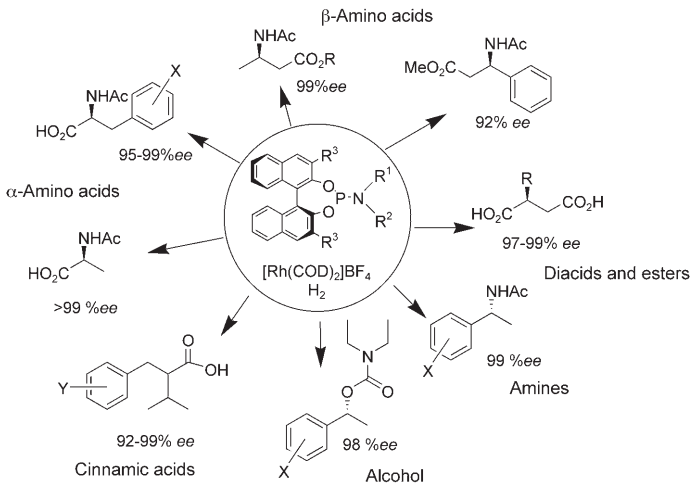
As the use of the MonoPhos ligands in asymmetric hydrogenation has been reviewed a number of times,[18] we will not dwell on these asymmetric hydrogenations per sé, but rather concentrate on the HTE and combinatorial catalysis aspects from the perspective of industrial application.



Scheme 1. Products obtained via asymmetric hydrogenation with Rh/MonoPhos.

Parallel to our development of the monodentate phosphoramidites, Pringle et al. have developed the use of monodentate phosphonites[19] and Reetz and co-workers developed the use of monodentate phosphites[20] as ligands for asymmetric hydrogenation. In particular, this latter class has similar possibilities in terms of a library approach as the phosphoramidites.

It is important to note that different substrates require different members of the phosphoramidite family. Moreover, from our own experiences we know that most new types of substrates may require a new type of ligand. To fulfil the demands of our customers most efficiently, we realised that a huge, highly diverse ligand library is desired.

Instant Ligand Libraries

At the time we started this enterprise, very few people had made libraries of phosphorus ligands. Many researchers would have made up to a dozen ligands by conventional means using chromatography for purification and used these for screening a reaction of interest. However, larger libraries of phosphorus ligands were not readily available. Upon perusal of the literature, we only found three previous examples. Gilbertson and Wang had synthesised a phosphine-containing amino acid and had incorporated this in libraries of peptides.[21] Unfortunately, this appealing concept was not rewarded: all combinations led to poor enantioselectivities when used as ligands in rhodium-catalysed asymmetric hydrogenation. In another example, a library of aminomethyl phosphines was made by Lapointe in parallel fashion through condensation of a secondary phosphine, an arylaldehyde and a primary or secondary amine (2 phosphines × 6 aldehydes × 8 amines = 96 ligands).[22] Purity of the library ligands varied between 80–95% upon analysis by ^{31}P NMR spectroscopy of 20 of the library members. The last example was a library of phosphoramidite ligands synthesised on solid phase by Waldmann; these ligands were tested while still attached to the resin as their copper complexes in the asymmetric addition of Et_2Zn to cyclohexenone.[23] Although Waldmann found good correlations between the *ee* obtained with the library ligands "on the bead" and the corresponding purified ligands, this approach is not useful for asymmetric hydrogenation, as here we need to have two ligands per metal.

We thus looked into methods for solution-phase, parallel synthesis of phosphoramidite ligands. The ideal setup would allow a fully automated sequence starting with solution phase ligand synthesis, followed by screening and completed by analysis as depicted in Figure 1.

A major bottleneck in parallel ligand synthesis is the ligand purification. In the case of the phosphoramidites, the first step of the synthesis, that is, the reaction between BINOL (or another chiral diol) and PCl_3, proceeds with essential 100% selectivity, obviating any need for purification in this step. In the next step, the chlorophosphite is treated with an amine as in Equation (1a). The chemical purity of

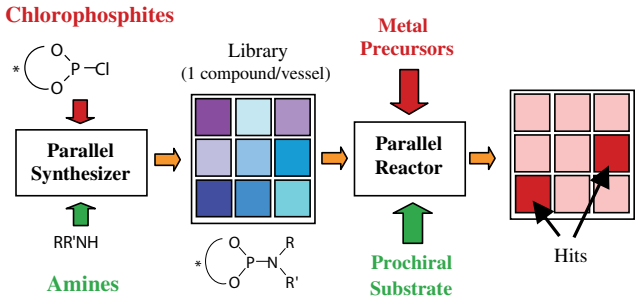
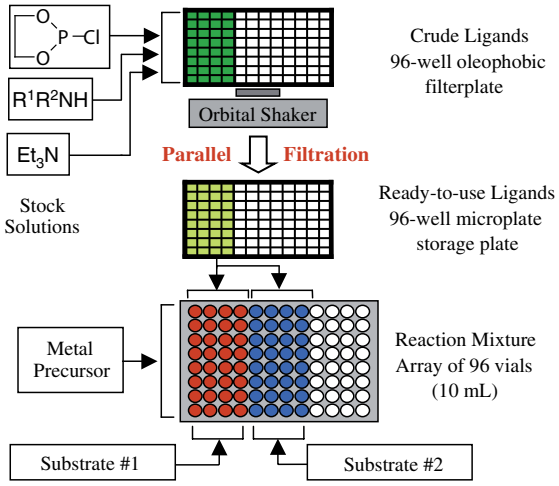


Figure 1. Fully automated ligand synthesis, screening and analysis (reprinted with permission from the American Chemical Society from reference [25]).

the ligand is usually between 90–95% (based on phosphorus) in most of the cases we checked. The major real impurity is the triethylammonium hydrochloride salt. Upon testing, the crude product of the reaction between BINOL-based chlorophosphite and piperidine in the rhodium-catalysed hydrogenation of methyl 2-acetamido-cinnamate, we found that reaction was much slower and the product was obtained in only 60% *ee*, whereas 99% was obtained with pure **1d**. Evidently, the reason for this poor performance is the presence of a stoichiometric amount of chloride, which functions as a catalyst poison.[24] Remarkably, performing the coupling reaction in toluene and removing the salt by a simple filtration led to a crude ligand, which after removal of toluene performed quite satisfactorily in the above hydrogenation reaction. In this case, the conversion went to 100% and the product was obtained with 96% *ee*, which is only slightly lower as with the purified ligand.

Next, we transferred this simple protocol to a liquid handling robot, set up in a glove box (Figure 2).

The coupling reactions were performed in a 96-well microtiterplate equipped with an oleophobic filter. After 2 h of reaction, the microplate was placed on a manifold, vacuum was applied and the filtered ligand solutions were collected in another 96-well plate. We have tested this protocol initially on a series of 32 ligands, which were subsequently screened in the Rh-catalysed asymmetric hydrogenation of two model substrates (see Figure 3).[25]



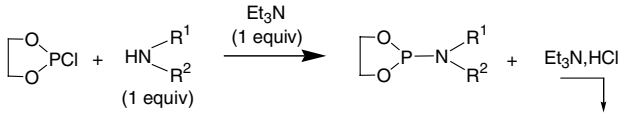


Figure 3. Phosphoramidite library synthesis and screening protocol (reprinted with permission from the American Chemical Society from reference [23]).

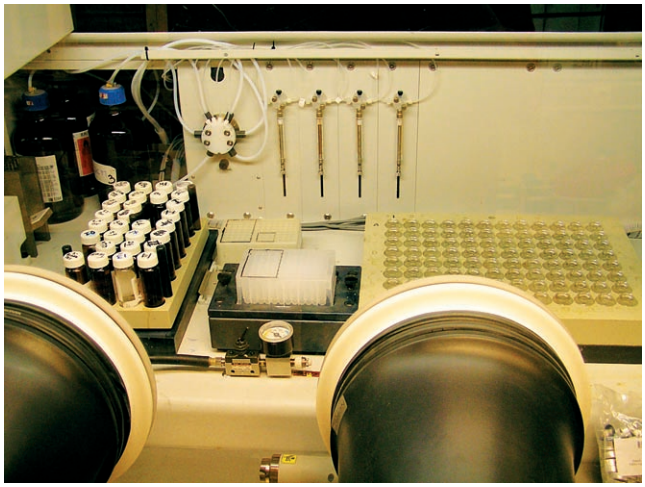


Figure 2. Liquid handling robot in glove box. (Stock solutions on the left. In the middle, the oleophobic filter on a vacuum manifold. On the right the tray with vials in which ligands, metals and substrates are mixed.)

In Figure 4, we show the result of this library of 32 phosphoramidites in the asymmetric hydrogenation at 6 bar H_2 of methyl 2-acetamido-cinnamate and methyl *Z*-3-acetamido-2-butenoate. For the first substrate, almost all of the members of the library led to full conversions, indicating that most of the ligands were formed with an acceptable degree of purity. ^{31}P NMR spectroscopy revealed the presence of trace amounts of other phosphorus species, which, remarkably, did not affect the performance of the catalyst. The best results were obtained with ligands based on secondary amines, such as PipPhos (**1d**, position B7), and **1b** (A7); in addition, two new good ligands (in positions A8 and C7) were found. The enantioselectivities are on average 5% lower than with the purified ligands.

The results of the hydrogenation of methyl *Z*-3-acetamido-2-butenoate resulted in more surprises. Although we had already found that ligand **1i**, based on a primary amine, gave an excellent performance in these hydrogenation reactions, the library shows that in general all BINOL ligands that contain a primary amine with branching in the α-posi-

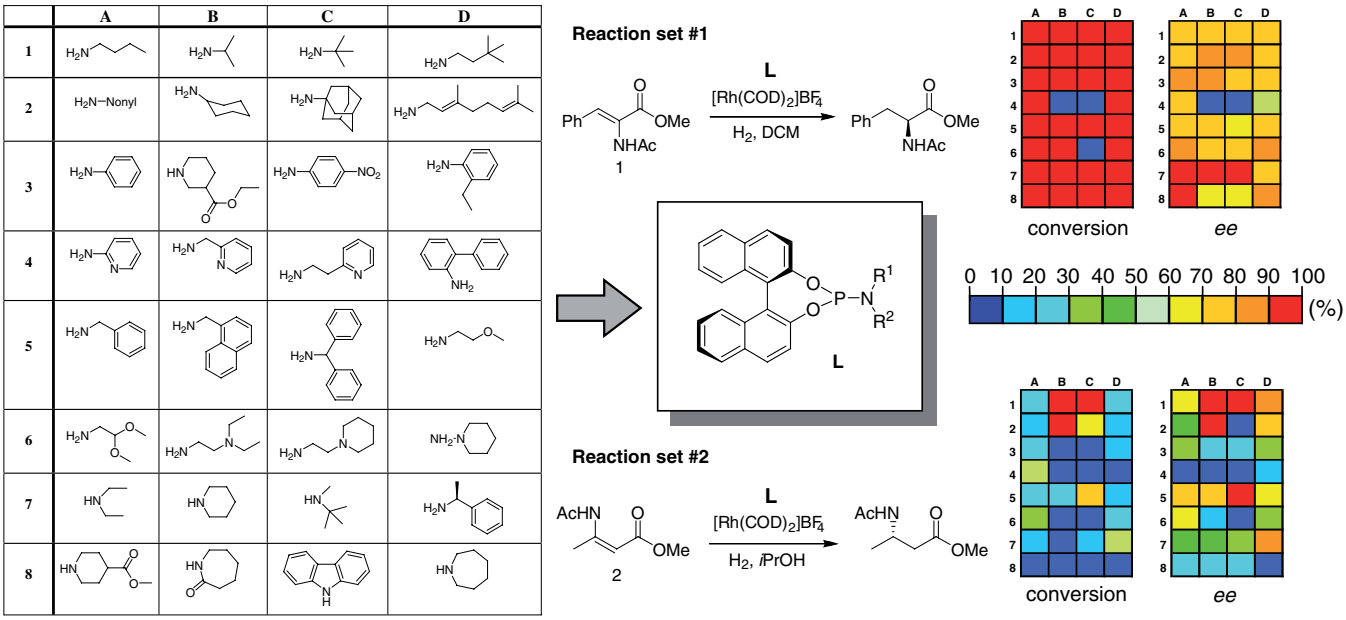


Figure 4. Parallel synthesis and screening of monodentate phosphoramidites in asymmetric hydrogenation.

tion give excellent results. We have taken four ligands from this library and compared the results of the parallel screen with the results obtained with the purified ligands (Table 1).

Table 1. Comparison of library ligands with purified ligands.

	Purified ligands		Library ligands	
	Conv. [%]	*ee* [%]	Conv. [%]	*ee* [%]
1b	8	46	11	41
1d	11	55	7	43
1i	96	94	51	88
1m	100	95	95	92

This comparison clearly shows that there is some erosion of rate and enantioselectivity due to the impurities present in the library ligands. However, the relative order remains the same. The results thus have an excellent predictive value.

This means that we have finally achieved our objectives of building up the capability to find a new ligand for a given substrate within a period of weeks. We now routinely use this method of screening for our customer's requests.

Evidently, the method can also be used for other monodentate ligands. We have already shown that the method works equally well with phosphite ligands. In addition, using this library approach for other chemistries is even easier. We have applied the library approach to rhodium-catalysed asymmetric C–C bond formation as well.[26] In this case, the reaction is accelerated by chloride, obviating the need for filtration of the crude library mixture.

Asymmetric Hydrogenation with Mixtures of Ligands

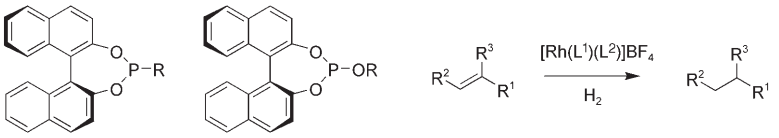
It seems clear that in the MonoPhos hydrogenation reactions the active catalysts contain two ligands. Proof for this assumption was obtained by the observation of nonlinear effects on the enantioselectivity and by the work described in this subchapter.[12d] One of the more interesting aspects of the use of monodentate ligands is the possibility to create catalysts containing two different ligands. This could in principle increase the number of accessible catalysts to a large extent. Initially, it does not seem very appealing to use mixtures of two different ligands as one would expect the formation of an equilibrium mixture of the two homocomplexes and the heterocomplex (Scheme 2).

Scheme 2. Mixture of catalytic complexes obtained when using mixtures of ligands.

However, it is possible that the mixed catalyst becomes the dominant one, either if it is more stable and thus formed in large excess, or if it is a more active, kinetically dominant catalyst. Recently, both Reetz et al. and we in collaboration with the group of Feringa/Minnaard have shown that this approach can be beneficial. Earlier attempts by Chen and Xiao using mixtures of monodentate phosphites based on bisphenol and a chiral alcohol were not successful.[27]

In the Reetz work, rhodium catalysts based on mixtures of monodentate phosphites, monodentate phosphonites and combinations of the two were screened in the asymmetric hydrogenation of α- and β-*N*-acetyldehydroamino acid

Table 2. Use of mixtures of monodentate phosphonites and or phosphites in the rhodium-catalysed hydrogenation of substituted olefins.



La R = CH_3
Lb R = *c*-C_6H_{11}
Lc R = $C(CH_3)_3$

Lp R = CH_3
Lq R = 2,6-diMeC_6H_3
Lr R = 9-fluorenyl

	$R^1=CO_2Me$ $R^2=H$ $R^3=NHAc$	$R^1=CO_2Me$ $R^2=Ph$ $R^3=NHAc$	$R^1=Ar$ $R^2=H$ $R^3=NHAc$	$R^1=CH_2CO_2Me$ $R^2=H$ $R^3=CO_2Me$	$R^1=Me$ $R^2=CO_2Me$ $R^3=NHAc$
La	92	90	76	90	95
Lb	92	–	–	22	66
Lc	93	69	13	57	45
Lp	77	–	–	–	75
Lq	32	–	–	–	–
Lr	94	–	–	–	–
La/Lb	98	97	–	89	–
La/Lc	98	99	96	96	–
Lp/Lq	85	–	–	–	–
Lb/Lp	96	–	–	–	92
Lc/Lp	98	–	–	–	99
Lc/Lr	97	–	–	–	–
Lb/Lr	96	–	–	–	–

esters, enamides and dimethyl itaconate.[28] In Table 2 we have summarised a number of the more striking results. The effect seems to be strongest with combinations of two phosphonites or one phosphonite and one phosphite, in particular when one of the ligands carries a bulky substituent and the other a small one.

We have independently developed this approach using the monodentate phosphoramidites. In this research we screened mixtures of two phosphoramidite ligands, namely, **1a**, **1f**, **1i**, **1j**, **1k** and **2a**, in the asymmetric hydrogenation of an aliphatic and an aromatic (*Z*)-β-dehydroamino acid ester (**5a** and **5b**; Figure 5). In Figure 5, the results of the screening are displayed. Entries 1–6 show the results with the homocatalysts. We then started to screen mixtures of these ligands. Not surprisingly, most combinations of two different ligands induced lower enantioselectivity. However, there was one marked exception: all combinations that included the NH ligand **1i** led to better results (Figure 5, entries 7–11).[29] Particularly striking is the combination of ligand **1j**, which was the worst performer in the homoseries in combination with **1i** (entry 9).

Gennari and Piarulli created a library of 16 bisphenol-based phosphite and phosphoramidite ligands made from chiral alcohols and chiral amines, respectively. In addition to the homocatalysts, they tested 115 mixed combinations in the rhodium-catalysed hydrogenation of methyl 2-acetamido-acrylate. They found that neither combinations of two different phosphites nor of two different phosphoramidites improved the enantioselectivity. On the other hand, they found 16 combinations of phosphites with phosphoramidites that induced higher enantioselectivity than the "homocatalysts" whilst retaining the high rate induced by the phosphite ligands.[30]

The simple concept of mixtures of monodentate ligands allows one to generate large libraries of catalysts. For instance ten ligands can lead to 55 possible combinations, while a library of 96 ligands leads to 4656 combinations; a finding which tremendously increases the scope of these hydrogenation reactions.[31]

In collaboration with the Gennari group, we have explored another parameter in the ligand mixture concept, namely the ratio between the two ligands.[32] In this research, we were able to show that a 1:1 mixture of the two monodentate ligands L^1 and L^2 (while keeping the (L^1+L^2)/Rh ratio

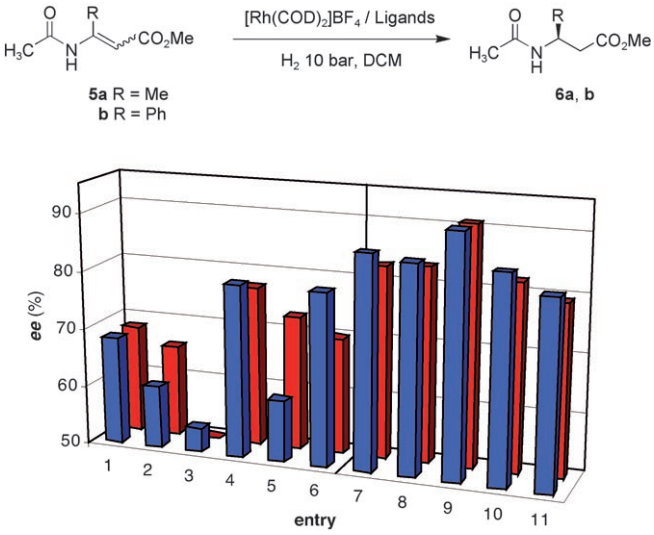


Figure 5. Rh/phosphoramidite-catalysed hydrogenations using homo- (entries 1–6) and hetero- (entries 7–11) catalysts (blue bars: results with **5a**, red bars: results with **5b**; 1=**1a**, 2=**2a**, 3=**1j**, 4=**1k**, 5=**1f**, 6=**1i**, 7=**1a+1i**, 8=**2a+1i**, 9=**1j+1i**, 10=**1k+1i**, 11=**1f+1i**). Reprinted by permission of the RSC from reference [29].

equal to 2) was not necessarily the best ratio. The best *ee* (98% *ee*) for the hydrogenation of methyl 2-acetamidocinnamate was obtained for a ratio L^1/L^2 equal to 0.25:1.75. In Figure 6, a striking case is reported where 59% *ee* is obtained (with a 0.25:1.75 ratio) instead of 34% *ee* (with a 1:1 ratio). This finding can be explained by the different activities of the less enantioselective homocomplexes RhL^1L^1 and RhL^2L^2 under the assumption that the heterocomplex is

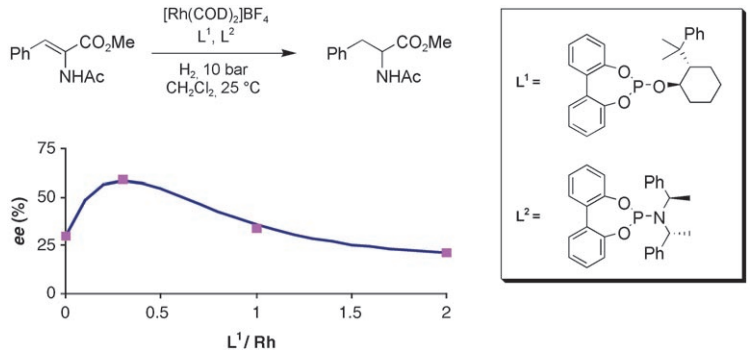
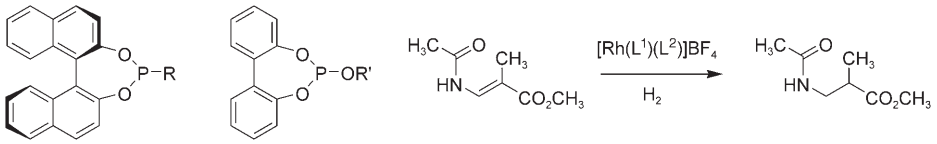


Figure 6. The *ee* obtained in the Rh-catalysed hydrogenation of methyl 2-acetamidocinnamate versus ligand ratio.



Lc R = *t*Bu
Lp R = OMe

Lv R = Me
Lw R = CH_2Ph

Scheme 3. Use of mixtures of ligands increases enantioselectivity.

more enantioselective than the homocomplexes (i.e., beneficial effect of the ligand mixture). In this case, RhL^1L^1 is a fast catalyst and RhL^2L^2 is slow relative to the heterocomplex. Thus, using an excess of L^2 strongly minimises the amount of the faster RhL^1L^1 complex. Although the homocomplex RhL^2L^2 is the major complex present in solution, this is inconsequential since it has a low activity. Consequently, the observed enantioselectivity is mainly due to the catalytic action of the heterocomplex, that is, the most enantioselective catalyst. We also confirmed by kinetic measurements that the homocomplex RhL^1L^1 was fast, whilst RhL^2L^2 was slow—this fact is consistent with our explanation. The ratio L^1/L^2 in the case of mixtures of ligands must thus be considered as an important parameter that needs to be fine-tuned.

Mixtures of MonoPhos and Nonchiral Ligands

In addition to complexes based on the combination of two different chiral monodentate ligands, combinations of a single chiral monodentate ligand with other nonchiral ligands are also possible. Reetz et al. have published about this approach using mixtures of chiral monodentate phosphites or phosphonites with nonchiral phosphines in asymmetric hydrogenations. This led to large changes in the enantioselectivity of the reaction; in one case reversal of enantioselectivity was observed from 92% (*S*) to 59% (*R*).[28b] In a more recent paper, Reetz and Li describe the use of mixtures of a chiral phosphonites and a biphenyl-based phosphite in the rhodium-catalyzed asymmetric hydrogenation of aliphatic β-dehydroamino acid esters. These biphenyl-based ligands are fluxionally atropisomeric. Here, the enantioselectivity increases from 45% to 98% upon switching from the homocatalyst based on phosphonites **Lc** to a 1:1 mixture of **Lc** and **Lv** or a 1:1 mixture of **Lc** and **Lw** (Scheme 3). In addition, they found that in several cases the enantioselectivity could be improved by using mixtures of either **Lc** or **Lp** with an achiral monodentate phosphine or phosphite.[33]

Here we present an example in which the addition of nonchiral phosphines, for example, PPh_3, to chiral phosphoramidites results in a large enhancement of both rate and *ee*. Such a catalyst combination is currently used by DSM in a large-scale process.

Chiral dihydrocinnamic acid derivatives are key intermediates in the synthesis of several bioactive compounds, including the renin inhibitor Aliskiren.[34] One of the key steps in the synthesis of this renin inhibitor is the asymmetric hydrogenation of the cinnamic acid derivative depicted in Figure 7. The asymmetric hydrogenation of this class of substrate, let alone the actual substrate, has hardly been investigated. Recently, Walphos, a ferrocene-based bisphosphine compound, was found to give good results with this particular substrate, while other well-known bisphosphine ligands are not suitable.[35]

When we tested MonoPhos (**1a**) in the asymmetric hydrogenation of the key cinnamic acid derivative, we were happy to see that the in situ derived catalyst of $[Rh(COD)_2]BF_4$ (COD = cyclooctadiene) and two equivalents of **1a** gave 50% conversion and 20% *ee* after 5 h in isopropanol at 60 °C and 25 bar of hydrogen. Other phosphoramidites, like the sterically demanding ligand **1j** were slightly better in activity and enantioselectivity. However, the rate of the reaction worried us. In hydrogenation reactions with rhodium, the oxidative addition of hydrogen is the rate-determining step. The rate of this reaction is strongly influenced by the electron density of the complex, which in term can be greatly influenced by the nature of the ligands.[36] Since phosphoramidites are good π acceptors but poor σ donors, we decided to probe the effect of using additional ligands. Among others, we used good σ donors such as phosphines and amines as a way to increase the electron density on the metal.

In Figure 7, we show the effect of a range of additives on the asymmetric hydrogenation of the cinnamic acid precursor. One trend that emerges from this screen is the positive

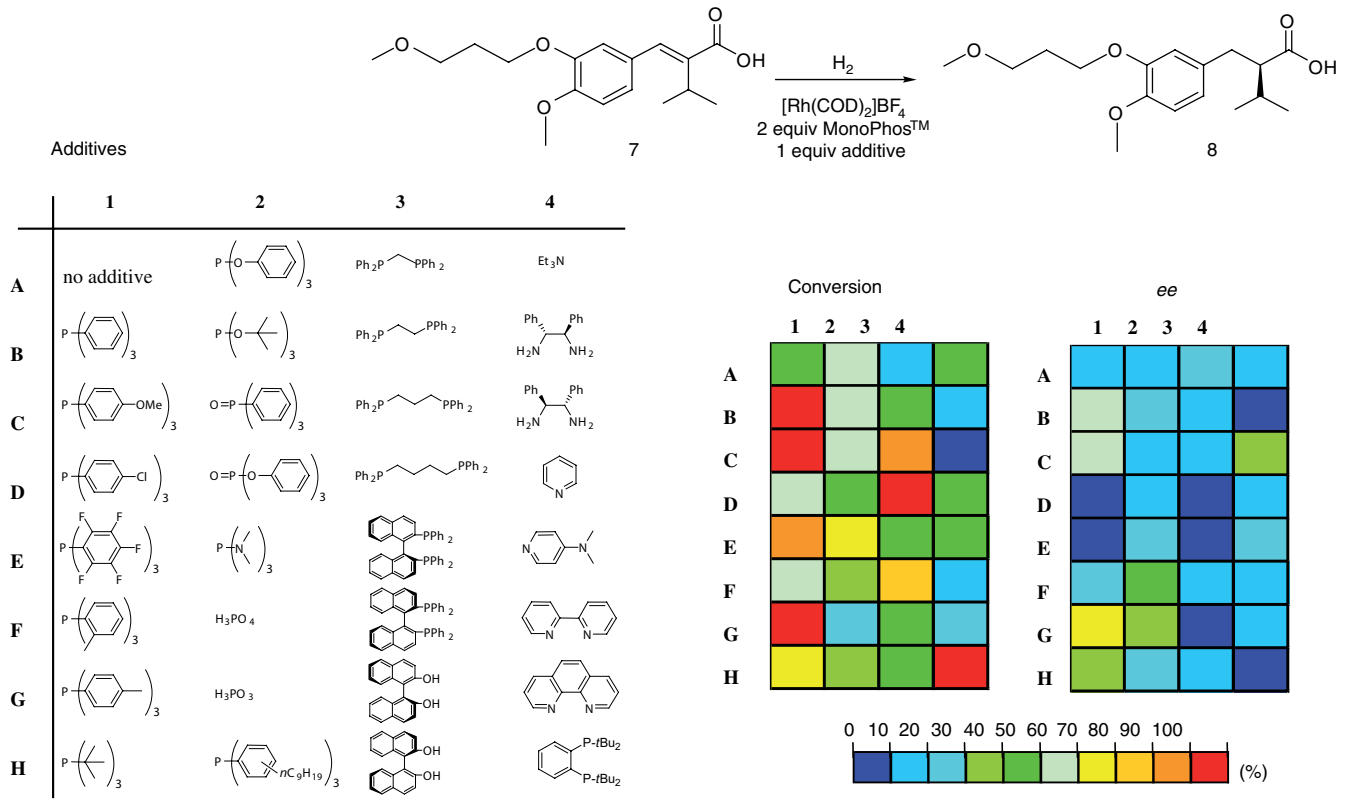
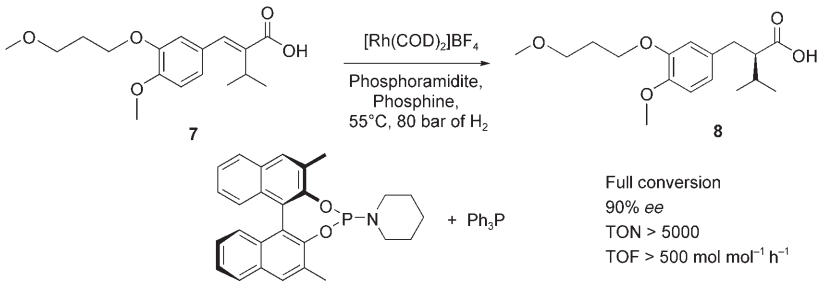


Figure 7. Screening additives for the asymmetric hydrogenation of α-alkylcinnamicacids.

effect of the monodentate phosphines. In particular, the result with tri-*p*-tolylphosphine looked very promising.

Further library screening resulted in the finding of the 3,3′-dimethyl-substituted ligand **1l**. The reaction temperature is a compromise between rate and enantioselectivity. At 55 °C, the reaction is fast allowing an economic substrate/catalyst ratio of 5000. The enantioselectivity of the product is 90 % (Scheme 4).[37]



Scheme 4. Asymmetric hydrogenation of the Aliskiren intermediate.

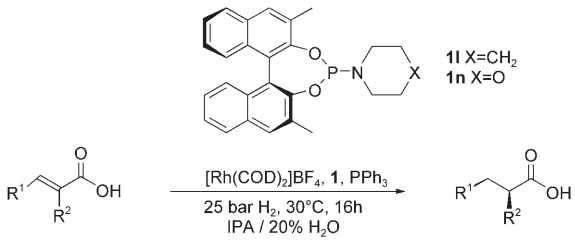
In this case, the instant ligand library concept combined with the mixing of monodentate ligands allowed us not only to find a ligand that induced sufficiently high enantioselectivity, but also to improve the rate by a factor of 100!

In collaboration with the Feringa/Minnaard group, we have further extended the scope of this cinnamate hydrogenation (Table 3).[12h] In all cases a pronounced effect of the added triarylphosphine was found; usually the best results were obtained with a combination of ligands **1l** or **1n** in combination with tri-*ortho*-tolylphosphine. In practice, we found that the ratio Rh/phosphoramidite/Ar_3P of 1:2:1 gives the best results. NMR spectroscopic studies revealed that under these conditions we find the mixed complex [Rh(phosphoramidite)(PAr_3)(COD)]BF_4 is present in addition to a substantial amount of [Rh(phosphoramidite)$_2$]BF_4. However, we know this latter complex leads to a catalyst that is 100 times slower than the mixed complex, hence it has no effect. If on the other hand a ratio of 1:1:1 is used the NMR spectra shows substantial amounts of [Rh-(PAr_3)$_2$]BF_4, a fast catalyst leading to racemic product.

Ruthenacycles for Asymmetric Transfer Hydrogenation

Asymmetric hydrogenation of carbonyl compounds using ruthenium/MonoPhos catalysts is currently under development. However, in the mean time we have been working on new concepts for asymmetric transfer hydrogenation that

Table 3. Asymmetric hydrogenation of acrylates and cinnamates.[a,b]

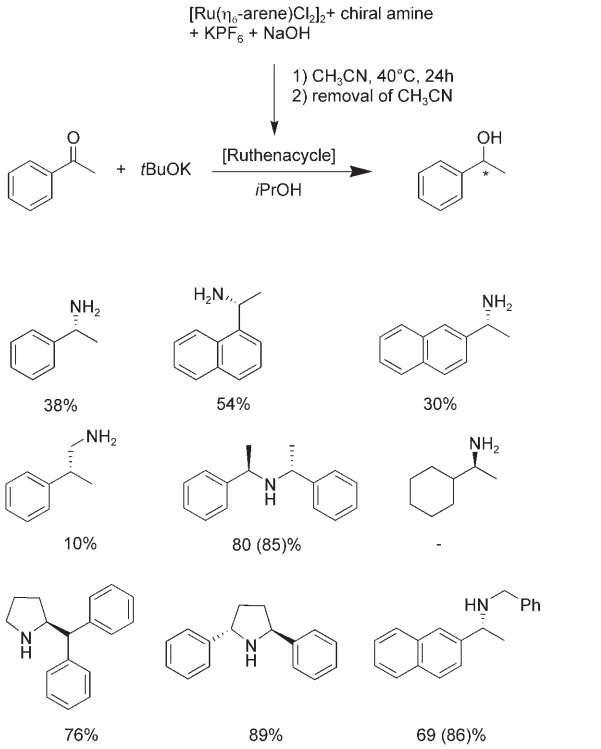


9 R^1 = Me, R^2 = Me
10 R^1 = Ph, R^2 = Me
11 R^1 = Ph, R^2 = *i*Pr
12 R^1 = 3,4-MeOPh, R^2 = *i*Pr
13 R^1 = 4-CF_3Ph, R^2 = *i*Pr
14 R^1 = Ph, R^2 = Ph

15 R^1 = Me, R^2 = Me
16 R^1 = Ph, R^2 = Me
17 R^1 = Ph, R^2 = *i*Pr
18 R^1 = 3,4-MeOPh, R^2 = *i*Pr
19 R^1 = 4-CF_3Ph, R^2 = *i*Pr
20 R^1 = Ph, R^2 = Ph

	Substrate	Product	Ligand	Ar	*ee*[c]
1	**9**	**15**	**1n**	*m*-Tol	87
2	**10**	**16**	**11**	–	2[d]
3	**10**	**16**	**11**	Ph	88
4	**10**	**16**	**11**	*o*-Tol	**97**
5	**11**	**17**	**11**	*o*-Tol	**99**[e]
6	**12**	**18**	**11**	Ph	92
7	**13**	**19**	**11**	*m*-Tol	95
8[f]	**14**	**20**	**11**	*o*-Tol	95

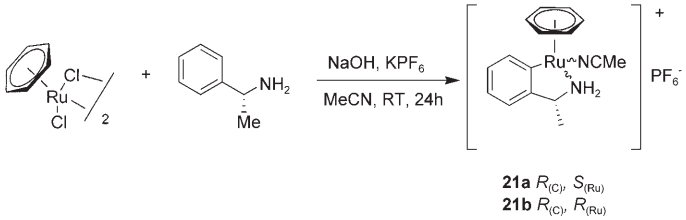
[a] Reaction conditions: substrate (1 mmol) in solvent (4 mL) with [Rh(COD)$_2$]BF_4 (0.01 mmol), phosphoramidite (0.02 mmol) and PR_3 (0.01 mmol). [b] Reactions were run for 16 h. [c] In all cases the *R* enantiomer of ligand gave the *S* enantiomer of product. [d] 34% conversion. [e] 98% conversion. [f] Reaction was performed at 60°C.



Scheme 6. Instant ruthenacycle-catalysed transfer hydrogenation of acetophenone (enantioselectivity given below ligand structure; values between brackets obtained at 0°C).

would fit in the instant ligand library concept. In collaboration with the group of Pfeffer from ULP Strasbourg, we have developed an entirely new class of catalysts based on ruthenacycles. These chiral ruthenacycles are easily synthesised from an enantiopure aromatic compound with an aminoalkyl side chain and a commercially available ruthenium precursor in a single step as shown in Scheme 5.[38]

It turns out these compounds are remarkably good catalysts for the asymmetric transfer hydrogenation of ketones.[39] Better still, it is possible to perform the catalyst synthesis in the robot, immediately followed by screening of its catalytic activity for the substrate of interest. It is necessary to remove the acetonitrile that was used as a solvent for the ruthenacycle synthesis, as it disturbs the catalytic activity in the transfer hydrogenation. In this way, a number of enantiopure primary and secondary amines were tested as ligand in the asymmetric transfer hydrogenation of acetophenone (Scheme 6).



21a $R_{(C)}$, $S_{(Ru)}$
21b $R_{(C)}$, $R_{(Ru)}$

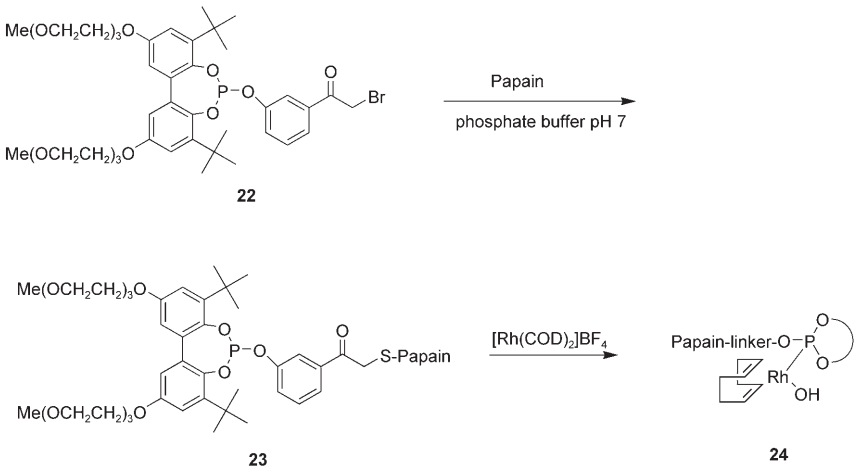
Scheme 5. Synthesis of ruthenacycles.

It turns out that the majority of ligands leads to catalysts with interesting activity; in particular, the catalyst based on 1-naphthylethylamine turned out to be very fast. The 2,5-diphenylpyrrolidine-based catalyst induced a relatively high enantioselectivity. It is clear that once the library of chiral amines has been extended, this is an excellent method to rapidly find a catalyst for an asymmetric ketone reduction.

Artificial Enzymes

In all the cases described above the basic reactivity has been provided by the metal; the ligand mainly serves as a source of chirality. There is another source of chirality that we have not considered so far. Enzymes are of course interesting biocatalysts and perform well in a number of asymmetric reactions, such as hydrolytic reactions and some addition reactions. Recent advances in genetic engineering have allowed the production of extensive libraries of enzymes.[40] We were intrigued by the possibility to wed the best properties of a transition-metal catalyst with the chirality of an enzyme. In this concept, the natural activity of the enzyme is not important. It merely serves as a source of chirality. Thus it would be possible to make enzymatic catalysts that can perform reactions for which no enzymes exists, such as hydroformylation reactions, or for which existing enzymes do not perform well, such as in olefin hydrogenation reactions. Recently, a number of groups have developed enzyme–transition-metal

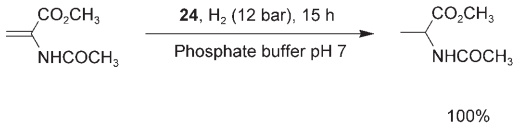
conjugates as catalysts for asymmetric transformations, such as hydrogenation and epoxidation reactions.[41] The very first publication in this area stems from Whitesides, who covalently attached a nonchiral rhodium–bisphosphine catalyst to biotin.[41a] Subsequent binding of this conjugate to the protein avidin resulted in an enantioselective hydrogenation catalyst. Ward has further refined this concept and obtained very high enantioselectivities in asymmetric hydrogenation with these catalysts.[41b–d] Reetz has published the attachment of catalysts and ligands to papain by using a maleimide linker.[41h] The catalysts were active, but the enantioselectivity in these reactions remained at very low levels. He also reported the attachment of a bisphosphine ligand, without reporting further catalytic use.



Scheme 7. Modification of papain to create an artificial enzyme.

We had independently decided to develop a ligand system that can easily be anchored on certain classes of enzymes through a linker that has known affinity for the active site of the catalyst.[42] Once this concept is proven, it can be applied to large libraries of enzymes, which can then be tested again on the substrate of choice. We decided to test out the concept on papain, a well-characterised enzyme with a cysteine residue in position 25. Phenacyl bromides are known to selectively bind to the thiol group of this amino acid residue. We thus devised a phosphorus ligand that could be attached to phenacyl bromide. In view of the high electrophilicity of phenacyl bromide, the ligand cannot be a phosphine. We thus decided on a phosphite, decorated with bulky *tert*-butyl groups to enhance hydrolytic stability. In addition, these bulky groups increase the cone angle of the ligand to such an extent that only a single ligand can bind to the metal. Examples are known in which such monoligated catalysts were shown to be extremely active in hydroformylation[43] or in aromatic substitution reactions.[44] Finally, we had to attach triethylene glycol tails to the ligand in order to increase the solubility in water. With the ligand attached to the linker (**23**) we then modified papain in an aqueous buffered solution containing 10% dioxane. The progress of this reaction was monitored by measuring the hydrolytic activity of the enzyme with a chromogenic substrate. Addition of the rhodium precursor followed by purification over an ion exchange resin gave the pure modified enzyme (**24**) (Scheme 7). Its structure was proven with EI-MS. In addition, analysis of the tryptic digest showed modification at position 25.[45]

The enzyme conjugate **24** is an active hydrogenation catalyst. At a substrate catalyst ratio of 800, it was capable of hydrogenating methyl 2-acetamidoacrylate with 100% conversion in a buffered water solution overnight at 12 bar H_2 (Scheme 8).



Scheme 8. Hydrogenation of methyl 2-acetamido acrylate with metal-enzyme conjugate **24**.

Unfortunately, the product was racemic. This may be due to the fact that there still is a lot of conformational freedom for the transition-metal catalyst. We are currently reconsidering the mode of attachment. In addition, further enzymes will be tested as originally planned.

Conclusion

At the beginning of this research, we had set ourselves the target of being able to find a proper chiral hydrogenation catalyst for a new substrate within three weeks. We have reached this goal by implementation of HTE techniques, by developing new classes of catalysts and ligands that can easily be assembled in a robot and by developing a robotic protocol (instant ligand libraries), which allows synthesis of the ligands or catalysts and subsequent testing without isolation. In addition, we have shown that mixtures of ligands can be used to great advantage. These methods have revolutionised the manner in which we develop new catalysts for implementation in industrial processes. Indeed, using the methods described in this article we managed to find an economic catalyst for a process now run on ton scale.

Acknowledgements

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