36
High-Throughput Experimentation and Ligand Libraries

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36.1
Introduction

Following Knowles' initial success in enantioselective hydrogenation, there was a growing expectation that from now on it would be possible to produce all enantiopure chiral compounds by enantioselective catalysis [1]. Indeed, Kagan's finding of chiral bisphosphine ligands with chirality residing in the backbone made the challenge of developing new chiral ligands highly attractive to synthetic organic chemists [2]. This resulted in an avalanche of papers – which continues to the present day – describing the development of new chiral ligands which were tested in well-known reactions; an example is the enantioselective hydrogenation of methyl-2-acetamido-cinnamate [3]. Some of these developments, such as Noyori's BINAP, were highly successful and have resulted in industrial applications [4]. Yet, in retrospect, after what must have been an astonishingly massive research effort, the impact of enantioselective hydrogenation – and indeed of enantioselective catalysis using transition-metal complexes – is perhaps not as large as one might have expected. This is due to a number of factors. Scientifically, it soon became evident that the prediction of ligand structure required to affect the desired high enantioselectivity of a new substrate was an impossible affair, thereby making it necessary to test – and probably to invent – new ligands for every new substrate. In addition, the scope of the successful chiral catalysts was found to be limited to special classes of substrates, decorated either with an extra functionality in a position allowing additional ligation to the metal, or with extra π-orbitals near the functionality that needs to be reduced.

When examining more closely the impact that this technology had on the production of fine chemicals, the picture is even bleaker [4, 5]. Even today, the majority of enantiopure chemicals (most of which are intermediates for drugs) is produced either by fermentation or by classical resolution – that is, the separation of diastereomeric salts. There are a number of reasons for this, which can be summarized as follows [6]:

- Short development time. Time-to-market pressure does not leave sufficient time to identify the correct catalyst and develop a robust process. As every

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month of delay in launch of the new drug can mean a substantial loss of revenue, the choice is often made for reliable, readily implemented and well-known chemistry; in this case classical resolution.

- Cost of the catalyst. The transition metals used, such as rhodium, ruthenium, iridium or palladium, are extremely expensive. The same holds for complicated chiral ligands that often take six to ten synthetic steps for their production. An excellent way to beat these costs is to develop a highly active catalyst. A substrate : catalyst ratio (SCR) of 1000 is often quoted as a minimum requirement. In the celebrated Metolachlor process, a SCR of over 100 000 is possible. Factors determining the rate of reaction are numerous and often poorly understood. Deactivation of the catalyst also has a profound effect on the overall rate of the reaction.
- Fit of the catalytic step in the overall total synthesis. Many cases are known where the catalytic step proceeded beautifully, but the number of synthetic steps was much higher than in the racemic route. Ultimately, the number of steps and costs of the starting materials are the determining factors in production costs.
- Availability of ligands, both on small scale for testing and on production scale. The synthesis and purification of a ligand is a long and cumbersome affair. Thus, until recently, most research groups did not possess more than a handful of ligands. If none of these worked for the customer substrate, then the company would lose the bid for the production, as insufficient time would be available to synthesize new ligands. Even worse is the situation regarding the availability of the kilogram quantities. These are produced in a manner akin to proper large-scale productions and require expensive process development, which will take a considerable amount of time. Few companies were willing to invest upfront in the production of kilogram amounts of ligands, and this forms a major barrier for implementation of the technology in first-generation processes.
- Robustness of the process. Many transition metal-catalyzed reactions function well at the laboratory scale, but on scaling up substrate and product inhibition may be an issue, and sensitivity to impurities may also become apparent. Increasing the SCR, which is often necessary for the economics of the process, also increases the impurity : catalyst ratio. It is also very important to keep the number of components to a minimum, as extraction, crystallization and distillation are the only economic means of purification. Ligands can be a nuisance in this respect, particularly if they are used in amounts over 5 mol%. Reproducibility also is a stringent requirement. Thus, possible inhibition mechanisms should be recognized in order to avoid unwanted surprises during production.

It is not surprising that in this frustrating situation many workers in the field – and in particular in industry – eyed with envy the developments in the area of combinatorial chemistry, and wondered if the same tricks such as split-and-mix [7] and high-throughput screening could be applied to the field of enantioselec-

tive catalysis [8]. Most people assumed that screening mixtures of ligands would provide meaningless results and, indeed, this is rarely a useful enterprise. However, the implementation of high-throughput screening techniques was much more appealing [6, 8, 9]. Even before the advent of combinatorial chemistry, research teams had engaged in the practice of performing multiple reactions at the same time, or even using a number of punctured vials containing different catalysts or substrates in a single autoclave. Indeed, apart from the desire to test as many ligands as possible, most people investigating homogeneous catalysis are well aware of the need to screen other variables of the reaction. We have recently compiled a list of parameters that we consider important both for screening as well as for optimizing reactions (Table 36.1) [6]. It is clear that, in the past, not many of these variables were tested in view of the repetitive nature of the experiments.

Apart from enantioselective catalysis, there is a more general need to perform large numbers of experiments. As most reactions catalyzed by transition metal catalysts proceed through a number of intermediates in a multistep sequence, it is often impossible to identify good structure–activity relationships. Although there are many parameters that affect the outcome of the overall reaction, the effect they have on the discrete steps may differ widely and may even be opposing, which makes it impossible to obtain linear correlations. This thwarts most attempts to direct the optimization approach with a rational choice of parameters based on analogies, which is the common approach in synthetic research. Thus, a slow and painful step-by-step approach in finding "leads" and optimization was common practice. Thus, also for nonchiral reactions, it will usually be impossible to predict what the best catalyst will look like, although there is of

Table 36.1 Parameters for HTS of homogeneous transition metal-catalyzed reactions.

1	Metal	
2	Counterion	
3	Ligand	Catalyst tuning
4	Ancillary ligand	
5	Metal : ligand ratio	
6	Method of catalyst preparation	
7	Substrate : catalyst ratio	
8	Reactant	
9	Solvent	
10	Temperature	Optimizing
11	Pressure	the reaction
12	Ratio of substrate to reactants	conditions
13	Concentration of catalyst, substrate and reactants	
14	Order of mixing catalyst and reactants	
15	Rate of addition of one or more reactants	
16	pH	
17	Additives such as acids, bases or tetra-alkylammonium salts	

course a very large body of literature available that will provide a number of starting points for the search. Nevertheless, extensive screening of metal precursors, ligands and solvents will be necessary in both the lead finding and the optimization phase.

In addition, the large number of experiments and the higher diversity space that can be accessed also greatly improve the quality of the data obtained. Trends are more easily observed as the correlation becomes more reliable with the increasing number of experiments.

In conclusion, it seems likely that high-throughput experimentation (HTE) will not only be a tremendous methodology to solve the time-to-market problem, but will also enhance the scope as well as the quality of academic research to a large extent.

36.2 High-Throughput Experimentation

What is the essence of HTE? It is the ability to perform a larger number of experiments than is manually possible. In the search for a new or improved hydrogenation catalysts, one necessarily needs to go through the following consecutive experimental steps:

- Synthesis of ligands/catalysts.
- Testing of the catalyst in the reaction of interest (including optimization following the parameters listed in Table 36.1).
- Analysis of the products formed during the catalytic reaction.

Consequently, any techniques leading to an acceleration (in terms of the number of experiments performed per unit of time) of one or several of these three experimental steps is sufficient to qualify the research endeavor as being part of an HTE effort. Several strategies can be envisaged to speed up the experiments, as follows.

36.2.1 Serial Mode

In a serial mode (Fig. 36.1), one experimental step (in catalysis research this is usually the preparation of the ligand or the catalyst) is repeated n times before moving on to the next step. The only difference with traditional research is that the complete experiment (synthesis/testing/analysis) is carried out for a set of catalysts rather than for an individual species. For example, a library of ligands from the same class can be assembled via traditional organic synthesis prior to its testing in catalysis. (A "library" of compounds is a rather large collection of different compounds with some common features and usually the same function, for example triarylphosphines or imidazolidinones.) Ideally, the compounds in the library can be structurally varied in at least two positions to cre-

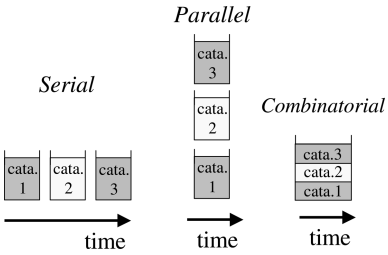


Fig. 36.1 Different modes to perform experiments.

ate a large diversity. No significant time reduction is expected unless rapid testing and/or analysis can be coupled to it.

36.2.2 Parallel Experimentation

A second strategy relies on parallel experimentation. In this case, the same experimental step is performed over *n* samples in *n* separated vessels at the same time. Robotic equipment such as automated liquid-handlers, multi-well reactors and auto-samplers for the analysis are used to perform the repetitive tasks in parallel. This automated equipment often works in a serial fashion as, for example, a liquid handler with a single dispensing syringe filling the wells of a microtiter plate, one after another. However, the chemical formation of the catalyst or the catalytic reaction are run at the same time, assuming that their rate is slow compared to the time needed to add all the components. The whole process appears parallel for the human user whose intervention is reduced.

36.2.3 Combinatorial Protocols

In combinatorial protocols, *n* experiments are performed at the same time in the same vessel. This methodology is the most efficient in terms of time and resources, but can only be applied in discrete cases in homogeneous catalysis. Indeed, the efficiency of a catalyst can only be measured when it is submitted to the reactants. Testing a mixture of catalysts in solution would give the overall efficiency of the mixture, without any indications about individual performances.

To date, only living polymerization catalysts have been tested in a combinatorial fashion, using electrospray mass spectrometry (EMS) to discover the best-performing catalyst [10]. This protocol would seem less-suited for hydrogenation. Elaborate techniques have nevertheless been designed to test pooled catalysts. They involve immobilization of the catalysts on polymer beads and testing these in a reaction with a chromogenic substrate in a viscous medium, which limits the diffusion of the colored products to the neighborhood of the active bead [11]. In the extreme case of an entirely new reaction where the expectation is that most of the catalytic species will not be active, such a combinatorial testing

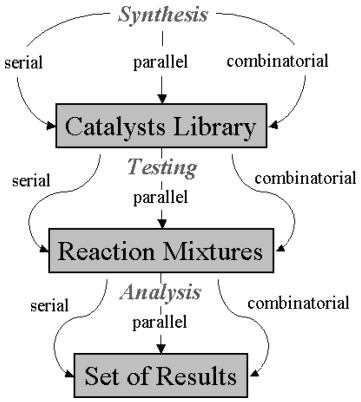


Fig. 36.2 Steps for the development of new or improved catalysts and HTE modes.

could nevertheless be used. Deconvolution strategies such as those used for libraries of small organic molecules would allow identification of the active catalyst by performing a minimum number of experiments. For example, using the so-called deconvolution by orthogonal libraries, the active species among *n* catalysts could be identified by performing only 3.3 log*n* experiments [12].

The ideal HTE set-up should be composed of accelerated procedures for each step of the experiment (Fig. 36.2). The reason for this is that in a set of consecutive steps, the slower step is rate-determining. Ideally, the most efficient set-up would combine a combinatorial synthesis of a diverse library of catalysts with a one-pot catalytic testing coupled to identification of the best candidate. Unfortunately, such a protocol has not been implemented yet for the discovery of new hydrogenation catalysts, and most HTE protocols involve at best a succession of steps involving parallel procedures. As can be seen from Fig. 36.2, there can be no HTE without a library of catalysts. In homogeneous hydrogenation, this is usually synonymous to a library of ligands. Methodologies to prepare libraries of ligands/catalysts are described in Section 36.3. Following the advent of parallel pressure reactors, parallel catalytic testing has become possible, and its application in hydrogenation – as well as new methodologies for fast catalytic testing – will be discussed in Section 36.4. Details of fast analysis will be outlined in Section 36.5.

36.3
Generating and Testing Libraries of Catalysts and Ligands

36.3.1
Libraries of Individually Synthesized Ligands

It is clear that the high-throughput approach is only possible if there are sufficient catalysts available. Fortunately, in hydrogenation it is usually possible to form the pre-catalyst simply by mixing a metal precursor and the ligand in a

suitable solvent. Several groups have taken advantage of the commercial availability of numerous metal precursors and ligands to set up high-throughput protocols.

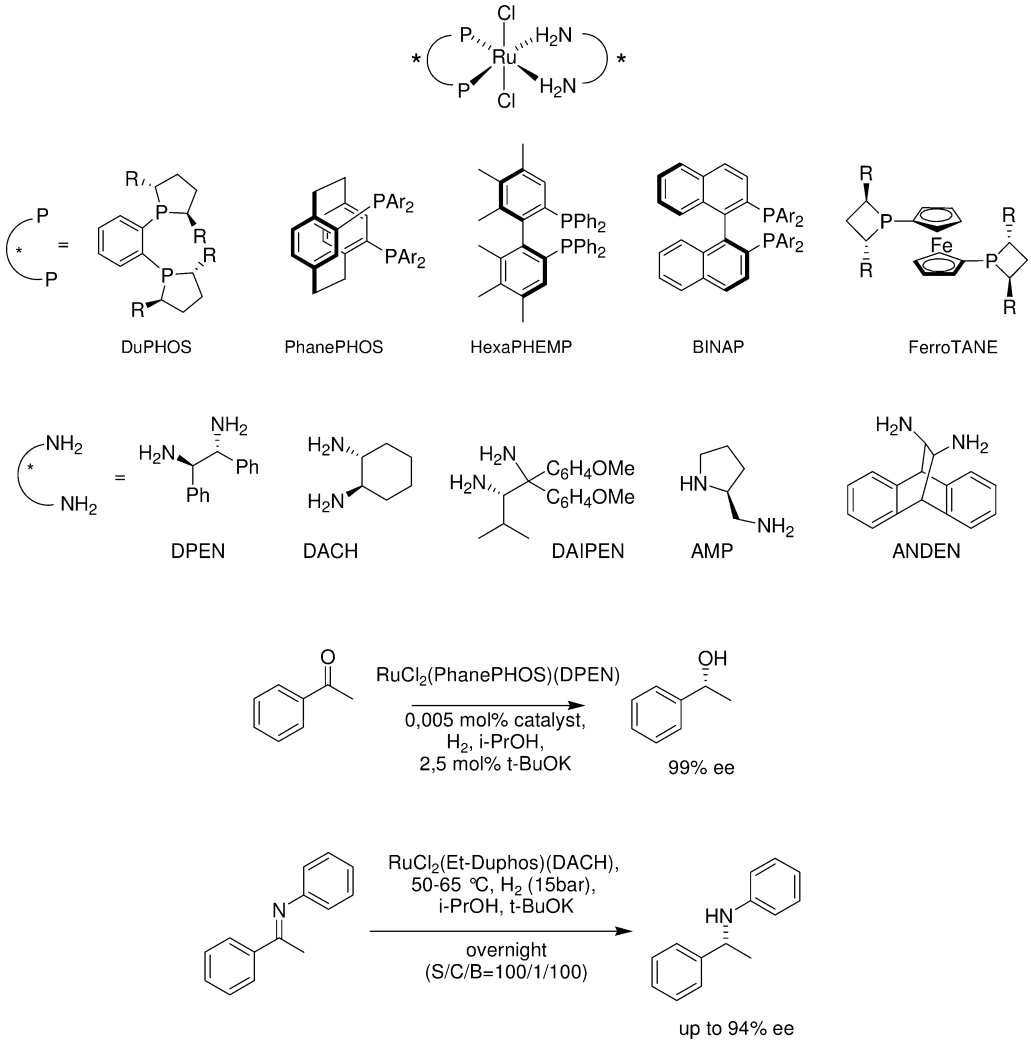
Nugent prepared a library of 256 catalysts by combining 32 commercially available chiral phosphines with eight metal precursors based on Rh, Ir and Ru [13]. All the catalysts were generated *in situ* simply by mixing stock solutions of the metal sources and stock solutions of the ligands. The catalysts were tested in the enantioselective hydrogenation of 3-alkylidene-2-piperidones. The best result was obtained with 2,4-bis(diphenylphosphino)pentane (BDPP) in combination with $[Ir(COD)_2]BF_4$; this was quite surprising as this system was known to be unselective in related reactions due to its high degree of flexibility.

Jessop et al. used 29 metal salts and five ligands to identify a catalyst for the hydrogenation of CO_2 [14]. These authors were able to identify a highly active catalyst outside the platinum group. Indeed, the known $NiCl_2$(dcpe) (dcpe = $Cy_2PCH_2CH_2PCy_2$) was found to be able to catalyze the formation of formic acid in up to 4400 TON.

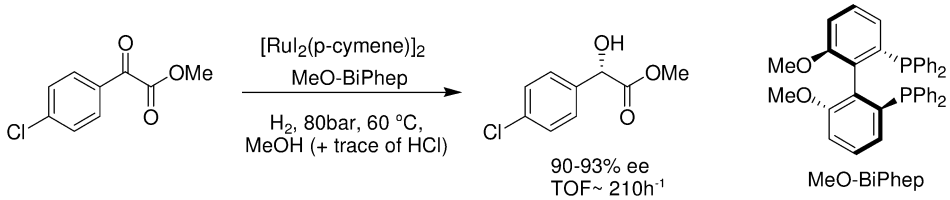
Researchers at Chirotech focused on the use of Noyori's Ru(II) dichloride(diphosphine)(diamine) complexes for the enantioselective hydrogenation of non-olefinic compounds [15]. Taking advantage of the large libraries of structurally diverse bisphosphines and diamines they had at their disposal, they were able to generate an array of catalysts with very different stereoelectronic properties (Scheme 36.1). The pre-catalyst preparation required nothing more than boiling $[RuCl_2C_6H_6]_2$ and the diphosphine in DMF, followed by treatment with the diamine at room temperature. In the case of ketone hydrogenation, the research team discovered that Phanephos was the best-performing diphosphine. In combination with DPEN or DACH, it forms a highly efficient catalyst for the enantioselective hydrogenation of simple aromatic, heteroaromatic, and α,β-unsaturated ketones [15c]. By testing the hydrogenation of imines, the combination of Et-Duphos and DACH was found to give the best results for *N*-(phenylethylidene)aniline (up to 94% ee after optimization). Overall, these authors observed that the best diphosphine/diamine combination was different for each substrate [15a].

Blaser et al. carried out an extensive screening of homogeneous catalysts for the enantioselective hydrogenation of *p*-chlorophenylglyoxylic acid derivatives [16]. A broad range of chiral electron-rich bisphosphines combined with Rh or Ru was used. While no satisfying catalyst was found for phenylglyoxylic amides, Ru/MeO-BiPhep achieved ee-values of 90–93%, with TONs up to 4000 and TOFs up to 210 h^{-1} for the methyl ester (Scheme 36.2).

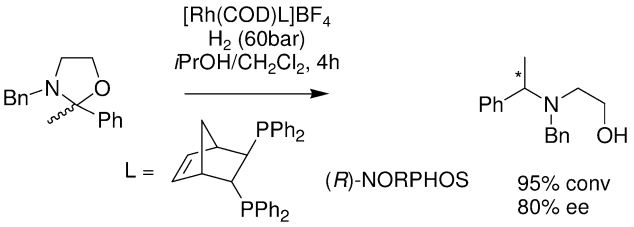
After some mechanistic studies showing that the reduction of *N,O*-acetals proceeds via a prochiral iminium cation, Börner et al. aimed at finding an enantioselective catalyst for this transformation by preparing a library of 144 catalysts [17]. Pre-catalysts were generated *in situ* by mixing one ligand out of a library of 48 members with either $[Rh(COD)_2]BF_4$, $[Rh(COD)_2]OTf$, or $[Rh(COD)Cl]_2$. The best catalyst obtained was a combination of $[Rh(COD)_2]BF_4$ and Norphos, which gave up to 80% ee (Scheme 36.3).



Scheme 36.1 Library approach in enantioselective ketone hydrogenation.



Scheme 36.2 Enantioselective hydrogenation of methyl *p*-chlorophenylglyoxylate.

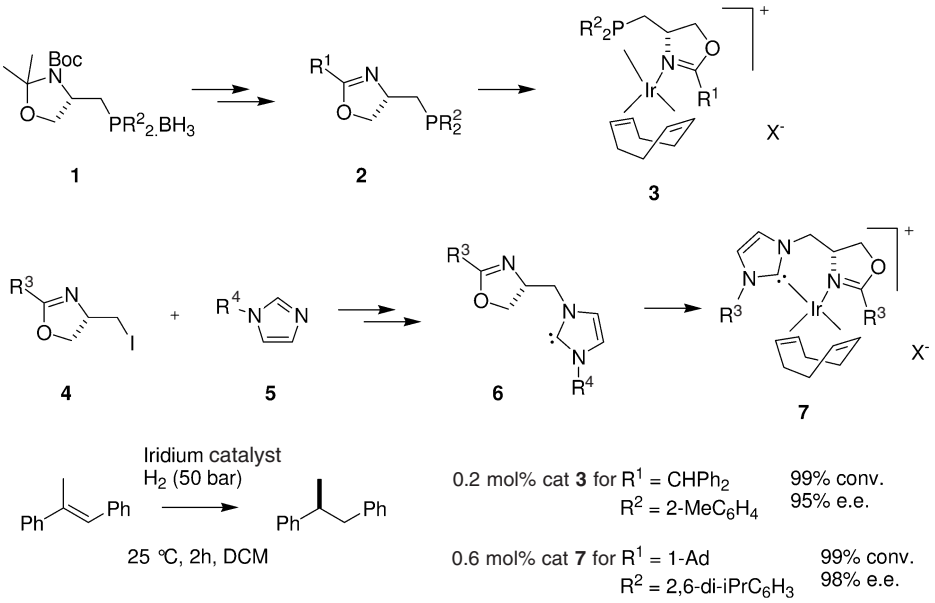


Scheme 36.3 Enantioselective hydrogenation of *N,O*-acetals.

The solvent plays an important role in the outcome of a homogeneous hydrogenation reaction. Consequently, variation of the solvent can be seen as another, highly relevant means of generating a library of catalytic systems. Feng et al. used ionic liquids (IL) as solvent, and studied their influence on the enantioselective hydrogenation of the traditional benchmark substrates (MAA, MAC) catalyzed by various diphosphine/Rh systems [18]. In their screening endeavor, these authors included seven classes of chiral bisphosphines and four different ILs. The ILs were tested pure and mixed with water (wet ILs), which can generate triphasic mixtures depending on the water:IL ratio. The wet ILs were superior to the usual organic solvent in terms of enantioselectivity. This, however, was true only for the ferrocene-based chiral bisphosphines. It was also shown that recycling of the catalyst was possible, since the Rh complex remained almost entirely in the IL phase.

Using traditional synthetic methods, other groups aimed at preparing their own library of ligands from the same family. Each ligand is synthesized and purified individually, thus limiting the size of the library to, at the most, a few dozen members. Diversity is introduced along the way via divergent synthesis. In this approach, a key advanced intermediate (enantiopure in the case of enantioselective hydrogenation) is prepared on a large scale and used to synthesize many different ligands [19a].

Burgess et al. prepared libraries of phosphine-oxazoline and *N*-heterocyclic carbene-oxazoline ligands for the enantioselective hydrogenation of arylalkenes (Scheme 36.4) [19]. The chiral P,N-ligands, initially introduced by Pfaltz, allow the formation of enantioselective versions of the Crabtree catalyst, $[Ir(COD)(Pyridine)PCy_3]^+PF_6^-$ [20]. Ten phosphine-oxazoline ligands (**2**) were prepared from the common intermediate (**1**) by three different routes [19a] and tested in the enantioselective hydrogenation of several arylalkenes [19b]. The best results (full conversion, 95% ee) were obtained with $R_1 = CHPh_2$ and $R_2 = 2\text{-}MeC_6H_4$ in the hydrogenation of *E*-1,2-diphenylpropene. The nature of the R_1 substituent was observed to be crucial, since changing from $R_1 = CHPh_2$ to $R_1 = CMePh_2$ led to poor results (12% conversion, 14% ee), thus validating the necessity to screen a set of related ligands. For the *N*-heterocyclic carbene-oxazoline, a larger library was prepared by reacting two small libraries of synthetic constituents (i.e., oxazoline electrophiles and imidazole nucleophiles) with each other [19c]. Up to 108 ligands could be generated from six oxazolines and 18 imidazoles, prepared



Scheme 36.4 Libraries of P,N- and C,N-ligands in the Ir-catalyzed enantioselective hydrogenation of unfunctionalized olefins.

via three different routes. Several ligands appeared to be quite efficient in the enantioselective hydrogenation of a range of arylalkenes. Again, the high sensitivity of the catalysis to both substituents, R^3 and R^4, was demonstrated. The carbene-oxazoline ligands appeared to be superior to their phosphine-oxazoline counterparts as they are not sensitive to air/moisture and they allow the hydrogenation to be performed under milder conditions.

Salzer et al. prepared a set of planar-chiral diphosphine ligands based on the arene chromium tricarbonyl backbone (Fig. 36.3) [21]. The straightforward four-step synthetic route allowed the preparation of 20 ligands of this family. These ligands were tested in Ru- and Rh-catalyzed enantioselective hydrogenation of various substrates, including the standard C=C substrates (dimethyl itaconate, methyl-2-acetamidocinnamate, methyl-2-acetamidoacrylate) as well as MEA-imine (1-(methoxymethyl)ethylidene-methylethylaniline) and ethyl pyruvate. Moderate conversions and ee-values were obtained.

A small library of ten chiral amino-alcohol ligands was assembled by Pericàs et al. [22]. The synthesis involved a three-step route starting from enantiomerically pure phenylglycidol obtained by Sharpless epoxidation. Diversity can be introduced in two positions, by varying the protecting group of the primary alcohol or the alkylating reagent of the amino group (Scheme 36.5). These ligands were tested in the Ru-catalyzed transfer hydrogenation of aromatic ketones, leading to an ee-value of up to 76% in the case of acetophenone.

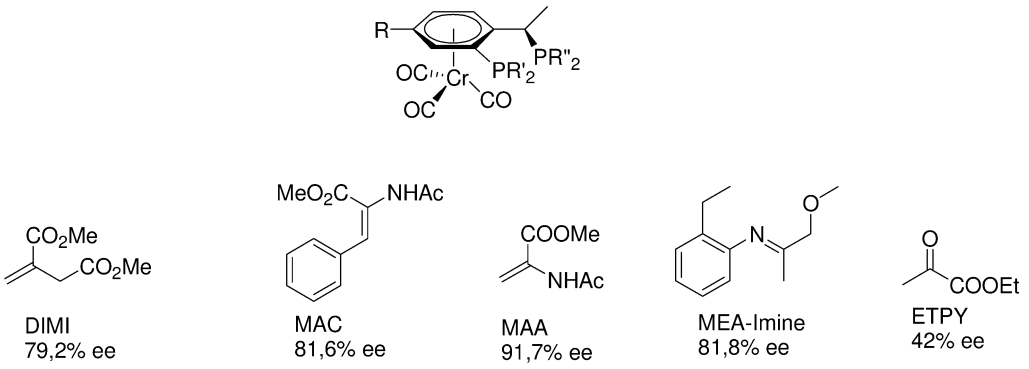
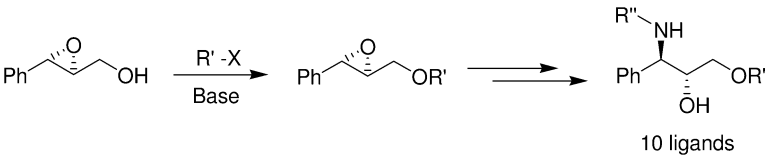
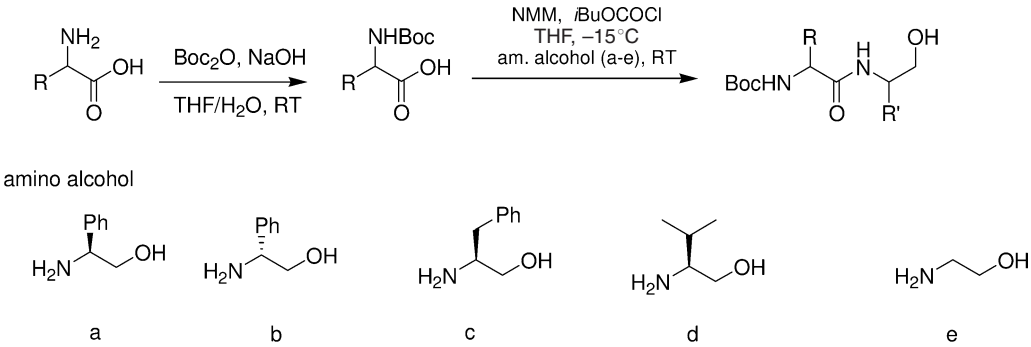


Fig. 36.3 Library of planar-chiral diphosphine ligands.



Scheme 36.5 Library of aminoalcohol ligands.

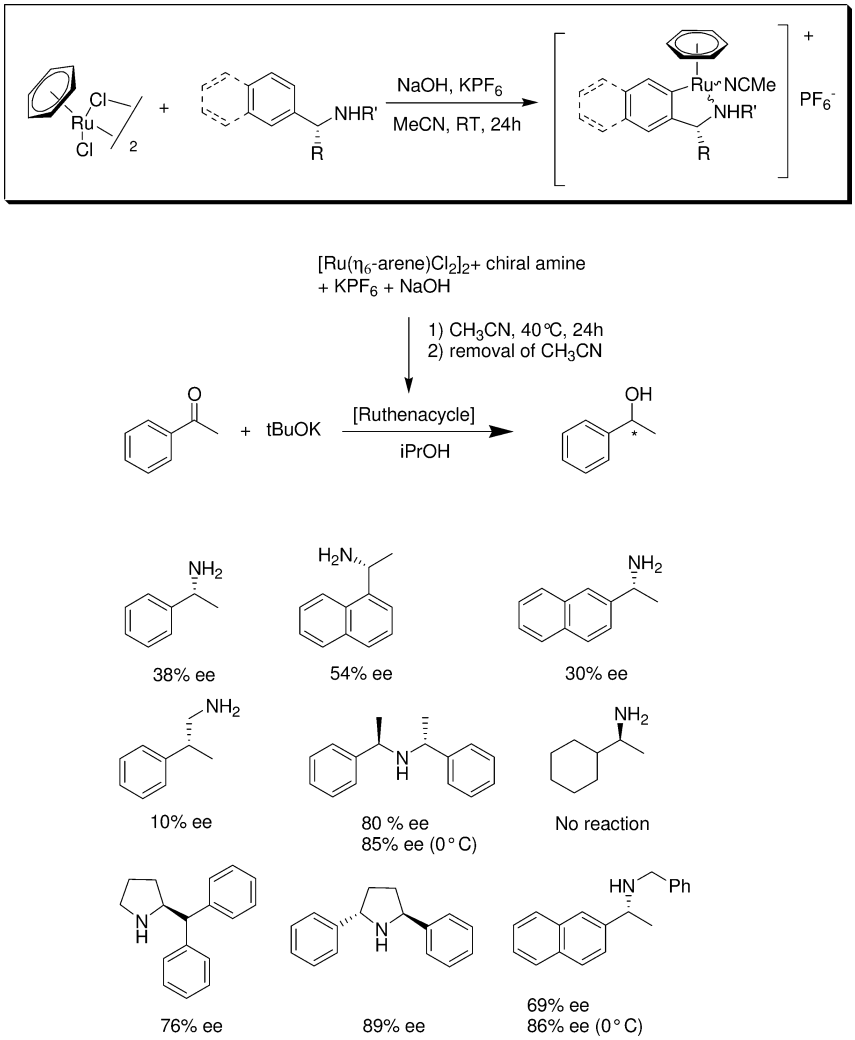
Adolfsson et al. prepared a library of modular dipeptide-analogue ligands [23]. The 45 members of this library were synthesized manually, via a two-step straightforward synthesis, by combining nine amino acids with five amino alcohols (Scheme 36.6). The library was tested in the Ru-catalyzed transfer hydrogenation of aromatic ketones with isopropanol as the hydrogen source. With few exceptions, all the ligands gave good enantioselectivities (>85% ee), whilst the catalytic activity varied significantly within the library. Steric hindrance appeared to be the most important parameter influencing the activity. The influence of



Scheme 36.6 Library of ligands for transfer hydrogenation.

the *N*-terminal protecting group on the ee-value was also investigated, with ligands based on N-Boc-protected alanine and phenylglycinol proving superior.

Pfeffer, de Vries and coworkers developed the use of ruthenacycles, based on chiral aromatic amines as enantioselective transfer hydrogenation catalysts. These authors were able to develop an automated protocol to produce these catalysts by reacting ligand and metal precursor in the presence of base, KPF_6 in CH_3CN. After removal of the solvent, isopropanol was added followed by the substrate, acetophenone, and KO*t*Bu. In this way, a library of eight chiral

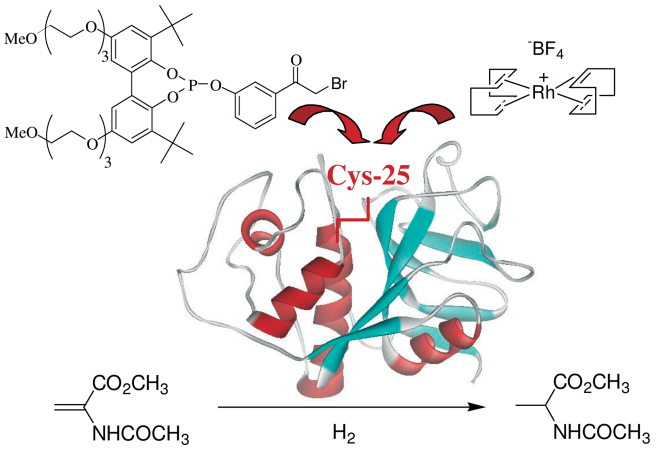


Scheme 36.7 Parallel ruthenacycle preparation and screening in asymmetric transfer hydrogenation.

amines and two metal precursors was screened in a single run. The best results were obtained with 2,5-diphenylpyrrolidine as ligand and $[Ru(benzene)Cl_2]_2$ as metal precursor (Scheme 36.7) [24].

One limiting factor in all approaches towards ligand libraries is the limited availability of chiral starting materials. Thus, several groups have turned towards Nature to obtain a boundless supply of chiral materials. In a seminal approach, Whitesides et al. attached a nonchiral rhodium–bisphosphine complex to biotin. This conjugate was subsequently complexed to the protein avidin. Enantioselective hydrogenation of 2-acetamido-acrylate using this superstructure proceeded with 44% ee [25]. Ward has subsequently refined this concept by using genetically modified forms of avidin, which resulted in a catalyst that could hydrogenate the same substrate with 96% ee [26]. In order to broaden this concept, several groups have developed approaches to covalently modify enzymes with metal catalysts. It is clear that with current capabilities for the genetic modification of proteins, very large libraries of enzymes could, in principle, become available. Reetz has reported the attachment of catalysts and ligands to papain using a maleimide linker [27]; the catalysts proved to be active, but the enantioselectivity in these reactions remained at very low levels. Reetz also reported the attachment of a bisphosphine ligand, though without further catalytic use.

De Vries and coworkers managed to attach a bulky phosphite ligand to Cys25 in papain via a phenacyl bromide linker (Scheme 36.8). Treatment of this modified enzyme with $[Rh(COD)_2]BF_4$ followed by purification gave an enzyme containing exactly one rhodium atom (ES-MS). This construct was an active hydrogenation catalyst capable of completely hydrogenating methyl 2-acetamidoacrylate in an aqueous phosphate buffer at 12 bar overnight at a SCR of 800. However, the hydrogenation product was racemic [28].



Scheme 36.8 Papain-bound rhodium complex as a hydrogenation catalyst.

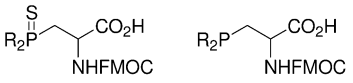
36.3.2
Automated Synthesis of Ligand Libraries

In all of the previous examples, the library of ligands was assembled by synthesizing one ligand at a time using traditional synthetic methods. This tedious approach constitutes a major bottleneck for the application of HTE in homogeneous hydrogenation. Drawing inspiration from the techniques used in combinatorial chemistry for the automated synthesis of large libraries of small organic molecules, a few groups have developed a number of new solutions based on solid-phase synthesis to prepare libraries of ligands.

Gilbertson used the diversity available from the use of the 20 natural amino acids in peptides by creating two new phosphine-containing amino acids **9a** and **b**; these were incorporated in the form of their thiooxides **8** into random peptide sequences (Fig. 36.4) [29].

Using the Multipin method, Gilbertson then synthesized 27 undecapeptides on solid phase, which were presumed to have a helical conformation. This was induced by frequent use of the α-alkylated amino acid aminoisobutyric acid. The phosphine-thiooxide-containing residues were positioned in the i and $i + 4$ positions, which would lead to the two phosphines being adjacent in the helical peptide chain. In addition, Gilbertson synthesized 36 peptides containing phosphines in the i and $i + 1$ positions.

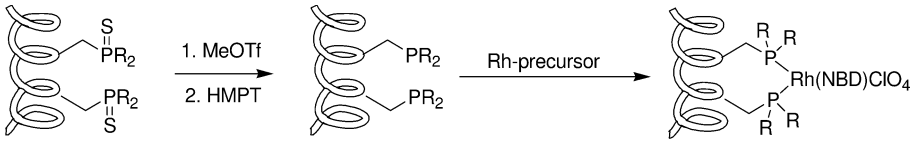
When the peptide synthesis was complete, the phosphines were deprotected by sequential treatment with MeOTf and HMPT (Scheme 36.9). Addition of the rhodium precursor then created the catalyst library, which was screened, on the pin in the enantioselective hydrogenation of methyl-2-acetamidoacrylate (see Scheme 36.10). Unfortunately, this beautiful concept was poorly rewarded with rather low enantioselectivities.



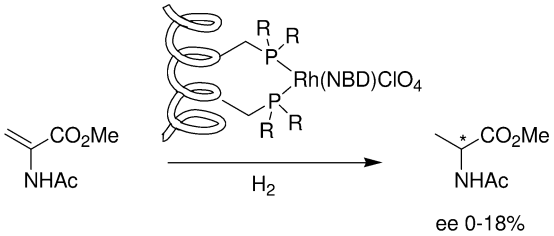
8a R = Ph
8b R = Cy

9a R = Ph
9b R = Cy

Fig. 36.4 Phosphorus-containing amino acids.



Scheme 36.9 Libraries of phosphine-containing helical undecapeptides.



Scheme 36.10 Enantioselective hydrogenation using libraries of peptide-based rhodium catalysts.

There is one more report on the synthesis of a library of phosphorus ligands on solid phase. Waldmann et al. prepared a library of phosphoramidites on beads (Fig. 36.5), but these were only applied in enantioselective C–C-bond formation. In fact, as two ligands need to be bound to the catalyst, the use of an immobilized monodentate ligands should most likely be avoided unless the proximity between the ligands is sufficiently close. In addition, crosslinking by the metal may have a negative impact on the permeability of the polymer for the substrate.

The screening of catalysts attached to beads is not a straightforward task [30]. The presence of the polymeric support in the vicinity of the catalytic site can have a significant influence on its activity and selectivity. If, ultimately, the goal is to prepare homogeneous catalysts, important discrepancies can be faced between the performances obtained with the supported catalysts and those obtained with its soluble counterpart, which places in doubt the validity of screening ligands on supports [31]. There is also the problem of slow diffusion of the reagents into and products out of the beads affecting the outcome of the catalysis. De Bellefon believes that mass-transport limitation was indeed the main reason for the low ee-values obtained by Gilbertson [32]. Ranking the catalysts attached to a polymer can also be problematic. A rigorous comparison of the activity of two catalysts is possible only if both have the same number of active sites. For supported catalysts, this quantity is difficult to evaluate as most of the solution-phase analytical techniques can no longer be applied. In order to avoid these difficulties, it would be highly desirable to design a rapid, automated protocol for the synthesis of libraries

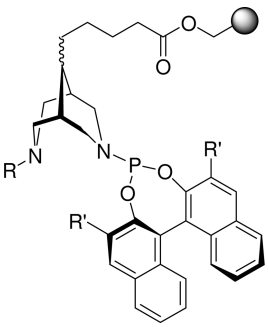
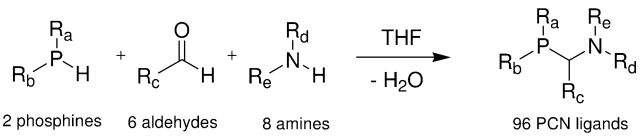


Fig. 36.5 Library of immobilized phosphoramidite ligands.

of ligands in solution. This can be accomplished either via solid-phase synthesis, with the ultimate step being cleavage of the ligand from the bead, or directly via solution-phase synthesis. If examples of libraries of ligands in solution can be found in the literature [33], almost none is related to hydrogenation, for the simple reason that most of the ligands used in hydrogenation are phosphorus-based and involve lengthy syntheses, which are difficult to adapt to automation. Not surprisingly, only two examples have been identified for the rapid automated synthesis of large libraries of phosphorus ligands in solution.

While the first synthesis does not pertain to hydrogenation, it is worthy of mention as it involves a three-component condensation reaction leading directly to the formation of ligands with a purity (wt%) ranging from 79 to 95%. Lapointe prepared a library of 96 aminomethylphosphines by condensation of a secondary phosphine, an arylaldehyde and a primary or secondary amine (2 phosphines×6 aldehydes×8 amines) (Scheme 36.11) [34]. The reaction is high-yielding, obviating the need for purification. One ligand prepared via the library protocol was used successfully to synthesize a Pd complex, with the yield being only slightly lower than for a pure ligand. No examples of the use of this library of ligands in catalysis have been reported.

The second example of rapid automated synthesis of large libraries of phosphorus ligands in solution was reported by DSM. Feringa/Minnaard/De Vries developed the use of simple BINOL-based monodentate phosphoramidites as ligands for enantioselective hydrogenation (see Chapter 28) [35]. Since these ligands are easily prepared, a protocol for their automated synthesis in solution became an attainable goal. The first step of the most common phosphoramidite synthesis – the formation of the phosphochloridite from the BINOL or diol and PCl_3 – proceeds essentially quantitatively, and purification is effected by distilling off excess PCl_3. The robotic synthesis can thus begin with stock solutions of the stable phosphochloridites, leaving only a single synthetic step. This last step usually yields the ligands in a purity with respect to phosphorus of 90–95%, the main contaminant being triethylammonium chloride. Thus, it is clear that the final purification is the only hurdle that needs to be taken in order to effect this robotic ligand synthesis. Although parallel column chromatography is feasible, this solution is not very appealing. To verify if purification is really necessary, a known phosphoramidite (derived from (*R*)-2,2′-binaphthol and diethylamine) was synthesized and tested without purification in the Rh-catalyzed hydrogenation of methyl-2-acetamidocinnamate. This led to very poor results: both conversion and enantioselectivity were substantially lower than with



Scheme 36.11 Parallel synthesis of a library of aminophosphine ligands.

the purified ligand. Since the main culprit is the presence of soluble chloride (a known catalyst inhibitor), the solvent for the ligand synthesis was switched to toluene, allowing complete removal of the chloride salt by filtration. Remarkably, the ligand purified in this manner had a very similar performance in the hydrogenation reaction as the purified ligand. This simple finding opened the door to automation. The coupling reactions between phosphochloridite and amine were performed in a 96-well microtiter plate 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. This protocol was initially tested on a set of 32 ligands, which were subsequently screened in the Rh-catalyzed enantioselective hydrogenation of two model substrates (see Fig. 36.6) [36].

Scheme 36.12 shows the results of this library of 32 phosphoramidites in the enantioselective hydrogenation at 6 bar H_2 of methyl-2-acetamido-cinnamate and methyl-*Z*-3-acetamido-2-butenoate. For the first substrate, almost all members of the library led to full conversions, indicating that most ligands were formed with an acceptable degree of purity. ^{31}P-NMR revealed the presence of trace amounts of other phosphorus species that remarkably did not affect the performance of the catalyst. Best results are obtained with ligands based on piperidines, such as Pipphos (B7) and A8; in addition, two other good ligands based on secondary amines were found (A7 and C7). The enantioselectivities are on average 5% lower than with the purified ligands.

The hydrogenation of methyl-*Z*-3-acetamido-2-butenoate resulted in more surprises. Although ligand D7 based on a primary amine was known to give good results with these substrates [37], the library shows that in general all BINOL-based phosphoramidites that contain a primary amine with branching in the *α*-

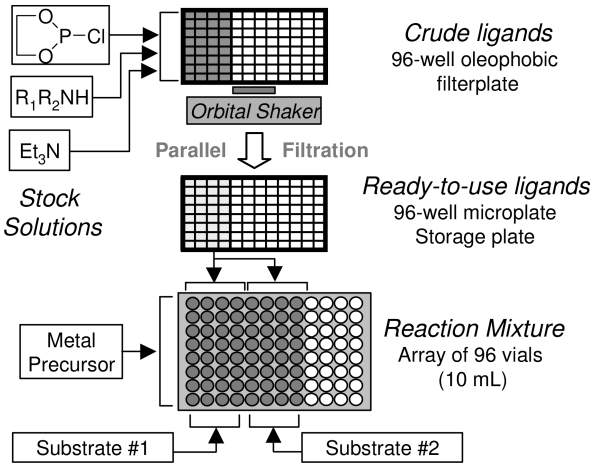
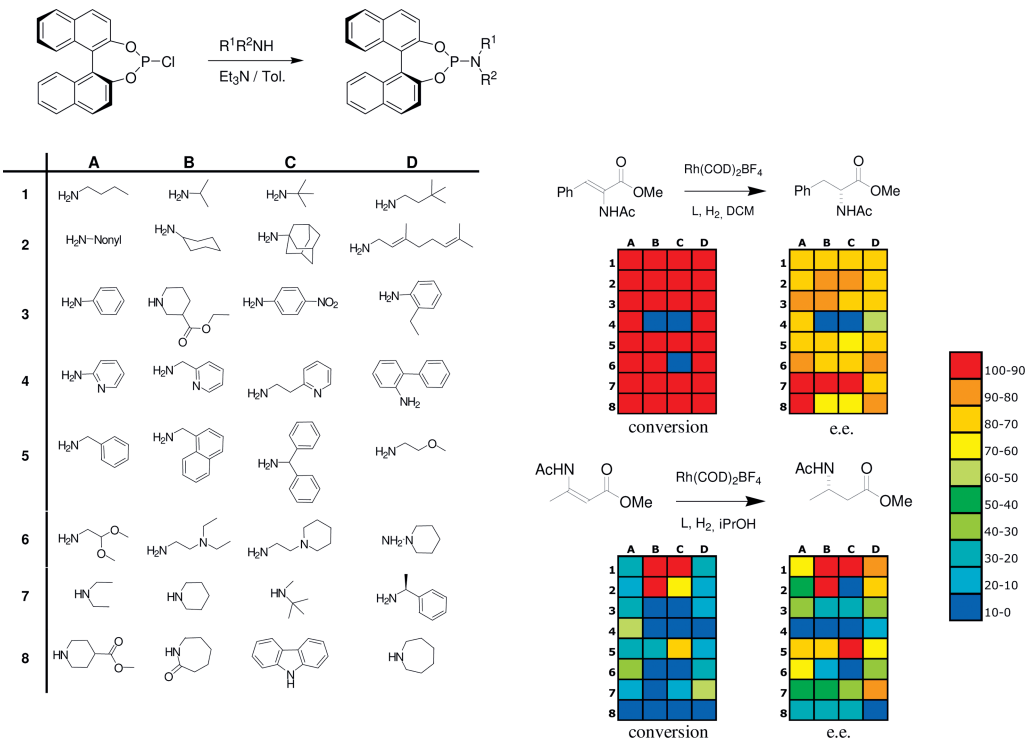


Fig. 36.6 Phosphoramidite library synthesis and screening protocol. (Reproduced by permission of the American Chemical Society from [36].)



Scheme 36.12 Parallel synthesis and screening of monodentate phosphoramidites in enantioselective hydrogenation.

Table 36.2 Comparison of library ligands with purified ligands.

Ligand	Purified ligands		Library ligands	
	Conversion [%]	ee [%]	Conversion [%]	ee [%]
A7	8	46	11	41
B1	100	95	95	92
B7	11	55	7	43
D7	96	94	51	88

position give excellent results (B1, C1, B2). A comparison of four ligands from this library with the results obtained with the purified ligands clearly shows that there is some erosion of rate and enantioselectivity due to the impurities present in the library ligands (Table 36.2). However, the relative order remains the same, and the results therefore have an excellent predictive value.

This "Instant Ligand Library" concept is now routinely used by DSM Pharma Chemicals for customer's requests.

Clearly, the method can also be used for other monodentate ligands such as phosphites. The application of this library approach to copper-catalyzed enantioselective C–C-bond formation has also been reported [38].

36.3.3 Mixtures of Chiral Monodentate Ligands

It has been established that usually two monodentate ligands (phosphoramidites, phosphites or phosphonites) are present in their rhodium-based hydrogenation catalysts. This would allow the possibility of testing catalysts based on two different monodentate ligands. Initially, this does not seem very appealing, as the suspected outcome would be the formation of a mixture of the heterocatalyst and the two homocatalysts (Scheme 36.13).

However, it is possible that the heterocatalyst 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 Feringa/Minnaard/de Vries et al. 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 [39]. In our experience, the majority of catalysts based on mixtures of monodentate ligands show a poorer performance than the individual homo-catalysts. However, in a few instances there is a positive effect.

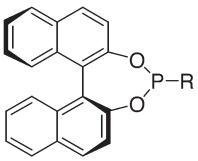
In the studies conducted by Reetz, rhodium catalysts based on mixtures of monodentate phosphites, monodentate phosphonites and combinations of the two were screened in the enantioselective hydrogenation of *α*- and *β*-*N*-acetyl-dehydroamino acid esters, enamides and dimethyl itaconate [40], and a number of the more striking positive results are listed in Table 36.3. An enhanced ee-value was found mostly 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.

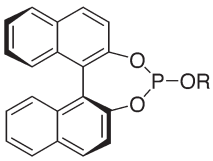
The DSM group simultaneously developed this approach using the monodentate phosphoramidites. In this research, mixtures of two phosphoramidite ligands were screened using ligands **10a–f** in the enantioselective hydrogenation of an aliphatic and an aromatic *Z*-*β*-dehydroamino acid ester (**11a** and **b**; Fig. 36.7). The results of the screening are displayed in Fig. 36.7; entries 1–6 show the results with the homo catalysts. Upon screening mixtures of these ligands, most combinations of two different ligands induced lower enantioselectivity. However, there was one marked exception: all combinations including the NH ligand **10f** led to better results (Fig. 36.7, entries 7–11) [41]. Particularly striking is the combination of ligand **10c**, which was the worst performer in the homo catalyst series in combination with **10f** (entry 9).

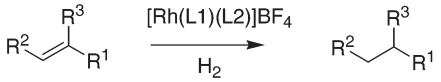
$$RhL^1L^2 \rightleftharpoons RhL^1L^1 + RhL^2L^2$$

Scheme 36.13 Mixture of catalytic complexes obtained when using mixtures of ligands.

Table 36.3 Use of mixtures of monodentate phosphonites and or phosphites in the rhodium-catalyzed hydrogenation of substituted olefins.[a)]







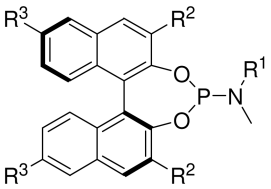
La R = CH_3
Lb R = *c*-C_6H_{11}
Lc R = $C(CH_3)_3$

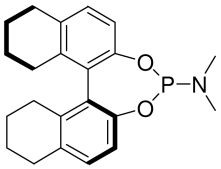
Lp R = CH_3
Lq R = 2,6-diMeC_6H_3
Lr R = 9-fluorenyl

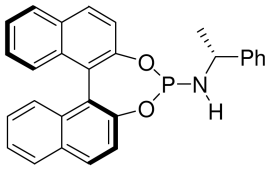
	$R^1=CO_2Me$, $R^2=H$, $R^3=NHAc$	$R^1=CO_2Me$, $R^2=Ph$, $R^3=NHAc$	$R^1=Ar$, $R^2=H$, $R^3=NHAc$	$R^1=CH_2CO_2Me$, $R^2=H$, $R^3=CO_2Me$	$R^1=Me$, $R^2=CO_2Me$, $R^3=NHAc$
La	92	90%	76%	90%	95%
Lb	92			22%	66%
Lc	93	69%	13%	57%	45%
Lp	77				75%
Lq	32				
Lr	94				
La/Lb	98	97%		89%	
La/Lc	98	99%	96%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

a) All hydrogenations performed in CH_2Cl_2. Hydrogen pressure 1.3–1.5 bar, except for *β*-dehydro amino acid esters (60 bar).
L/Rh = 2; SCR = 500 (aromatic enamides), 50 (*β*-dehydro amino acid esters) and 1000 for the other substrates.

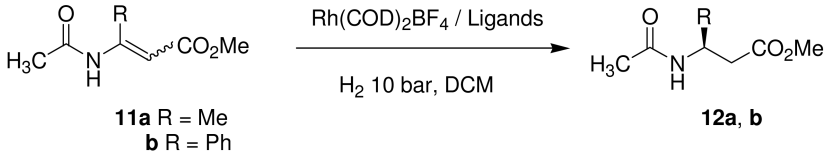
Gennari and Piarulli created a library of 16 phosphite and phosphoramidite ligands made from bisphenol and chiral alcohols and chiral amines, respectively. In addition to the homocatalysts, these authors tested 115 mixed combinations in the rhodium-catalyzed hydrogenation of methyl-2-acetamido-acrylate. Here, the picture is even more obscure, as the bisphenol can occur in two atropisomeric forms, which are not stable in the ligand, but tend to be fixed in the complex [39]. They found lower enantioselectivities using combinations of two different phosphites, or combinations of two different phosphoramidites. However, 16 combinations of phosphites with phosphoramidites were found that induced higher enantioselectivity than the "homocatalysts", whilst retaining the high rate induced by the phosphite ligands [42].







(*S*)-**10a** R^1 = Me, R^2 = R^3 = H, MonoPhos (*S*)-**10b** (*S,R*)-**10f**
(*S*)-**10c** R^1 = R^2 = Me, R^3 = H
(*S*)-**10d** R^1 = Me, R^2 = H, R^3 = Br
(*S*)-**10e** R^1 = Bn, R^2 = R^3 = H



11a R = Me
b R = Ph

12a, **b**

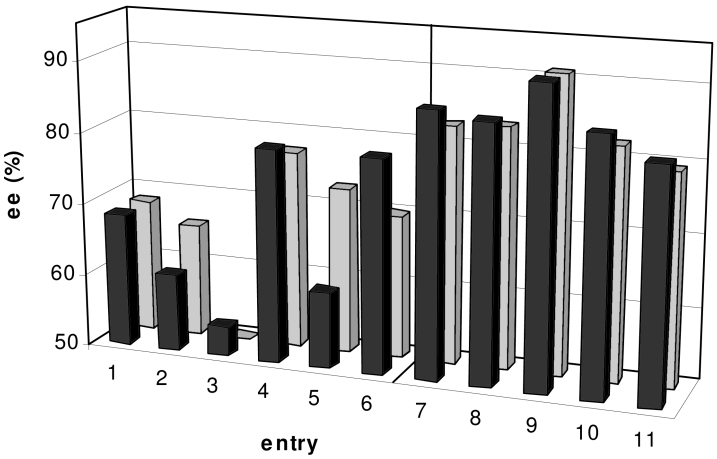


Fig. 36.7 Rh/phosphoramidite-catalyzed hydrogenations using homo (entries 1–6) and hetero (entries 7–11) catalysts (black bars: results with **11a**, light grey bars: results with **11b**; 1=**10a**, 2=**10b**, 3=**10c**, 4=**10d**, 5=**10e**, 6=**10f**, 7=**10f**+**10a**, 8=**10f**+**10b**, 9=**10f**+**10c**, 10=**10f**+**10d**, 11=**10f**+**10e**). (Reprinted by permission of the RSC from [41].)

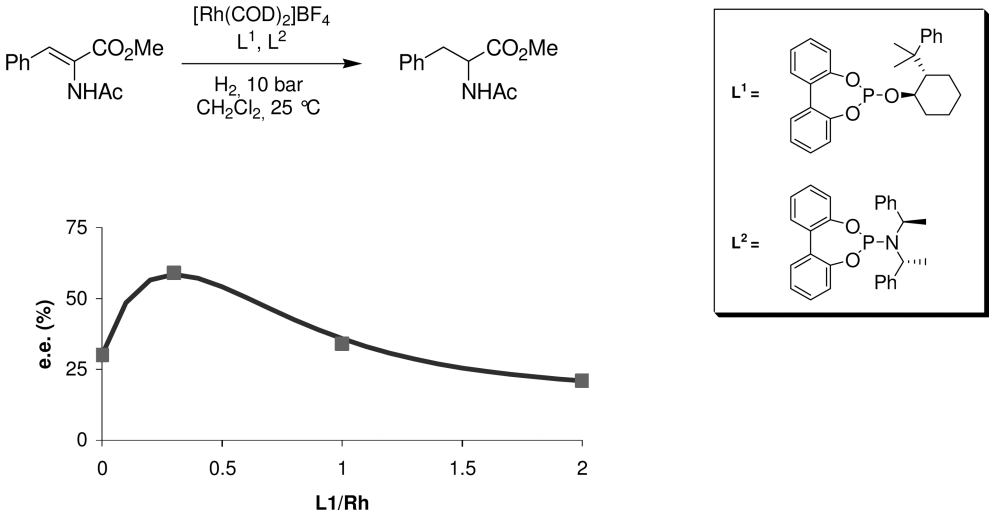


Fig. 36.8 ee-values obtained in the Rh-catalyzed hydrogenation of methyl-2-acetamidocinnamate, plotted against the ligand ratio (the ratio $(L^1 + L^2)$/Rh always remains 2).

The simple concept of mixtures of monodentate ligand allows one to generate large libraries of catalysts. For instance, 10 ligands can lead to 55 possible combinations, and a library of 96 ligands to 4656 combinations. Such as finding greatly increases the chance of identifying a catalyst that will induce high enantioselectivity in the hydrogenation of the substrate of choice [43].

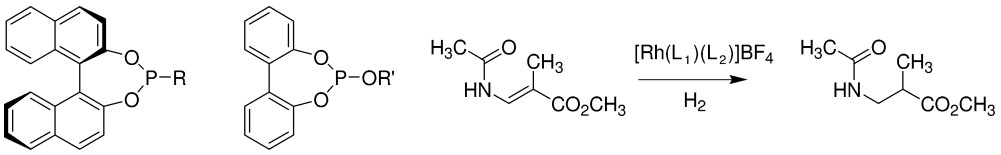
In a collaboration between the Gennari/Piarulli group and the DSM group, another parameter in the ligand mixture concept – namely the ratio between the two ligands – was explored [44]. These groups were able to show that a 1:1 mixture of the two monodentate ligands L^1 and L^2 (whilst keeping the (L^1+L^2)/Rh ratio equal to 2) was not necessarily the best ratio. The best ee-value for the hydrogenation of methyl-2-acetamidocinnamate was obtained for a ratio $L^1:L^2$ equal to 0.25:1.75 (59% ee instead of the 34% ee obtained with the 1:1 mixture; Fig. 36.4). This finding can be explained by the different activities of the less enantioselective homo complexes RhL^1L^1 and RhL^2L^2, under the assumption that the hetero complex is more enantioselective than the homo complexes (i.e., a beneficial effect of the ligand mixture). In this case, RhL^1L^1 is a fast catalyst and RhL^2L^2 is slow, both relatively to the hetero complex. Thus, using an excess of L^2 strongly minimizes the amount of the faster RhL^1L^1. Although the homo complex RhL^2L^2 is the major complex present in solution, this is inconsequential as it has a low activity. The observed enantioselectivity is thus mainly due to the catalytic action of the hetero complex – that is, the most enantioselective catalyst. The ratio $L^1:L^2$ in the case of mixtures of ligands must, therefore, be considered as an important parameter that needs to be fine-tuned.

36.3.4
Mixtures of Chiral Monodentate Ligands 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 reported this approach using mixtures of chiral monodentate phosphites or phosphonites with nonchiral phosphines in enantioselective hydrogenations. This led to large changes in the enantioselectivity of the reaction; in one case, a reversal of enantioselectivity was observed from 92% (*S*) to 59% (*R*) [40b]. In a more recent finding, Reetz and Li describe the use of mixtures of chiral phosphonites and a biphenyl-based phosphite in the rhodium-catalyzed enantioselective 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 **13a** to a 1:1 mixture of **13a** and **14a** or a 1:1 mixture of **13a** and **14b** (Scheme 36.14). In addition, it was found that in several cases the enantioselectivity could be improved by using mixtures of either **13a** or **13b** with an achiral monodentate phosphine or phosphite [45].

Similar mixed-ligand hydrogenations, based upon the combination of nonchiral phosphines (e.g., PPh_3) and chiral phosphoramidites were independently developed by DSM in search of an effective and economic catalyst for the enantioselective hydrogenation of an *α*-alkylated cinnamic acid derivative (Scheme 36.15). The product is a key intermediate in the synthesis of the renin inhibitor Aliskiren [46]. The enantioselective hydrogenation of this class of substrate has been investigated only minimally, although more recently Walphos (a ferrocene-based bisphosphine) was found to provide good results with this particular substrate, whereas other well-known bisphosphine ligands were not suitable [47].

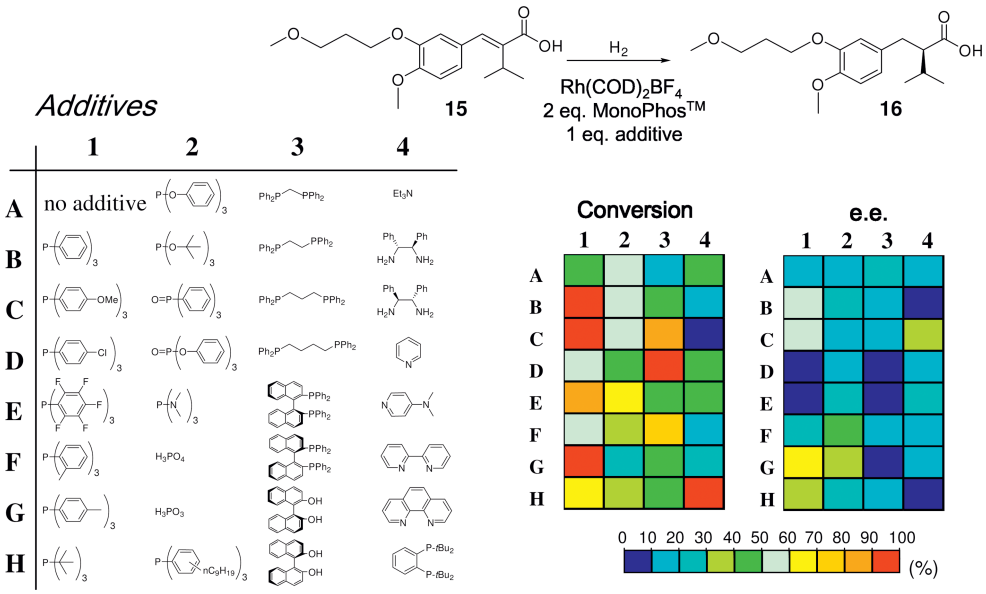
The use of 2 equiv. of MonoPhos (**10a**) in the rhodium-catalyzed enantioselective hydrogenation of the key cinnamic acid derivative **15** resulted in the formation of **16** in 50% conversion and 20% ee after 5 h in isopropanol at 60 °C and 25 bar of hydrogen. Other phosphoramidites, such as the sterically demanding ligand **10c**, resulted in slightly better activity and enantioselectivity. In seeking a



13a R = *t*Bu
13b R = OMe

14a R = Me
14b R = CH_2Ph

Scheme 36.14 Use of mixtures of ligands improves enantioselectivity (Rh:L^1;L^2:S=1:1:1:50, 60 bar H_2, CH_2Cl_2, r.t., 20 h).



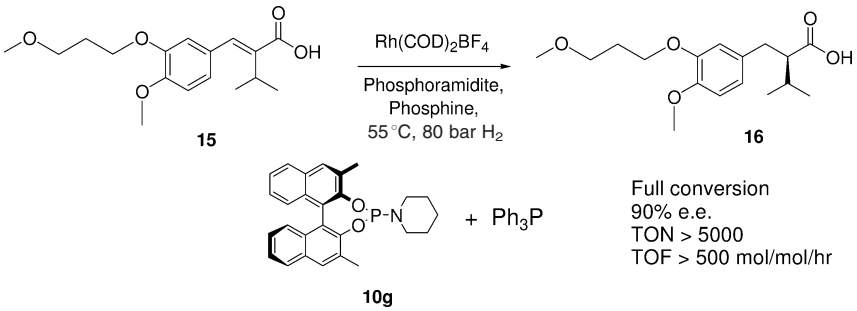
Scheme 36.15 Screening additives for the enantioselective hydrogenation of α-alkylcinnamic acids.

method to increase the reaction rate, a range of additives was tested, largely with a view to increasing electron density on rhodium, as this is known to be the main parameter affecting the rate of oxidative addition of hydrogen, the rate-determining step [48].

The effect of a range of additives on enantioselective hydrogenation of the cinnamic acid precursor is shown in Scheme 36.15. One trend that emerges from this screen is the positive effect of the monodentate phosphines, in particular, tri-*p*-tolylphosphine.

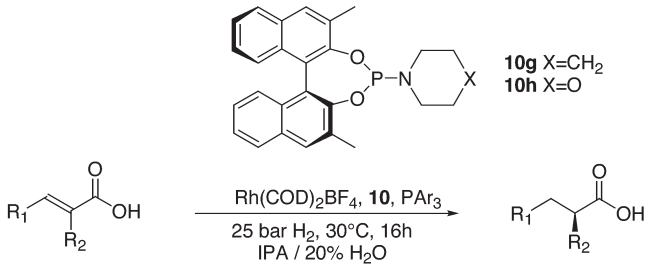
Further library screening resulted in finding an even better-performing 3,3′-dimethyl-substituted ligand **10g** (Scheme 36.16). The reaction temperature is a compromise between rate and enantioselectivity. In a solvent screen, a mixture of isopropanol and water was found to give the best results. At 55 °C, the reaction is fast, allowing an economic SCR of 5000. The enantioselectivity of the product is 90% (Scheme 36.16) [49]. In this case, the use of an achiral phosphine as additive increased not only the enantioselectivity rather drastically, but also the rate of hydrogenation 100-fold. This is a clear example where the power of HTE and random screening led to remarkable results that, otherwise, would never have been found. This reaction is now performed on ton-scale by DSM Pharma Chemicals.

The Feringa/Minnaard/de Vries group has further extended the scope of this cinnamate hydrogenation (Table 36.4) [50]. In all cases, a pronounced effect of the added triarylphosphine was found; usually, the best results were obtained with a combination of ligands **10g** or **10h** in combination with tri-*ortho*-tolyl-



Scheme 36.16 Enantioselective hydrogenation of the Aliskiren intermediate.

Table 36.4 Asymmetric hydrogenation of acrylates and cinnamates [a, b)]



17 R_1=Me, R_2=Me
18 R_1=Ph, R_2=Me
19 R_1=Ph, R_2=*i*-Pr
20 R_1=3,4-MeOPh, R_2=*i*-Pr
21 R_1=4-CF_3Ph, R_2=*i*-Pr
22 R_1=Ph, R_2=Ph

23 R_1=Me, R_2=Me
24 R_1=Ph, R_2=Me
25 R_1=Ph, R_2=*i*-Pr
26 R_1=3,4-MeOPh, R_2=*i*-Pr
27 R_1=4-CF_3Ph, R_2=*i*-Pr
28 R_1=Ph, R_2=Ph

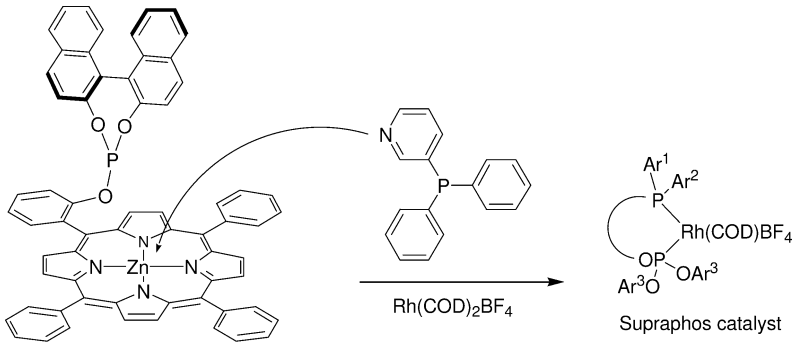
Entry	Substrate	Product	Ligand	Ar	ee [c)]
1	**17**	**23**	**10h**	*m*-Tol	87%
2	**18**	**24**	**10g**	–	2% [d)]
3	**18**	**24**	**10g**	Ph	88%
4	**19**	**24**	**10g**	*o*-Tol	97%
2	**19**	**25**	**10g**	*o*-Tol	99 [%e)]
3	**20**	**26**	**10g**	Ph	92%
4	**21**	**27**	**10g**	*m*-Tol	95%
5 [f)]	**22**	**28**	**10g**	*o*-Tol	95%

a) Reaction conditions: 1 mmol substrate in 4 mL solvent with 0.01 mmol $Rh(COD)_2BF_4$, 0.02 mmol phosphoramidite and 0.01 mmol PR_3.
b) Reactions 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 performed at 60 °C.

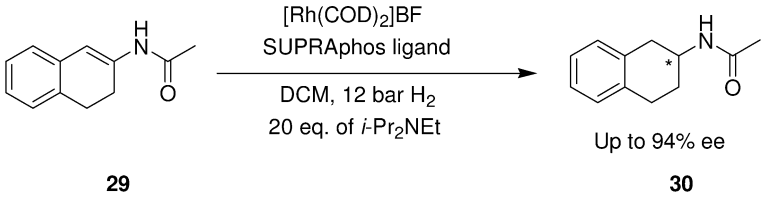
phosphine. In practice, the ratio Rh : phosphoramidite : $Ar_3P = 1:2:1$ gives the best results. NMR studies revealed that under these conditions the mixed complex [Rh(Phosphoramidite)(PAr_3)(COD)]BF_4 plus a substantial amount of [Rh(Phosphoramidite)$_2$(COD)]BF_4 is present. However, this latter complex leads to a catalyst, which is 100-fold slower than the mixed complex, and hence it has no effect. If, on the contrary, a ratio of 1:1:1 is used, the NMR shows substantial amounts of [Rh(PAr_3)$_2$(COD)]BF_4, a fast catalyst leading to racemic product.

36.3.5
Supramolecular Approaches to Ligand Libraries

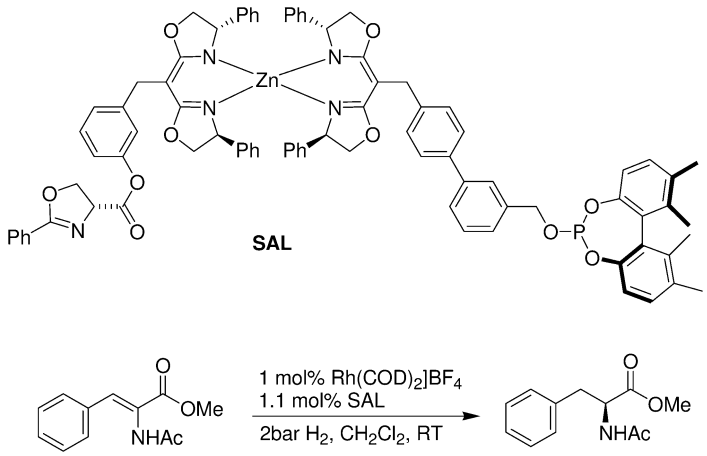
Having a modular ligand structure is a prerequisite for the preparation of libraries. This means that it should be possible to introduce the diversity at a late stage of the synthesis. For bidentate ligands, the preference would be to have two highly diverse building blocks that can be joined in the last stage of the synthesis. This coupling does not necessarily have to be through a covalent bond. Two research groups have developed this supramolecular concept quite successfully. Reek et al. have introduced the Supraphos concept, in which a library of bidentate phosphine phosphite ligands can be made from two building blocks: a zinc tetraphenylporphyrine, substituted with a phosphite group on one of the arene rings; and a phosphine (or phosphite) containing a pyridine group



Scheme 36.17 The Supraphos concept for ligand libraries.



Scheme 36.18 Use of a supramolecular ligand library in enantioselective hydrogenation.



Scheme 36.19 Use of self-assembled ligands in enantioselective hydrogenation.

capable of binding to the zinc of the porphyrine. In this way, the two building blocks can self-assemble *in situ* to form a bidentate ligand (Scheme 36.17) [51].

In collaboration with the DSM group, this concept was applied in enantioselective hydrogenation. Using a library of seven different phosphite-containing zinc porphyrines and 14 different nitrogen base-containing phosphines, a single hit was found in the rhodium-catalyzed enantioselective hydrogenation of 2-acetamido-3,4-dihydro-naphthalene. With the combination made from the (*S*)-BINOL-based porphyrine-phosphite and 3-pyridyldiphenylphosphine, the product was obtained in 94% ee, whereas the other ligands induced ee-values up to 56% [52]. Previous results with rhodium catalysts led to only 72% ee in the hydrogenation of this substrate, although with ruthenium catalysts 90% ee was obtained.

A similar approach has been reported by Takacs et al., who used the principle of self-assembly of two bifunctional units around a metal, typically zinc [53]. Each unit contains a ligating group, such as a phosphine, a phosphite or an oxazoline, that may or may not be chiral, which is linked via an aryl group or a biphenyl group onto a chiral bisoxazoline. The coordination of the two bisoxazoline units to the metal creates a bidentate ligand. In this way, these authors created a library of $10 \times 11 = 110$ different bidentate ligands that were tested in the enantioselective hydrogenation of methyl-2-acetamidocinnamate at 2 bar hydrogen pressure (an example is shown in Scheme 36.19). Enantioselectivities of up to 82% were obtained.

The use of supramolecular ligand libraries in homogeneous catalysis was reviewed by Breit [54].

36.4 Methodology for Testing Catalysts

Once a library has been produced, it must be screened for the desired properties. In catalysis, this property is of course the ability of the catalyst to catalyze a given transformation. Consequently, the screen consists of submitting all members of the catalyst library to a set of reagents and observing whether the desired products are selectively formed at an acceptable rate. As mentioned previously, the screening of pooled catalysts is rare, and high-throughput screening mostly involves the use of parallel reactors where each vessel of the reactor is filled with one single catalytic species. At an early stage, major chemical companies such as DuPont, Shell and DSM had begun the development of reactors for multiple reactions to speed up catalysis research for bulk chemicals and polymers, often in cooperation with fine-mechanical companies. Later, companies which specialized in combinatorial chemistry and catalysis (e.g., Symyx, Avantium and HTE) developed their own machinery, and some of this equipment is now commercially available. For hydrogenation reactions, these HTE reactors may consist of between eight and 348 high-pressure vessels. The equipment capable of handling these high numbers is often based on the use of a titer well-plate, confined in a pressure chamber. The following machines are useful for batch hydrogenations [55]:

- Parr MRS Series 5000: six vessels, independent P (up to 200 bar) and T (up to 300 °C), magnetic stirring.
- Argonaut Endeavor™: eight vessels, independent P (up to 30 bar) and T (up to 200 °C), overhead stirring.
- Amtec SPR16: 16 vessels, independent P (up to 150 bar) and T (up to 250 °C), overhead stirring.
- Chemspeed Autoplant A100: 40 vessels, independent P (up to 100 bar) and T (–20 to 250 °C), overhead stirring.
- Premex A96: custom-made for DSM, now commercially available, 96 vessels, same P (up to 100 bar) and T (up to 200 °C), magnetic stirring.

This list is not exhaustive, as it is beyond the scope of this chapter to review all the hardware available. Here, we would rather focus on original approaches to accelerate the testing of catalysts as, for example, that followed by de Bellefon [32, 56]. This group designed two systems for the fast serial testing of hydrogenation catalysts. While all the commercially available parallel reactors are batch reactors, de Bellefon uses a continuous flow-through, high-pressure reactor. The various catalyst/substrate/H_2 mixtures to be tested are injected by pulses into the reactor. The pulses are carried by a continuous liquid flow through the reactor, and the products collected at the outlet for analysis. In this set-up, a micromixer is used to insure the formation of a stable foam (H_2/aqueous solution of water-soluble catalyst) with small gas bubbles (ca. 200 μm average diameter), thus avoiding any mass-transport limitations [32]. By using this system, de Bellefon et al. were able very quickly to collect large amounts of kinetic data for

the enantioselective hydrogenation of methyl-2-acetamido-cinnamate by Rh/(*S,S*)-BDPPTS [the sulfonated analogue of the well-known BDPP (2,3-bis-diphenylphosphinobutane)]. A total of 214 experiments was carried out with a throughput testing frequency (i.e., the number of experiment carried out per unit of time) of 15 per day [56b]. In a subsequent set-up, de Bellefon used a mesh flow micro-reactor for the fast screening of a library of 20 hydrogenation catalysts [56a]. The main part of the reactor is a micro-contactor that ensures good contact between the two phases (liquid–gas), without agitation. The reactor can be fed continuously with mixtures of catalyst (as little as 10 nmol) and substrate under H_2 pressure, thus allowing a rapid screening of the catalyst library. In case of catalysts with low activities, the reaction time is increased by reducing the flow rate of the carrier solvent, or eventually by reducing to 0. Up to 20 chiral diphosphine/Rh complexes have been evaluated for the enantioselective hydrogenation of methyl-2-acetamido-cinnamate, and a fairly good agreement between the published and measured ee-values was obtained.

Another concept related to accelerated testing was introduced by Kagan in 1998 [57]. Instead of testing a large number of different catalysts, this procedure allows the rapid estimation of the scope of a given catalyst. The idea was to test a catalytic system with a set of different substrates in one single pot. The method is valid if the products do not interfere with the catalyst (i.e., there is no autoinduction). Otherwise, the only requirement is an analytical method capable of distinguishing between all species (including enantiomers in case of enantioselective catalysis) eventually present in the reaction mixture. Kagan applied this method to the enantioselective diborane reduction of ketones, catalyzed by oxazaborolidine, and was able to test five substrates at once. Later, Feringa/Minnaard/de Vries et al. used the same idea in enantioselective hydrogenation, and were able to test up to eight *N*-acyl enamides with Rh/monodentate phosphoramidites in one pot [58]. This method is rather simple to put in place, and permits rapid assessment of the substrate scope of a catalyst.

36.5 High-Throughput Analysis

As we have seen so far, libraries of hydrogenation catalysts are never composed of more than a few dozen members, up to 100 to 200 at the most. Consequently, modern analytical equipment such as gas chromatography (GC) or high-performance liquid chromatography (HPLC) equipped with an auto-sampler or even flow-through NMR systems are sufficient to handle the analysis of the entire library. Nevertheless, a few groups have initiated research towards the development of fast, sometimes parallel, analytical procedures. A few reviews have appeared on this subject [59]. Here, we will concentrate on the methods developed to analyze hydrogenation reactions, or methods that could likely be applied.

Crabtree et al. investigated the use of reactive dyes that change color upon undergoing catalytic reaction [60]. Two new dyes containing a C=C or C=N bond were

synthesized so that, upon reduction of the double bond, they would lose their coloration. The two dyes were used as substrate for the screening of a small library of hydrosilylation catalysts, and allowed rapid visual identification of the fastest catalyst. Clearly, these dyes may also be used in hydrogenation reactions.

Mioskowski et al. used immunoassays for the high-throughput analysis of a library of 88 catalysts for the enantioselective transfer hydrogenation of benzoyl formic acid (BF) [61]. The library was prepared by combining a set of 22 chiral diamine ligands with four metal precursors. Yields and ee-values were determined by competitive enzyme immunoassays (EIA), using two solid-supported monoclonal antibodies: mAb-15, which binds both enantiomers; and m-Ab-8, which exhibits high stereoselectivity towards (*S*)-mandelic acid (MA). After automated sample preparation, the activity and enantioselectivity of all library members could be measured in parallel with a plate absorbance reader. A total of 42 representative samples was also analyzed by HPLC. A good correlation between HPLC and EIA was obtained (average error in ee-value ca. ±9%). The best catalyst identified allowed quantitative reduction of BF to MA with an enantiomeric excess of 81%.

Morken et al. used high-throughput ^{13}C-NMR measurements to rapidly screen for the activity and enantioselectivity of a library of 30 catalysts in the enantioselective transfer hydrogenation of dialkyl ketones [62]. The idea was based on the fact that enantiotopic groups are rendered diastereotopic upon formation of a neighboring chiral center and consequently can be distinguished by NMR. The group prepared a ^{13}C-enriched ketone containing the requisite enantiotopic group attached to a stable stereocenter, and tested it as a substrate in Ru-catalyzed enantioselective transfer hydrogenation. The results obtained by NMR compared well with those obtained by GC (± 3% variation in ee-value). The best catalyst was based on hexamethylbenzene-$RuCl_2$ dimer and simple phenylglycinol.

Van Leeuwen et al. designed a high-throughput screening method based on IR spectroscopy to rapidly identify enantioselective hydrogen-transfer catalysts for acetophenone [63]. The idea was to screen for the reverse reaction – that is, the dehydrogenation of 1-phenylethanol. The difference in reaction rate between the (*R*)- or the (*S*)-alcohol is a measure of the enantioselectivity, and can be determined rapidly by infra-red monitoring of the CO group of both the reagent (acetone) and the product (acetophenone). The method was tested with two known catalysts, and appeared to provide quite accurate measurements of the ee-values.

36.6 Conclusions

The use of combinatorial and HTE methods in homogeneous hydrogenation has blossomed over the past five years. This has been fuelled first by the urgent need to identify useful catalysts for the production of fine chemicals, in particular enantiopure pharma intermediates. The second impetus came from academia, where many investigators realized that, with regard to enantioselective cat-

alysis, ligand design is a highly elusive concept. Thus, those workers in academia began to seek ways of increasing the chances of hitting the "right" ligand, inspired by the successes of combinatorial chemistry.

Although the introduction of automation in the laboratory created the possibility for high-throughput screening, this itself was not enough. The need to create large ligand libraries has induced many breakthroughs, such as the concept of modularity, monodentate chiral ligands, mixtures of ligands, supramolecular ligand libraries, and enzyme–metal conjugates. Moreover, new concepts for rapid testing have evolved, such as the flow systems.

HTE should never be considered as a mindless exercise to identify a catalyst. Rather, the design of a set of experiments requires a good overview of what really determines the diversity space for this particular reaction. For this reason, HTE will always remain linked with areas of more classical research, such as mechanistic studies.

Future challenges of major interest will be the creation of new catalysts and ligand types, and the identification of new catalytic reactions. While HTE can clearly be used to speed up this research, the large number of experiments associated with HTE has led in the past – and will continue to lead in the future – to totally unexpected findings. Ultimately, further applications outside the area of enantioselective catalysis are also expected.

Abbreviations

BF	benzoyl formic acid
EIA	enzyme immunoassay
EMS	electrospray mass spectrometry
GC	gas chromatography
HPLC	high-performance liquid chromatography
HTE	high-throughput experimentation
MA	mandelic acid
mAb	monoclonal antibody
SCR	substrate : catalyst ratio

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