M. T. Reetz

DOI: 10.1002/anie.200704327

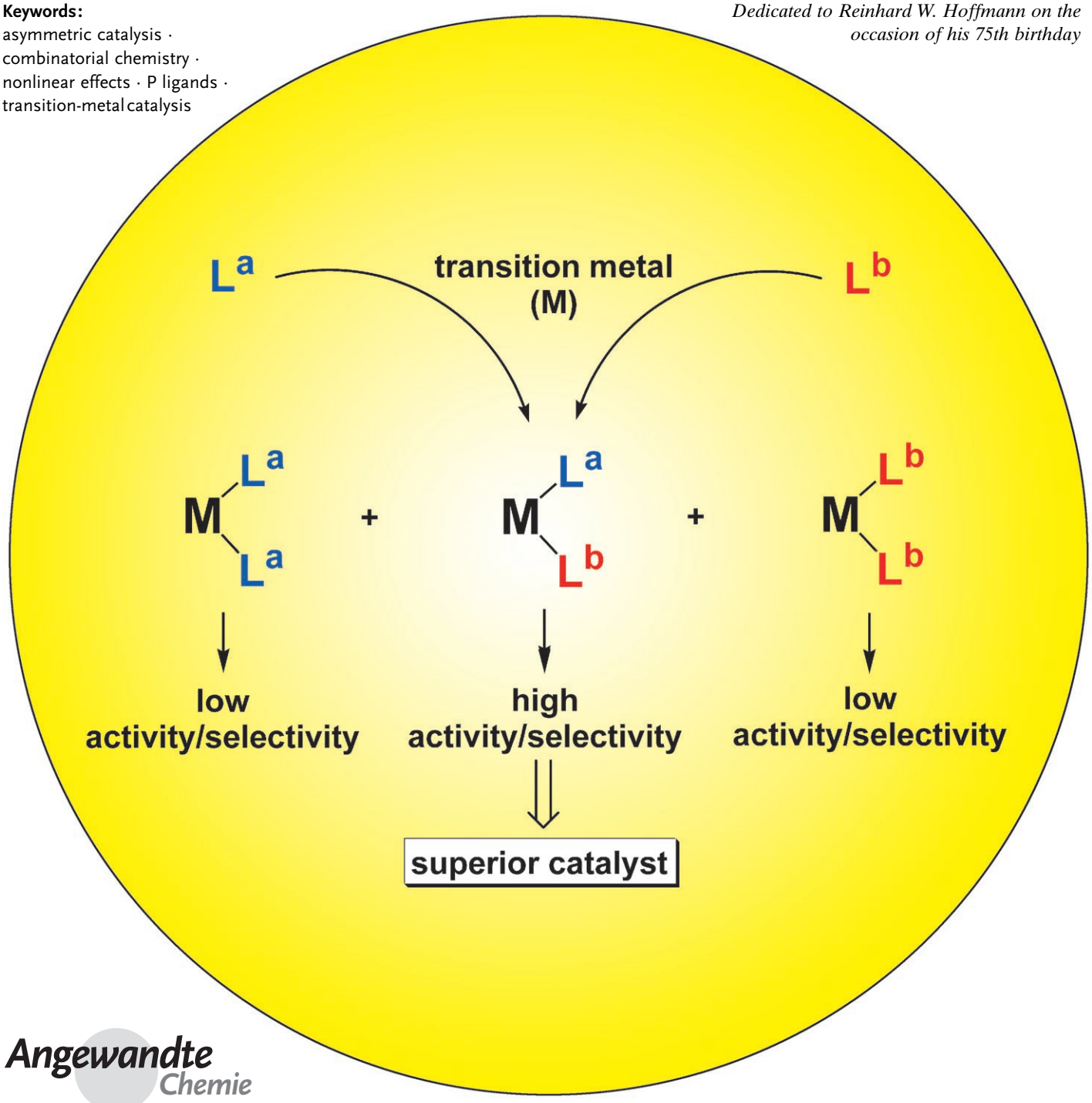
Combinatorial Catalysis

Combinatorial Transition-Metal Catalysis: Mixing Monodentate Ligands to Control Enantio-, Diastereo-, and Regioselectivity

*Manfred T. Reetz**

Keywords:
asymmetric catalysis · combinatorial chemistry · nonlinear effects · P ligands · transition-metal catalysis

Dedicated to Reinhard W. Hoffmann on the occasion of his 75th birthday



This review focuses on a new approach to combinatorial homogeneous transition-metal catalysis which goes beyond the traditional parallel preparation of modular ligands. It is based on the use of mixtures of monodentate ligands L^a and L^b, which upon exposure to a transition metal (M) form not only the two homocombinations $[ML^aL^a]$ and $[ML^bL^b]$, but also the heterocombination $[ML^aL^b]$. If the latter is more reactive and selective than the homocombinations, an improved catalyst system is formed without the need to synthesize new ligands. Thus, the control of enantio,- diastereo-, and regioselectivity is possible.

From the Contents

1. Introduction 2557

2. Modular Monodentate P Ligands in Combinatorial Asymmetric Transition-Metal Catalysis 2559

3. The Concept of Using Mixtures of Monodentate Ligands 2566

4. Controlling Diastereoselectivity by Using Mixtures of Monodentate P Ligands 2575

5. Controlling Regioselectivity by Using Mixtures of Monodentate P Ligands 2576

6. Mechanistic Challenges 2577

7. Supramolecular Assembly as an Alternative Approach 2579

8. Conclusions and Perspectives 2582

1. Introduction

During the last two decades combinatorial methods have pervaded many different areas of chemistry,[1] including therapeutic drug discovery and preparation, material science, as well as heterogeneous and homogeneous catalysis. In most general terms, the idea is to synthesize and screen large libraries of chemical entities as fast as possible using special techniques, rather than performing the task sequentially in a traditional and thus time-consuming manner. In organic chemistry two different strategies can be applied, namely the iterative split-and-mix (also termed split-and-pool) method developed by Furka[1b,2] or parallel synthesis employing appropriate laboratory equipment. Solution or solid-phase parallel methods are not new, and nowadays this approach is used routinely.[1] The important issue of automated solution-phase synthesis in an integrated system has been reviewed.[1d] Parallel screening of catalysts and biocatalysts is also practiced widely,[3] made possible by modern automation and robotics. Miniaturized equipment such as microreactors[4] or microfluidic chips (lab-on-a-chip)[5] may in the future allow for small-scale reactions and analyses within a single device in a high-throughput manner.

The term "combinatorial homogeneous catalysis" is not well defined.[3a,6] Most often, it simply means parallel synthesis and rapid evaluation of a large number of soluble catalysts. This includes not only the synthesis and testing of structurally different ligands/catalysts, but also the study of the influence of temperature, pressure, solvent, and additives. Multiple substrate screening as introduced by Kagan and Satyanarayana is another practical facet of combinatorial homogeneous catalysis.[7]

Success in developing new and highly enantioselective catalysts depends upon design, experience, intuition, trial and error, and/or serendipity. Thus, parallelization of laboratory efforts with creation of structural diversity is a desirable feature. The question of efficiency, meaning maximum exploitation of parallel approaches, becomes relevant when aiming for high throughput. Even in the absence of advanced equipment, well-trained experimentalists do not work serially nowadays, but run 15–20 reactions in parallel, for example by using simple vials positioned around a magnetic stirrer, each under inert gas if necessary. A drastic increase in throughput can be reached by applying appropriate robotic technology. Parallel synthesizers are commercially available, and automatic sample handlers in gas chromatography (GC)[8] or HPLC[9] allow for medium-throughput evaluation of catalyst activity or enantioselectivity. The split-and-mix method, which in principle is considerably faster than traditional serial/parallel syntheses, can also be employed in homogeneous catalysis, although the purity of the catalysts should not be neglected.

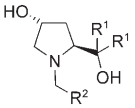
Several high-throughput analytical techniques for assessing enantiopurity have been developed,[3] including the Mülheim MS-based system in which up to 10000 precise *ee* values in desymmetrization reactions or kinetic resolutions can be determined in one to two days.[10] So far this *ee*-screening system has been used in the directed evolution of enantioselective enzymes[11] such as lipases,[12] epoxide hydrolases,[13] and nitrilases.[14] Very different analytical approaches are on the horizon, for example, the aforementioned microfluidic devices (lab-on-a-chip) which allow an asymmetric reaction as well as the *ee* determination to be performed on a single microchip.[5b] However, parallelization has yet to be accomplished. A highly interesting approach to increasing drastically the throughput of GC analyses, based on multiplexing, was recently reported by Trapp.[15] This method,

[*] Prof. Dr. M. T. Reetz
Max-Planck-Institut für Kohlenforschung
Kaiser-Wilhelm-Platz 1, 45470 Mülheim/Ruhr (Germany)
Fax: (+49) 208-306-2985
E-mail: reetz@mpi-muelheim.mpg.de
Homepage:
http://www.mpi-muelheim.mpg.de/mpikofo_home.html

which can be expected to revolutionize GC, will surely be adapted to include *ee* determinations.

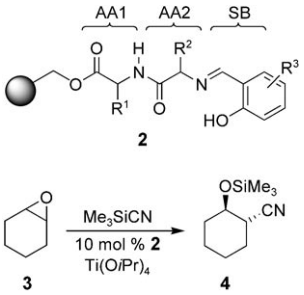
When addressing combinatorial (asymmetric) homogeneous catalysis, two different aspects need to be considered: parallel synthesis of the (chiral) ligands and parallel assessment of the respective transition-metal catalysts. In ideal cases both steps are performed in a single automated setup (Scheme 1). Since several reviews on combinatorial homogeneous transition-metal catalysis have appeared which cover the subject until about 2004,[3a,6] only the basics are reiterated here. In a seminal paper Ellman and Liu reported in 1995 the parallel solid-phase synthesis of a small library of substituted 2-pyrrolidine methanol derivatives **1** in six steps, the last being acid-catalyzed cleavage from the solid phase.[16] A variety of different R^1 and R^2 groups were introduced by Grignard reactions and N-acylation/reduction, respectively. Thereafter the modular amino alcohols were tested as catalysts in the enantioselective addition of Et_2Zn to aldehydes. On-bead reactions were likewise performed, with the best hits from a small library resulting in *ee* values of up to 85%. The *ee* determinations were accomplished by classical GC, meaning that high throughput was not strived for.[16]

Scheme 1. Parallel preparation and screening of chiral catalysts.



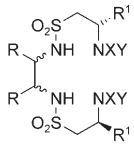
1

In another important contribution, Snapper, Hoveyda, and co-workers introduced the idea of modular peptides comprised of three variable subunits, Schiff base (SB), amino acid 1 (AA1), and amino acid 2 (AA2; Scheme 2).[17] Transition metals were expected to coordinate at site SB. An example is titanium, leading to a variety of structurally different chiral catalysts for the asymmetric ring opening of epoxides such as **3** (Scheme 2). The authors developed a search strategy which avoids the tedious testing of all permutations. Each of the three modular subunits was optimized successively while keeping the other two subunits of this type unchanged. Positional scanning of this type led to the identification of a catalyst showing 89% *ee* in the model reaction **3**→**4**. Since only 60 catalysts were tested, it is likely that even better results could be achieved with larger libraries. Later this type of combinatorial search was successfully applied to other reaction types.[6b,d,18]



Scheme 2. Ti-catalyzed ring-opening reaction of **3** in the presence of modular ligands **2**; ●: solid phase.[17]

Another combinatorial approach was described by Gennari et al.[6e,19] New members of a known family of modular chiral ligands incorporating sulfonamides were constructed using solution-phase reactions and a solid-phase extraction technique. Libraries of disulfonamides **5** were then tested in the $[Ti(OiPr)_4]$-mediated addition of Et_2Zn to aldehydes. This was accomplished by employing 30 reaction vessels in parallel, each containing four different aldehydes according to Kagan's concept of simultaneous screening of substrate mixtures.[7] 120 data points were collected, with the best *ee* values amounting to about 90%. Here again, classical GC was employed as the analytical tool. This particular strategy has since been extended and refined by Gennari[6e,19] and Liskamp et al.[20]

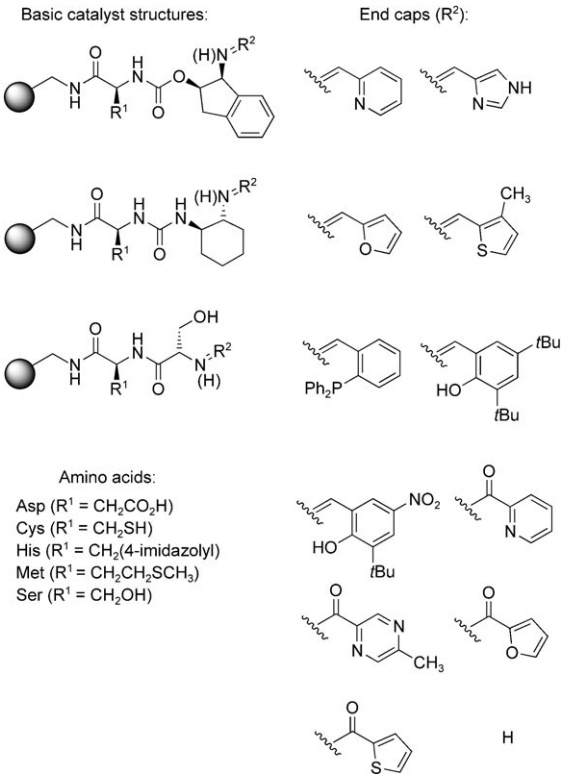


5

Following their early combinatorial work regarding the asymmetric Stecker reaction catalyzed by transition metals bound to modular ligands composed of amino acids, diamines, and thiourea, Jacobsen et al.[6a,21] showed for the first time that it is also possible to exploit combinatorial asymmetric catalysis in the quest to discover new lead ligand structures.[22] As a model reaction, the H_2O_2-mediated asymmetric epoxidation of *trans*-β-methylstyrene was chosen. The solid-phase synthesis of 192 ligands was performed (Scheme 3), and these were treated with 30 different metals. Following visual assessment by a color assay and an effective analysis, it was discovered that a pyridine-capped ligand in combination with $FeCl_2$ constitutes the best catalyst (20% *ee*). This type of ligand had never been considered previously.[22a]

The concept of utilizing libraries of modular ligands for asymmetric transition-metal catalysis was also championed by Burgess,[23] Gilbertson,[24] Kobayashi,[25] Waldmann,[26] Berkessel,[27] Schmalz,[28] Ding,[6f] and others.[6,29] For example, Adolfsson has described a concept in which in situ formation of modular ligands as well as catalyst formation and reaction are possible in an integrated system.[29a] Moreover, de Vries and co-workers at DSM have published informative reviews of high-throughput methods in asymmetric hydrogenation and other reactions.[6gh] Researchers in the emerging field of

Manfred T. Reetz carried out studies at Washington University and the University of Michigan, and completed his doctoral degree from the University of Göttingen (Germany) in 1969 with U. Schöllkopf. Following a postdoctoral stay with R. W. Hoffmann at the University of Marburg, he earned his Habilitation there in 1974 and became associate professor of organic chemistry at the University of Bonn in 1978. In 1991 he became director at the Max Planck Institute for Kohlenforschung in Mülheim/Ruhr (Germany). He is also affiliated with the Ruhr-Universität Bochum as an Honorary Professor. His current scientific interests focus on the directed evolution of selective enzymes as catalysts in organic chemistry and combinatorial transition-metal catalysis.

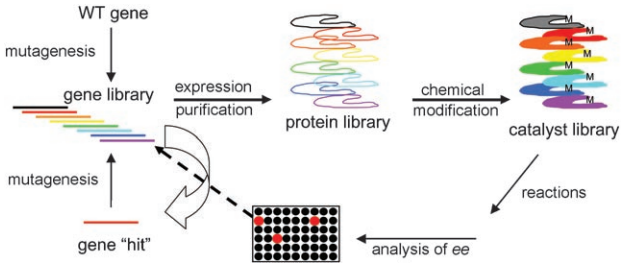


Scheme 3. Ligand libraries for the asymmetric metal-catalyzed epoxidation of *trans*-β-methylstyrene.[22a]

organocatalysis have also utilized combinatorial methods, as summarized by List and Hechavarría Fonseca.[30] A prime example is Miller and Lewis' intriguing work on small peptides as catalysts in enantio- and/or site-selective acylation and phosphorylation.[31a,b] The combinatorial approach by Reymond et al. based on dendritic peptides is another example.[31c] A novel strategy for catalyst discovery in split-and-mix libraries of peptides utilizing catalyst–substrate coimmobilization was described by Pfaltz and Wennemers.[32]

During the last few years computational techniques have been introduced which offer aid in the combinatorial search for selective homogeneous catalysts, an upcoming research area which has been reviewed by Burello and Rothenberg.[33] Such in silico design includes the utility of descriptor models relying on semiempirical and molecular mechanics calculations, 2D topological descriptors, graph theory, and data-mining tools based on artificial neural networks, linear regression, and classification trees. Along these lines, Corma et al. has described an advanced software application for increasing efficiency in the discovery of new catalytic materials.[1g]

The effects of additives are not always considered to be part of combinatorial asymmetric transition-metal catalysis. Irrespective of the nomenclature, however, such concepts as asymmetric activation,[34] chiral poisoning,[35] and ligand acceleration[36] constitute highly useful tools in synthetic organic chemistry. These important developments have been reviewed elsewhere. The emerging concept of directed evolution of hybrid catalysts[37] (transition metals anchored to a host protein), for which proof of principle was recently provided,[38] has been reviewed.[39] The overall process involves iterative cycles of gene mutagenesis/expression, bioconjugation, and screening, leading to the evolution of the proper protein environment around the synthetic transition-metal moiety and consequently to high enantioselectivity (Scheme 4).



Scheme 4. Directed evolution of selective hybrid catalysts in which the metal (M) or ligand is anchored covalently or noncovalently to a host protein.[38]

Although not directly related to catalyst optimization, the approach to reaction discovery based on DNA-templated organic synthesis as proposed and implemented by Liu et al. needs to be mentioned here.[40] Pools of DNA-linked substrates are combined in one solution, and subsequently all possible pairwise combinations of substrates are simultaneously selected for bond formation in a single experiment. Since the results can be amplified by PCR (polymerase chain reaction), the process can be performed on a femtomolar scale, for example, in 96- and 168-reaction matrices. An example is the discovery of a Pd-catalyzed macrocyclization as illustrated in Figure 1.[40] This approach should be amenable to catalyst development.

This review focuses on a new and practical concept in combinatorial transition-metal catalysis which was first proposed in 2002/2003.[41,42] It features the use of mixtures of monodentate ligands, a simple and practical concept that is useful not only in the quest to influence enantioselectivity, but also in the control of diastereo- and regioselectivity of transition-metal-catalyzed reactions. Before presenting all details of this combinatorial approach (Sections 3–6) and related supramolecular concepts (Section 7), it is instructive to review briefly the chemistry of monodentate P ligands (Section 2).

2. Modular Monodentate P Ligands in Combinatorial Asymmetric Transition-Metal Catalysis

The roots of asymmetric Rh-catalyzed olefin hydrogenation go back to the early work of Horner[43a] and Knowles et al.,[43b] who replaced triphenylphosphine in the Wilkinson catalyst by chiral monodentate phosphines such as **6a**,**b**. The enantioselectivity turned out to be poor (ca. 15% *ee*), but a revolutionary step had been undertaken. Subsequently it was shown that the methoxy derivatives **7a**,**b** perform better in some cases.[44] However, the truly important next step forward was the discovery by Kagan et al.[45] and independently by

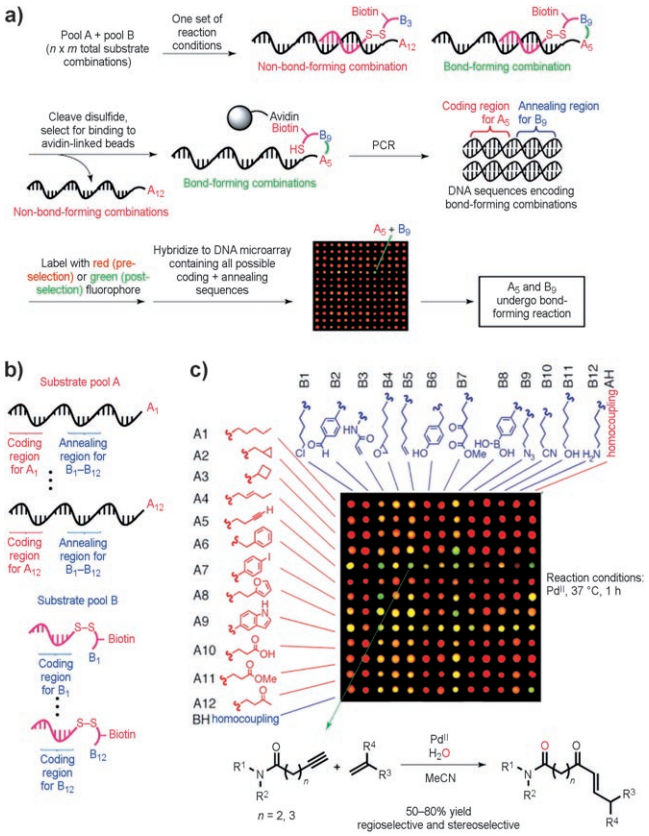
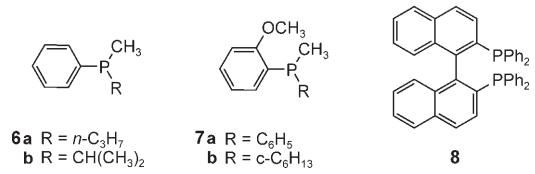
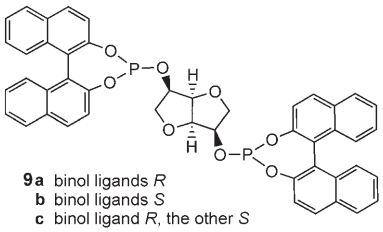


Figure 1. Reaction discovery enabled by DNA-templated synthesis and in vitro selection.[40] a) A general one-pot selection and analysis strategy for the detection of bond-forming reactions between DNA-linked substrates. b) Two pools of DNA-linked small molecules self-assemble into 168 substrate pairs, each identified by a unique DNA sequence. c) Array-based analysis of DNA sequences surviving selection for bond formation has led to the discovery of a novel alkene–alkyne oxidative coupling reaction.



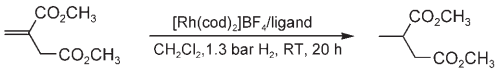
Knowles et al.[46] that chiral diphosphines lead to considerably higher enantioselectivity, probably because the chelation effect reduces degrees of freedom. Shortly thereafter a number of other diphosphines[47] were developed, with 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl (binap, **8**)[48] emerging as the "winner". All of this pioneering work led to a dogma in asymmetric hydrogenation, namely that chiral diphosphines are required for high enantioselectivity.[47,48,49] Indeed, to this day research is continuing along this line, and several other useful bidentate P ligands have been developed recently.[49]

About a decade ago we were studying chiral diphosphites as possible ligands in Rh-catalyzed asymmetric olefin hydrogenation.[50] Numerous chiral bidentate phosphite ligands had already been described in the literature, mainly in the area of hydroformylation as described, for example, in patents by Union Carbide/Dow,[51] but in the less-studied asymmetric olefin hydrogenation the best results were far from satisfactory (maximum 34% *ee*).[52] Hoping nonetheless that appropriately designed diphosphites could lead to high enantioselectivity, we prepared binol-derived ligands (binol = 2,2′-dihydroxy-1,1′-binaphthyl) of the type **9**, in which the



(chiral) backbone originates from a carbohydrate (mannose). Two diastereomers **9a**,**b** were synthesized, allowing for the study of matched or mismatched combinations[53] in subsequent transition-metal catalysis.[50a]

We were pleased to discover that these diphosphites are excellent ligands in asymmetric Rh-catalyzed olefin hydrogenation. Indeed, they are the first ones in the literature that enable significant degrees of enantioselectivity (> 95% *ee*). For example, in the asymmetric Rh-catalyzed hydrogenation of itaconate **10** [Eq. 1], the diphosphite containing two (*R*)-binol units, namely **9a**, turned out to be the matched case (95% *ee* (*R*)). Mismatched **9b** led to a lower enantioselectivity (88% *ee* (*S*)) and to a distinctly lower reaction rate.[50a]



(1)

In collaboration with Donna Blackmond, a detailed kinetic study was undertaken using **9a** and **9b** separately as well as a 1:1 mixture of the two diastereomeric bidentate ligands.[50b] The mixture was included to uncover possible nonlinear effects (NLEs) in a diastereomer system. The use of a 1:1 mixture of **9a** and **9b** led to an *ee* value of 54% in favor of (*R*)-**11**. Conventional NLEs are most often interpreted as evidence for the interaction between different catalytic species in solution with formation of new species displaying enantioselectivities different from the original catalysts. In this case, however, a simpler possibility is that the reaction proceeds independently to a greater extent through different channels involving **9a** and **9b**.[50b]

In all experiments $[Rh(cod)_2]BF_4$ (cod = 1,5-cyclooctadiene) was treated with one equivalent of a bidentate ligand **9** with formation of the precatalyst $[Rh(cod)(\mathbf{9})]BF_4$. As shown by other researchers using other ligands,[49] the cod-containing precatalyst is transformed into the active catalyst by hydrogenative cleavage of cod. The reaction rate curves in the hydrogenation of **10** using the "*R*,*R*" and the "*S*,*S*" catalyst **9a** and **9b**, respectively, are shown in Figure 2, and reveal that

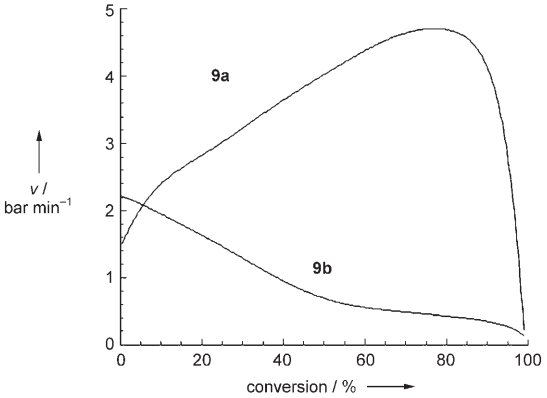


Figure 2. Reaction rate v as a function of the conversion of substrate for the catalysts **9a** and **9b**.[50b]

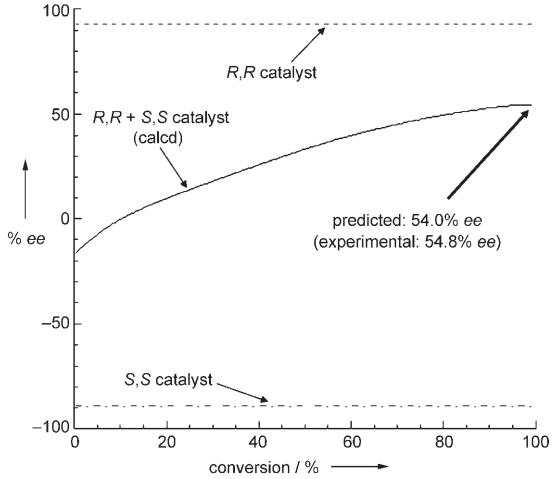


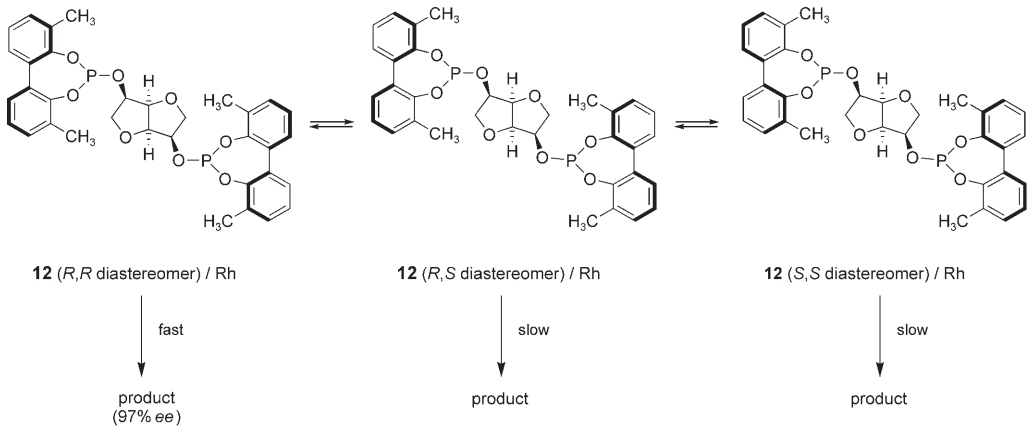
Figure 3. Experimental and calculated enantioselectivity as a function of conversion of substrate **10**; -----: experimentally determined for **9a**; –•–•–: experimentally determined for **9b**; ——: enantioselectivity calculated according to Equation (1) for a 1:1 mixture.[50b]

the catalysts exhibit strikingly different kinetic profiles. This is due to the inherently different activities of the two active catalysts (matched versus mismatched) and to the different rates of cod cleavage. By using Equation (2), it was possible to model the kinetic behavior of a 1:1 mixture of the two diastereomeric catalysts.

$$ee_{x_A} = \frac{\left(\frac{1+ee^{RR}}{2}\int_0^{x_A} r^{RR}\,dx_A + \frac{1+ee^{SS}}{2}\int_0^{x_A} r^{SS}\,dx_A\right) - \left(\frac{1-ee^{RR}}{2}\int_0^{x_A} r^{RR}\,dx_A + \frac{1-ee^{SS}}{2}\int_0^{x_A} r^{SS}\,dx_A\right)}{\left(\frac{1+ee^{RR}}{2}\int_0^{x_A} r^{RR}\,dx_A + \frac{1+ee^{SS}}{2}\int_0^{x_A} r^{SS}\,dx_A\right) + \left(\frac{1-ee^{RR}}{2}\int_0^{x_A} r^{RR}\,dx_A + \frac{1-ee^{SS}}{2}\int_0^{x_A} r^{SS}\,dx_A\right)} \quad (2)$$

Figure 3 shows the calculated enantioselectivity over the course of the reaction, predicting that an initial enantioselctivity of 16% *ee* for the *S* product would ultimately shift to a final enantioselectivity of 54% *ee* for (*R*)-**11**. The experimentally determined endpoint value of 54.8% *ee* for the *R* product is in excellent agreement with this prediction.[50b]

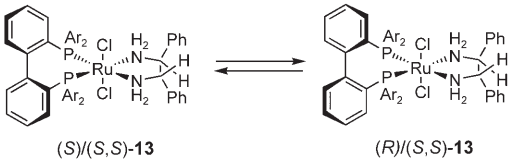
Upon replacing each binol moiety by two achiral alkoxy groups originating from alcohols such as 2-naphthol, enantioselectivity proved to be poor (21% *ee*).[50a] It became clear once more that it is the binol unit in ligand **9** which is mainly responsible for the high enantioselectivity. Especially the lower reaction rate resulting from the use of the mismatched *S*,*S* combination caught our attention. We speculated that if an achiral building block such as diphenol or *o*,*o*-dimethyldiphenol were to replace binol, as in **12**, then a mixture of three rapidly interconverting catalysts should result, namely the *R*,*R*, *R*,*S*, and *S*,*S* diastereomers (Scheme 5). The respective P heterocycles are axially chiral, but owing to their fluxional behavior, they are not configurationally stable (tropos, from the Greek for turn). Based on our experience with **9a** and **9b**, we expected that the matched *R*,*R* diastereomer should be more reactive and more selective than the other two diastereomers. Indeed, in the Rh-catalyzed hydrogenation of **10**, an *ee* value of 97% was observed. Thus, although a mixture of catalysts is involved, one of them, the *R*,*R* diastereomer, dictates the overall catalytic profile. This result is significant both from a theoretical and a practical viewpoint. The chiral information essential for high enantioselectivity is provided by the system "free of charge" because



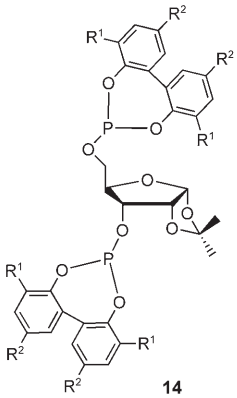
Scheme 5. Mixture of three rapidly interconverting diastereomeric bidentate P ligands in the hydrogenation of itaconate **10**.[50]

the original building block (*o*,*o*-dimethyldiphenol) is achiral.[50]

Such a positive effect of this intriguing phenomenon, which is possible whenever a catalyst system is composed of one fluxional axially chiral moiety (or more) and a configurationally stable chiral component, was described independently by Mikami, Noyori, et al., also in 1999.[54] They used a Ru complex **13** comprised of a chiral diamine and a fluxional diphosphine in an asymmetric ketone reduction [Eq. (3); up to 60% *ee*]. In the same year Pàmies et al. reported the use of ligands of the type **14** (which they correctly described as being axially fluxional) in Cu-catalyzed conjugate addition reactions (up to 53% *ee*).[55a–e] Ligands containing central chirality and fluxional axial chirality were described previously,[55f] but the special role of the fluxional unit was not addressed.

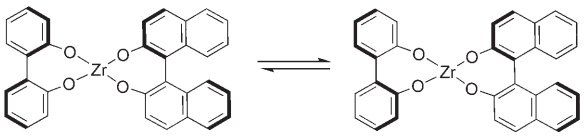


(*S*)/(*S*,*S*)-**13** (*R*)/(*S*,*S*)-**13** (3)

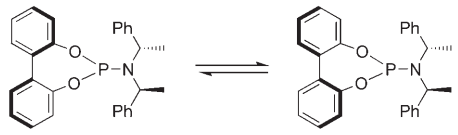


14

Bolm and Beckmann described the use of fluxional Zr catalysts of the type **15** in asymmetric Baeyer–Villiger reactions (up to 84% *ee*),[56] which again means a mixture of two competing diastereomers [Eq. (4)]. At about the same time, Alexakis et al. reported yet another system involving **16** as a ligand in Cu-catalyzed conjugate addition reactions [Eq. (5)]; up to 87% *ee*].[57] Numerous other examples of ligands with tropos-like P entities attached to moieties having central chirality are known,[58] although notable effects in catalysis were not reported. The observation of positive effects means that "achiral" components can be exploited, which in catalysis behave as chiral auxiliaries in the most reactive matched diastereomer. More recently numerous authors, for example, Gagne,[59a,b] Hoppe,[59c] and Moberg,[59d] have reported further positive examples. An interesting variation of this principle concerns the clever use by Walsh et al. of "achiral" diamines such as *meso*-1,2-diaminocyclohexane as ligand components in enantioselective C–C bond formation.[60a,b] This compound is really a mixture of rapidly interconverting enantiomers.[60c] The intriguing work by Sibi et al. on configurationally fluxional substrates and/or additives involves the same type of phenomenon.[61] Thus, in all of these reactions mixtures of diastereomeric species occur, in which one stereoisomer is most reactive and selective.

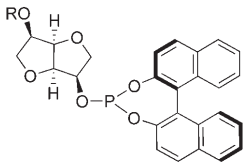


(*R*)/(*S*)-**15** (*S*)/(*S*)-**15** (4)



(*R*)/(*S*,*S*)-**16** (*S*)/(*S*,*S*)-**16** (5)

We planned the synthesis of the bidentate binol-derived *R*,*S* diastereomer **9c**, which is the third possible diastereomer. Since the two binol moieties with opposite absolute configuration can be expected to counteract each other in catalysis, we did not expect a high enantioselectivity. In the multistep synthesis (which was never completed), we first prepared the *O*-methyl- and *O*-benzyl-protected monophosphites (*R*)-**17a,b**. Prior to the envisaged deprotection/phosphorylation,

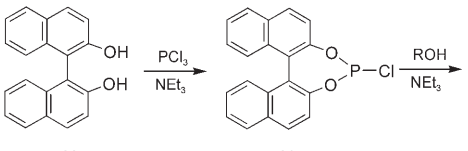


17a R = CH_3
b R = $CH_2C_6H_5$

we tested these monodentate ligands in the Rh-catalyzed hydrogenation of itaconate **10**. To our surprise, the *ee* value was found to be 97%.[62a]

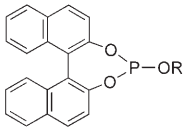
We were astounded, because this observation seemed to be contrary to the long-standing dogma that chelating bidentate ligands are necessary for high enantioselectivity in transition-metal-catalyzed olefin hydrogenation, as delineated above. Thinking that one of the oxygen groups of the monophosphites (*R*)-**17** might be functioning as a hemilabile donor, which would mean that the compound is actually behaving as a bidentate ligand, we prepared and tested several monophosphites **20** derived from binol (**18**) and simple achiral alcohols ROH [Eq. (6)]. Since these compounds lack potential hemilabile donor functions, we expected poor results when using them as ligands in Rh-catalyzed olefin hydrogenation.

The synthesis of a few of the monophosphites **20** had been described earlier in the literature,[63] but their application in asymmetric transition-metal-catalyzed reactions was not very rewarding,[64] and Rh-catalyzed olefin hydrogenation had not been mentioned in any previous publication. Upon testing **20g** as a ligand in the Rh-catalyzed hydrogenation of itaconate **10**, we were again surprised to observe an *ee* value



(6)

18 19

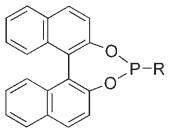


20 **a** R = CH_3
b R = C_2H_5
c R = *c*-C_6H_{11}
d R = $C(CH_3)_3$
e R = C_6H_5
f R = 2,6-$(CH_3)_2C_6H_3$
g R = $CH(CH_3)_2$
h R = 9-fluorenyl
i R = $CH_2C(CH_3)_3$
j R = $CH_2C_6H_5$
k R = 2-BrC_6H_4
l R = 2,6-$(C_6H_5)_2C_6H_3$
m R = $CH_2CH_2OCH_3$

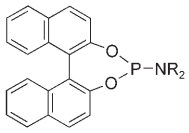
of 98%.[62a] Therefore, our original hypothesis regarding the possible role of a hemilabile donor moiety was wrong. This experiment also showed that the use of a somewhat complicated chiral alcohol derived from a carbohydrate as one of the components in the monodentate phosphite is not necessary for high enantioselectivity. Upon performing the model reaction with various other monophosphites **20a–m** as ligands, it became clear that the *ee* value depends critically upon the nature of the alcohol ROH used in the synthesis (Table 1). It was also shown that two monodentate P ligands bind to the metal.[62] The poorest ligand is **20l**, which leads to 28.6% *ee* (Table 1, entry 12), which may be due to the extreme bulkiness of the compound so that the usual double ligation is prevented.

We then discovered that other prochiral olefins can also be hydrogenated with high enantioselectivity.[62] The standard protocol is to treat $[Rh(cod)_2]BF_4$ with two equivalents of a monophosphite **20**, which forms the precatalyst $[Rh(cod)L_2]BF_4$ (L = **20**). Once hydrogenation is initiated, the remaining cod is reduced and thereby cleaved as in other systems,[48,49] leaving vacant coordination sites at Rh which are occupied by the substrate to be hydrogenated. Results of the type summarized in Table 1 are significant for several reasons. Firstly, binol (**18**) is available in both enantiomeric forms and is currently one of the cheapest chiral auxiliaries,[65] making ligands of the type **20** extremely attractive for industrial applications.[66] Secondly, phosphites are not as sensitive to undesired oxidation as phosphines. Thirdly, the hydrogenation rate is much higher than in the case of phosphines.[67] Finally, a hitherto unknown effect causing high enantioselectivity must be operating, making basic research of this kind challenging.[67] A limitation concerns the nature of the solvent that can be used; protic solvents such as methanol should be avoided because these cause decomposition of the ligands.

Our initial results were published in 2000, the same year in which Pringle, Claver, et al.[68] as well as our group[69] independently reported that the analogous binol-derived monophosphonites **21** are also well suited for asymmetric hydrogenation. Moreover, in an independent study Feringa, de Vries, et al. published their first paper on the use of the analogous monophosphoramidites **22** in hydrogenation.[70] Several synthetic methods for the preparation of ligands **22** exist, the simplest one being the reaction of binol (**18**) with $P(NR_2)_3$.[70]



21 **a** R = CH_3
b R = C_2H_5
c R = *c*-C_6H_{11}
d R = $C(CH_3)_3$
e R = C_6H_5

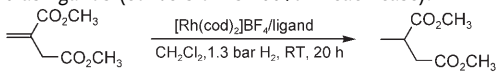


22 **a** R = CH_3
b R = C_2H_5
c R = $CH(CH_3)_2$
d R = (*R*)-$CH(CH_3)(C_6H_5)$
e R = (*S*)-$CH(CH_3)(C_6H_5)$
f R+R = $(CH_2)_5$

These early studies opened a new chapter in asymmetric hydrogenation. Numerous derivatives of ligands **20–22** can be envisioned simply by varying the nature of the R groups, which can originate from achiral or chiral building blocks. The modular nature of these compounds allows for combinatorial asymmetric transition-metal catalysis. They can be considered to be "privileged" ligands. We have prepared more than 60 derivatives of phosphites **20** and about 10 phosphonites **21**, and others have contributed as well.[66,71] It is also possible to prepare further analogues by using derivatives of binol, for example, **23**,[72a] **24**,[73] or **25**[74] although this entails additional synthetic effort. A fair number of phosphoramidites have also been prepared, **22a–f** being the most often used ligands in hydrogenation and in other transition-metal-catalyzed reactions.[6g–h,70,75] Haysahi's monodentate MOP ligand has not been applied in hydrogenation.[71q] Not surprisingly, no single ligand is "universal", because there cannot be such a thing as a general catalyst. Nevertheless, using these sets of ligands, numerous representatives from five different types of olefins have been hydrogenated successfully, namely **10** (or the monoester), **26–29** (>95% *ee*).

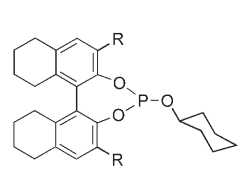
When encountering cases in which enantioselectivity is insufficient, several solutions to this problem can be considered. One possibility is to prepare further derivatives of these

Table 1: Rh-catalyzed hydrogenation of itaconate **10** using monophosphites **20** as ligands (conversion is 100% in each case).[62]

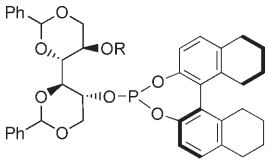


10 **11**

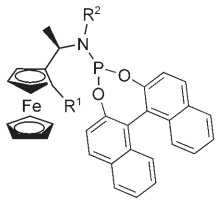
Entry	Ligand	*ee* [%]
1	**20a**	89.2
2	**20b**	93.4
3	**20c**	96.8
4	**20d**	91.4
5	**20e**	96.6
6	**20f**	39.2
7	**20g**	97.6
8	**20h**	71.2
9	**20i**	98.6
10	**20j**	98.2
11	**20k**	89.8
12	**20l**	28.6
13	**20m**	96.0



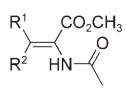
23 a R = H
b R = Br
c R = NO_2



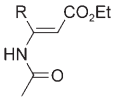
24 a R = CH_3
b R = CH_2Ph



25



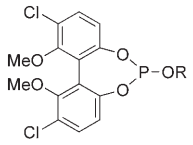
26



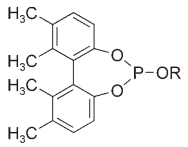
27

28

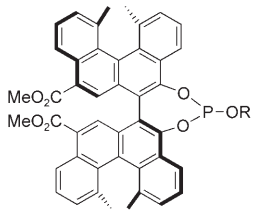
29



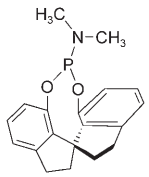
32



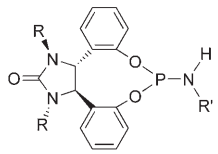
33



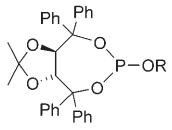
34



35

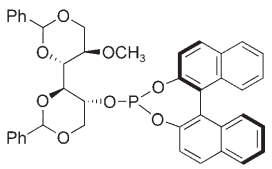


36

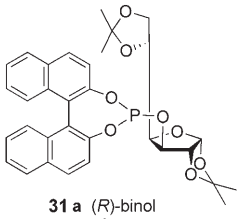


37

monodentate ligands. An important example is our discovery[75a] that the piperidine-derived monophosphoramidite **22 f** leads to a considerably more active and enantioselective Rh catalyst than the standard parent compound **22 a** or other analogues having, for example, additional stereoelements in the R groups (chiral amines as building blocks as in **22 d**,**e**).[75b,c] Another case is the mannitol-derived monophosphite **30** described by Zheng et al., which displays unusually



30

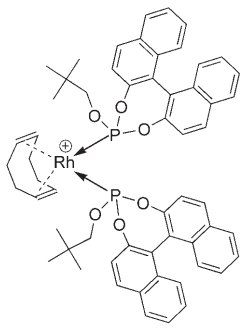


31 a (*R*)-binol
b (*S*)-binol

high enantioselectivity in the hydrogenation of several types of olefins.[76] The glucose-derived phosphite **31** is also well suited for Rh-catalyzed hydrogenation, especially of enol acetates **29**.[72b] Of course, the preparation of such ligands requires a greater synthetic effort.

Another way to create further structural diversity is to replace the binol component by other axially chiral moieties, as noted in the original patent.[62b] Examples are the Bayer ligands **32** (R = alkyl, aryl),[77a] ligands **33** (R = alkyl, aryl) by Ojima et al.,[71e,77b] and compounds of the type **34** (R = alkyl, aryl) described by Yamaguchi and Nakano.[77c] The analogous phosphoramidites can also be prepared. It is also possible to utilize spiro derivatives such as **35** reported by Zhou et al.,[78a–c] or ligands **36** (R = benzyl, R^1 = alkyl) reported by Ding et al.,[79] which are likewise excellent ligands in Rh-catalyzed olefin hydrogenation. A chiral spirophosphoramidite designed by Zhang et al. also deserves mention.[78d] However, not all types of monophosphites or phosphoramidites that do not incorporate axial chirality ensure high enantioselectivity. For example, taddol-derived phosphites **37**[80] (R = alkyl, aryl; taddol = α,α,α′,α′-tetraaryl-2,2-dimethyl-1,3-dioxolan-4,5-dimethanol) are poor ligands in Rh-catalyzed olefin hydrogenation,[72c] but do perform better in other reaction types.[80]

In summary, the modular nature of all of these ligands allows the synthesis of a wide variety of representatives, thereby making a combinatorial approach possible. It was also of interest to uncover the source of enantioselectivity in these unusual hydrogenations.[62c,d,67] As already pointed out, the precatalysts $[Rh(cod)L_2]BF_4$ contain two monodentate ligands L. This was shown by NMR spectroscopy in all three systems **20**,[62] **21**,[62] and **22**[70] in representative cases. The same applies to analogues of the type **33**.[71e] For example, in the case of the neopentyl phosphite derived Rh complex **38**, the ^1H, ^{13}C, and ^{31}P NMR spectra are in accord with the proposed structure.[67] A single P signal was observed, a doublet as a result of spin–spin coupling with Rh (100%), centered at $\delta = 120.8$ ppm. The stoichiometry of the [Rh-



38

(cod)L_2] complex was proven by the integrated intensities in the ^{1}H NMR spectrum, in line with the fine structure of the multiplets of the olefinic carbon atoms of the cod ligand. The single ^{31}P NMR signal is consistent with the ^{1}H and ^{13}C NMR spectra, showing that the two phosphite ligands in **38** are symmetrically equivalent.[67] Unfortunately, once hydrogenation was initiated with cleavage of the second cod ligand, it was not possible to obtain NMR data of the actual catalyst. In a recent study by Pringle et al., the Rh complex involving two bulky phosphonite ligands **21d** before and after cod cleavage was studied by NMR spectroscopy, revealing an equilibrium mixture of a solvato complex and a η-arene-coordinated dirhodium species. It is currently unclear whether this finding can be generalized.[81]

In our initial kinetic study, [Rh(cod)(**20g**)$_2$]BF_4 was used as the precatalyst in the hydrogenation of itaconate **10**.[67] It was demonstrated that this catalyst system in CH_2Cl_2 is considerably more active than the binap system [Rh(cod)-(binap)]BF_4. The effect of hydrogenative cleavage of cod was also studied by kinetics, analogous to earlier studies by Heller,[82a] and Blackmond[82b,c] involving diphosphines.[82] Using [Rh(cod)(**20j**)$_2$]BF_4 as the precatalyst, we were able to show that at a substrate/catalyst (S/C) ratio of 1000:1, which is a relatively high catalyst loading in hydrogenation, the reaction rate increases continuously and reaches a maximum at 83% conversion (Figure 4). Therefore, hydrogenative cleavage of cod increases the active catalyst concentration over a significant portion of the actual reaction. A qualitatively similar trend was observed at an S/C ratio of 5000:1; in this case the maximum is reached at 65% conversion. At still higher S/C ratios, the reaction is close to zero order in substrate over the entire course of the reaction.[67]

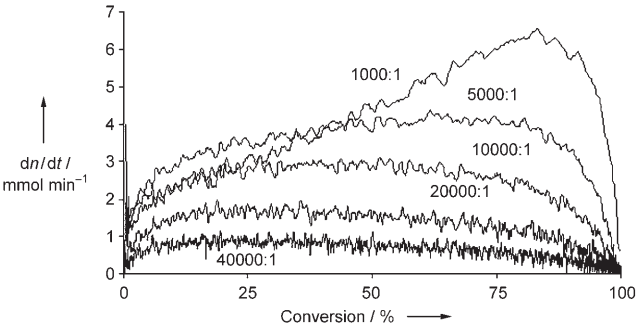


Figure 4. Rate of hydrogenation of itaconate **10** using [Rh(cod)-(**20j**)$_2$]BF_4 at different S/C ratios.[67]

The influence of H_2 pressure was also examined.[67] Figure 5 shows that the hydrogenation rate depends linearly on the H_2 pressure, which is evidence that oxidative addition of hydrogen constitutes the rate-determining step. Halpern,[47b,83] Brown,[47c,49a] Noyori,[48] Landis,[84] and others[49] have likewise reached the same conclusion in the case of diphosphines as ligands. Moreover, the linearity of the conversion versus time plot implies strong binding of the substrate **10** (saturation kinetics). We also observed that the enantioselectivity remains constant in the pressure range of 1 to 12 bar (98.0% *ee*), which is of practical importance in industrial applications. This situation is different from some diphosphines which show a significant dependence (lower *ee* values at high pressure).[47–49]

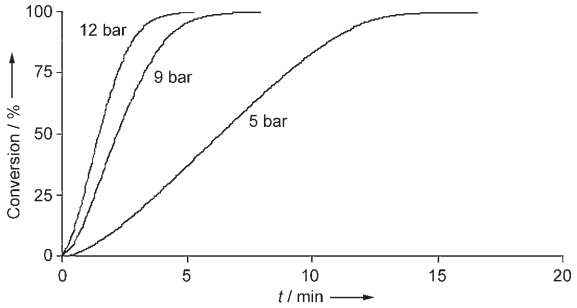


Figure 5. Influence of pressure in the hydrogenation of **10** with [Rh(cod)(**20j**)$_2$]BF_4.[67]

To define the optimal Rh/ligand ratio, the kinetics of hydrogenation of **10** was studied at a substrate/Rh ratio of 20000:1 using **20j** as the ligand.[67] Figure 6 shows that a Rh/ligand ratio of 1:2 is optimal, which is in line with the original hypothesis that two monophosphites are bound to the metal in the transition state of hydrogenation. Several other phosphites **20** were shown to behave similarly. Finally, steric and electronic effects became apparent when studying the kinetics of several other ligands **20**. Electron-withdrawing groups in the alkoxy moiety, as in **20m**, decrease the reaction rate. The sulfur analogue of **20e** derived from thiophenol also results in a lower hydrogenation rate and somewhat lower enantioselectivity (86% *ee*).[62d] In general, phosphites **20** lead to catalyst systems which are more active than those utilizing phosphoramidites **22**.

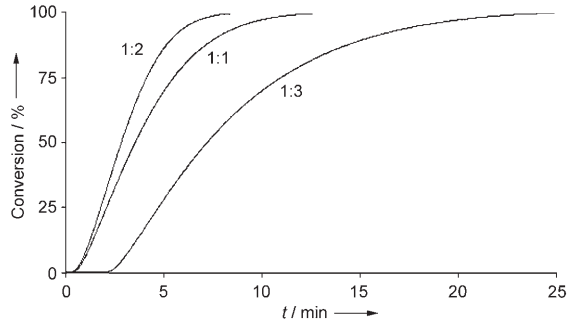


Figure 6. Influence of the Rh/**20j** ratio in the hydrogenation of **10** with [Rh(cod)(**20j**)$_2$]BF_4.[67]

We also studied nonlinear effects in the hydrogenation of itaconate **10** using the isopropyl–phosphite **20g** as the ligand.[67] Figure 7 demonstrates that a conventional positive NLE operates, which constitutes evidence that two ligands are attached to Rh in the transition state. The data was interpreted satisfactorily on the basis of the Kagan/Blackmond model of NLEs.[85]

Finally, a DFT investigation of the Rh-catalyzed hydrogenation of **10** using **20g** as the ligand was carried out with the aim of shedding further light on the mechanism.[67] Landis

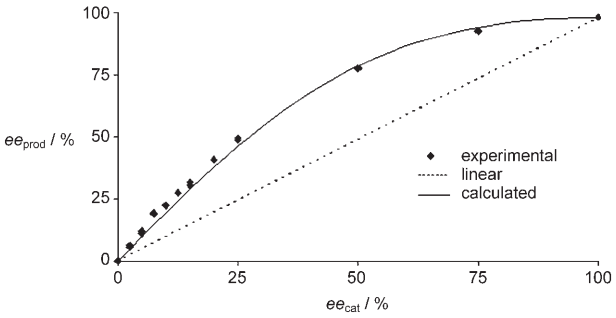


Figure 7. Nonlinear effects in the hydrogenation of **10** with [Rh(cod)-(**20g**)$_2$]BF$_4$.[67]

et al. had previously performed similar quantum mechanical (QM) studies of Rh-catalyzed olefin hydrogenations in which diphosphines serve as bidentate ligands.[84] In our reaction, as in classical hydrogenations utilizing diphosphines, the prochiral olefin first coordinates to Rh on its pro-*R* and pro-*S* side (following cod cleavage), leading to diastereomeric Rh complexes. In the case of C_2-symmetric diphosphines, two such complexes are formed, namely the more stabile (major) and the less stabile (minor) intermediates (Halpern nomenclature in parentheses).[83,84] Researchers in the field agree that subsequently hydrogen arrives from the side of the metal, which defines the chemical pathway. In the Halpern system, it is the minor diastereomer which leads to the observed stereochemical outcome.[83]

In the case of [Rh(**10**)(**20g**)$_2$]BF$_4$, the situation is more complex relative to Rh–olefin complexes involving diphosphines because two monodentate P ligands participate. Since C_2 symmetry no longer holds, four different catalyst/substrate complexes need to be considered, namely two diastereomeric pairs. In the case of C_2-symmetric diphosphines, only two catalyst/substrate complexes are relevant. Furthermore, it was found by DFT calculations that in each case a number of low-energy conformers exist, which makes the analysis more complicated than originally anticipated.[67] The lowest-energy pro-*S* and pro-*R* conformers are shown in Figure 8. The difference in energy was calculated to be $\Delta G^{\ddagger}_{298} = 2.2$ kcal mol^{-1}. The most significant result of the DFT study is the finding that the more stable (major) intermediate leads to the observed absolute configuration of product **11**. Therefore, an anti-Halpern system is operating, which means that the reaction proceeds through the thermodynamically favored intermediate.[67] Previously, Heller et al. had demonstrated unambiguously the existence of an anti-Halpern system in another case involving traditional C_2-symmetric diphosphines and β-acylamino acrylates as the substrates.[86] Still another case had been suggested by Evans et al.[87] Thus, the question of Halpern versus anti-Halpern behavior depends on the nature of the ligand and on the type of olefin. Indeed, Halpern himself had never claimed generality.[83] Unfortunately, it is currently impossible to make reliable predictions without extensive QM calculations, and even then the answer may remain ambiguous. Obtaining new and efficient ligands for asymmetric hydrogenation on the basis of design, meaning in the absence of trial and error, remains a challenge. For this reason combinatorial approaches constitute a logical option, a conclusion that may also be relevant in other types of reactions.

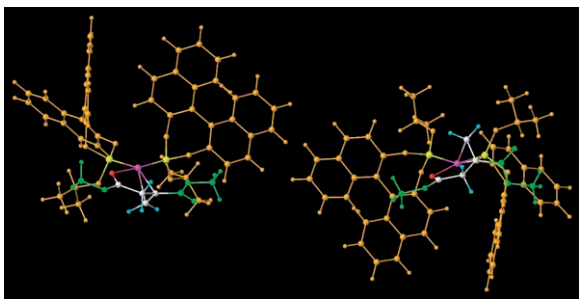
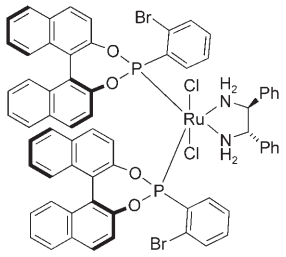


Figure 8. Lowest-energy pro-*S* and pro-*R* conformers of [Rh(olefin)-(**20g**)$_2$]$^+$ with **10** as the olefin. Left: $\Delta G_{298} = 2.2$ kcal mol^{-1}; right: $\Delta G_{298} = 0$ kcal mol^{-1}. Colors: catalyst framework uniformly brown with P yellow and Rh magenta; in the central part of the olefin: C white, H cyan, O red; outer parts of olefin are uniformly green.[67]

Although mechanistically not (yet) well understood, the work of Wills et al. on the Ru-catalyzed asymmetric transfer hydrogenation of prochiral ketones using binol-derived monophosphonites deserves attention.[88a] It was shown that two such ligands in addition to a chiral diamine are bound to ruthenium. Only the 2-bromo (**39**) and 2-methoxy derivatives



39

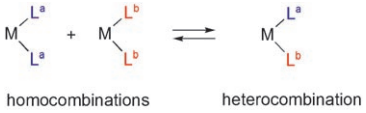
lead to a high enantioselectivity, whereas the α-methyl or α-ethyl derivatives are poor ligands. Although these observations are difficult to explain, they do show that monodenate P ligands can be useful in ketone reductions and not just in olefin reductions. However, a chiral diamine is required, which is not the case when using binol-derived diphosphonites.[88b]

3. The Concept of Using Mixtures of Monodentate Ligands

3.1. Prerequisites

The synthetic and mechanistic work described above (Section 2) inspired us to propose a new method in combinatorial homogeneous transition-metal catalysis: the use of mixtures of monodentate ligands. The idea of mixtures may sound counterintuitive because chemists traditionally aim for single well-defined homogeneous catalysts. However, as first demonstrated in 2002/2003,[41,42,62c,d] the concept is viable if applied properly.

The methodology is relevant whenever at least two monodentate ligands L are coordinated to the metal M of the active catalyst [ML_n] in the transition state of a reaction.[41,42,62c,d] The simplest case involves a mixture of two such ligands L^a and L^b, in which three different catalysts exist in equilibrium with one another, namely the two homocombinations [ML^aL^a] and [ML^bL^b] and the corresponding heterocombination [ML^aL^b] (Scheme 6). If the ratio



Scheme 6. Illustration of the concept of using mixtures of monodentate ligands L^a and L^b in a transition-metal-catalyzed reaction.[41,42,62c,d]

of components M, L^a, and L^b is chosen to be 1:1:1, then the ratio of [ML^aL^a]/[ML^bL^b]/[ML^aL^b] is not necessarily statistical (1:1:2). Rather, under thermodynamic conditions very different ratios are likely to result. The ideal case would constitute an equilibrium completely in favor of the heterocombination [ML^aL^b] because then only a single well-defined catalyst would exist in the reaction flask. If ligand exchange is fast and reversible (which is the general case), the position of the equilibrium can be influenced by adjusting the amounts of the ligands L^a and L^b relative to each other and relative to the metal. Even if a mixture of catalysts exists, the concept is valid, provided the heterocombination is more reactive and more selective than either of the two homocombinations. This applies to every kind of selectivity, including enantio-, diastereo-, and regioselectivity. If such selectivities are not relevant in a given reaction, this approach may still be of interest, namely when attempting to increase the rate of a reaction.[62d] The concept featured in Scheme 6 is related but certainly not identical to the idea of dynamic combinatorial chemistry as developed by Sanders et al.[89a] and Lehn.[89b]

Since the catalytic profiles of homocombinations [ML^aL^a] and [ML^bL^b] are already difficult to predict by theory (see Section 2), anticipating the catalytic properties of the respective heterocombination [ML^aL^b] is even more challenging. Therefore, to identify the optimal heterocombination from a library of ligands, an empirical combinatorial protocol is necessary.[41,42,62c,d] As time goes on and more experience accumulates, trends and hopefully theoretical models will emerge, which will aid the practicing chemist in new situations.

As the size of a library of *n* monodentate ligands increases, so does catalyst diversity as a consequence of mixing (Table 2). For example, once 20 different ligands have been prepared, not only are 20 different catalyst systems accessible according to traditional thinking, but also 190 additional catalysts in the form of the respective heterocombinations. Upon expanding the size of a library of monodentate ligands to 50, 100, or 200, the calculated number of heterocombinations increases drastically to 1225, 4950, and 19900, respectively. Thus, an explosion of catalyst diversity is possible without the need to synthesize any new ligands. Not all of the theoretically possible combinations may be meaningful in a given case, and these can be eliminated from further consideration on chemical grounds, thereby reducing the screening effort.

Table 2: Mixtures of monodentate ligands generate high catalyst diversity without the need to prepare new ligands.

Number of ligands (*n*)	$\frac{n(n+1)}{2}-n$ Heterocombinations
20	190
50	1225
100	4950
150	11175
200	19900
500	124750

When enantioselectivity is the focus, L^a and L^b are usually both chiral, as in the initial report.[41a] Nevertheless, in the patent[41b] and in academic papers,[41c,42] it was shown that in some systems only one ligand L^a needs to be chiral while the second one (L^b) can be achiral. Moreover, both L^a and L^b can be achiral when attempting to enhance or reverse diastereo-[90] or regioselectivity,[91] or simply when trying to increase the reaction rate.[62d]

All of the systems reported so far adhere to this description, but it is conceivable that more than two monodentate ligands can participate. It is well known that in some catalyst systems, [ML_n] is a nonactive resting state which upon dissociation of one ligand generates the catalytically active species [ML_{n-1}]. In this case *n* has to be at least 3, but the number of ligands can of course be higher. Consequently, reactions can also be considered in which three or more monodentate ligands are coordinated to the metal in the transition state of the reaction. In such cases three or more different ligands L^a, L^b, L^c, etc. can in principle be used in mixtures, which would give rise to very high catalyst diversity. To date this intriguing possibility has not been explored. If [ML_{n-2}] is the active species, then *n* needs to be at least 4. Finally, isolated cases of systems comprised of mixtures of chiral bidentate and achiral monodentate ligands have been described, as in the asymmetric Ir-catalyzed hydrogenation of quinolines, which will not be treated further in this review.[92]

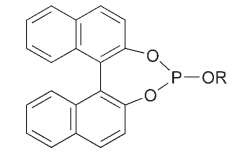
Thus far only monodentate P compounds have been tested in mixtures, although in principle monodentate C, N, O, or S ligands can also be considered. Rapid ligand exchange is necessary, which may not always be the case. C ligands of the nucleophilic carbene type may be such a case. The mechanistic dividing line between the concept described here and the traditional use of additives or activators may not be sharp in some cases.[34–36,60,61]

3.2. Controlling Enantioselectivity by Using Mixtures of Monodentate P Ligands

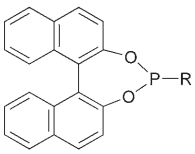
3.2.1. Mixtures of Two Chiral P Ligands

In the studies reported so far, only very small ligand libraries were constructed, which means that the full potential of the mixture concept has not been exploited. Nevertheless, significant results have accumulated. The seminal study involved Rh-catalyzed olefin hydrogenation using a relatively

small library of eight binol-derived phosphites **20a–h**, five phosphonites **21a–e**, and the chloride **19** as the monodentate ligands.[41a] The first type of prochiral olefins to be considered for asymmetric hydrogenation were *N*-acetamido acrylates

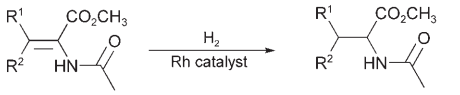


20a R = CH_3
b R = C_2H_5
c R = *c*-C_6H_{11}
d R = $C(CH_3)_3$
e R = C_6H_5
f R = 2,6-$(CH_3)_2C_6H_3$
g R = $CH(CH_3)_2$
h R = 9-fluorenyl



21a R = CH_3
b R = C_2H_5
c R = *c*-C_6H_{11}
d R = $C(CH_3)_3$
e R = C_6H_5

26a,**b**, which lead to the amino acid derivatives **40a**,**b** [Eq. (7)]. $[Rh(cod)_2]BF_4$ was treated with two equivalents of monodentate ligands with formation of the precatalysts $[Rh(cod)L_2]BF_4$.



(7)

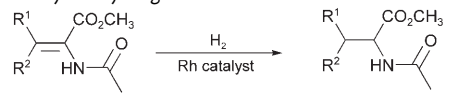
26a $R^1 = R^2 = H$
b $R^1 = H$, $R^2 = C_6H_5$

40a $R^1 = R^2 = H$
b $R^1 = H$, $R^2 = C_6H_5$

The library of 14 ligands under consideration allows for 91 heterocombinations, but only 31 were actually tested. This means that a mere 30% of chemical space was explored.[41a] Table 3 shows that several hits were identified, revealing moderately positive effects in several cases. An effect is defined as positive if the heterocombination results in an enantioselectivity which is higher than that of the best respective homocombination. One of the notable hits is the combination (*R*)-**20a**/(*R*)-**20f**, leading to an *ee* value of 84.6% (*S*), compared to the respective homocombinations (*R*)-**20a** and (*R*)-**20f**, which result in *ee* values of only 76.6% (*S*) and 32.4% (*S*), respectively (Table 3, entry 19 versus entries 1 and 6). The best catalyst in the whole library of homo- and heterocombinations is the heterocombination comprising (*R*)-**21a**/(*R*)-**21c**, which leads to an *ee* value of 97.9% (*S*; Table 3, entry 41). The respective homocombinations result in markedly lower *ee* values of 91.8% (*S*) and 92.0% (*S*), respectively (Table 3, entries 9 and 11). This initial set of experiments indicates that the combination of a sterically small ligand and a bulky ligand constitutes the mixture of choice. This observation was made in numerous subsequent cases as well, although exceptions exist.

Upon considering the hydrogenation of **26b** leading to the phenylalanine derivative **40b**, the combinatorial search was restricted to the six ligands **21a–e** and **19**.[41a] In this case, significant improvements were achieved by the process of mixing the ligands: (*R*)-**21a**/(*R*)-**21c** (96.7% *ee* (*S*)); (*R*)-**21a**/(*R*)-**21d** (99.2% *ee* (*S*)); (*R*)-**21b**/(*R*)-**21d** (94.6% *ee* (*S*)) versus (*R*)-**21a**/(*R*)-**21a** (89.9% *ee* (*S*)); (*R*)-**21b**/(*R*)-**21b** (89.2% *ee* (*S*)); (*R*)-**21d**/(*R*)-**21d** (69.1% *ee* (*S*)). Thus, the previously observed phenomenon regarding the combination

Table 3: Rh-catalyzed hydrogenation of **26a**.[a] [41a]



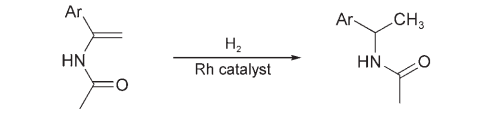
26a $R^1 = R^2 = H$ **40a** $R^1 = R^2 = H$

Entry	Ligands	*ee* [%] (config.)
Homocombinations		
1	(*S*)-**20a**/(*S*)-**20a**	76.6 (*R*)
2	(*S*)-**20b**/(*S*)-**20b**	83.6 (*R*)
3	(*R*)-**20c**/(*R*)-**20c**	94.6 (*S*)
4	(*S*)-**20d**/(*S*)-**20d**	95.4 (*R*)
5[b]	(*S*)-**20e**/(*S*)-**20e**	78.6 (*R*)
6[c]	(*S*)-**20f**/(*S*)-**20f**	32.4 (*R*)
7	(*S*)-**20g**/(*S*)-**20g**	94.4 (*R*)
8	(*S*)-**20h**/(*S*)-**20h**	92.4 (*R*)
9	(*R*)-**21a**/(*R*)-**21a**	91.8 (*S*)
10	(*R*)-**21b**/(*R*)-**21b**	94.4 (*S*)
11	(*R*)-**21c**/(*R*)-**21c**	92.0 (*S*)
12	(*R*)-**21d**/(*R*)-**21d**	93.3 (*S*)
13	(*R*)-**21e**/(*R*)-**21e**	72.8 (*S*)
14[d]	(*R*)-**19**/(*R*)-**19**	7.4 (*S*)
Heterocombinations		
15	(*R*)-**20a**/(*R*)-**20b**	80.0 (*S*)
16	(*R*)-**20a**/(*R*)-**20c**	76.6 (*S*)
17	(*R*)-**20a**/(*R*)-**20d**	89.0 (*S*)
18	(*R*)-**20a**/(*R*)-**20e**	77.4 (*S*)
19	(*R*)-**20a**/(*R*)-**20f**	84.6 (*S*)
20	(*R*)-**20a**/(*R*)-**20g**	87.2 (*S*)
21	(*R*)-**20a**/(*R*)-**21a**	81.9 (*S*)
22	(*R*)-**20a**/(*R*)-**21c**	96.4 (*S*)
23	(*R*)-**20a**/(R-)**21d**	98.0 (*S*)
24	(*R*)-**20b**/(*R*)-**20c**	79.0 (*S*)
25	(*R*)-**20b**/(*R*)-**20d**	91.2 (*S*)
26	(*R*)-**20b**/(*R*)-**20e**	80.8 (*S*)
27	(*R*)-**20b**/(*R*)-**20g**	90.0 (*S*)
28	(*R*)-**20c**/(*R*)-**20d**	94.2 (*S*)
29	(*R*)-**20c**/(*R*)-**20e**	73.6 (*S*)
30	(*R*)-**20c**/(*R*)-**20g**	94.6 (*S*)
31	(*R*)-**20c**/(*R*)-**21a**	94.4 (*S*)
32	(*R*)-**20c**/(*R*)-**21d**	94.6 (*S*)
33	(*R*)-**20d**/(*R*)-**20e**	92.2 (*S*)
34	(*R*)-**20d**/(*R*)-**20g**	94.8 (*S*)
35	(*R*)-**20d**/(*R*)-**21a**	93.0 (*S*)
36	(*R*)-**20d**/(*R*)-**21c**	91.8 (*S*)
37	(*R*)-**20e**/(*R*)-**20g**	91.2 (*S*)
38	(*R*)-**20h**/(*R*)-**21c**	95.6 (*S*)
39	(*R*)-**20h**/(*R*)-**21d**	97.2 (*S*)
40	(*R*)-**21a**/(*R*)-**21b**	92.6 (*S*)
41	(*R*)-**21a**/(*R*)-**21c**	97.9 (*S*)
42	(*R*)-**21a**/(*R*)-**21d**	97.8 (*S*)
43	(*R*)-**21c**/(*R*)-**21d**	94.1 (*S*)
44	(*R*)-**21d**/(*R*)-**21e**	75.8 (*S*)
45	(*R*)-**21d**/(*R*)-**19**	racemic

[a] Rh/substrate ratio 1:1000; Rh/P ratio 1:2. Solvent: CH_2Cl_2; $p(H_2) = 1.3$ bar; $T = 20$°C; reaction time: 20 h; conversion: 100%. [b] Conversion: 93%. [c] Conversion: 62%. [d] Conversion: 1%.

of a small and a large ligand as being the best catalyst system is operating here as well.

In the Rh-catalyzed asymmetric hydrogenation of *N*-acyl enamines **28a–c** with formation of chiral amines **41a–c** [Eq. (8)], the combinatorial search was again confined to the use of the minilibrary **21a–e** and **19**.[41a] The positive effect of mixing ligands proved to be much more dramatic than in the case of the previous substrates. Upon performing a total of only 30 hydrogenation experiments, several highly selective combinations were discovered. For example, the best catalyst for the hydrogenation of substrate **28a** is again the "small/large" heterocombination (*R*)-**21a**/(*R*)-**21d** (96.1% *ee* (*S*)).[41a] This positive effect needs to be compared to the performance of the respective homocombinations: (*R*)-**21a**/(*R*)-**21a** (75.6% *ee* (*S*)) and (*R*)-**21d**/(*R*)-**21d** (13.2% *ee* (*S*)).



(8)

28 a R = C_6H_5
b R = *p*-ClC_6H_4
c R = 2-naphthyl

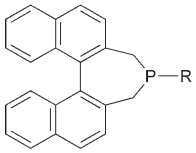
41 a R = C_6H_5
b R = *p*-ClC_6H_4
c R = 2-naphthyl

For **28a**:
(*R*)-**21a**/(*R*)-**21a** : 75.6% *ee* (*S*) [homocombination]
(*R*)-**21d**/(*R*)-**21d** : 13.2% *ee* (*S*) [homocombination]
(*R*)-**21a**/(*R*)-**21d** : 96.1% *ee* (*S*) [heterocombination]

Similar results were observed in the hydrogenation of olefin **28b**, for which the product **41b** (95% *ee*) is an important chiral intermediate in the plant-protecting industry. In the case of the naphthyl derivative **28c**, the effect of mixing ligands **21a** and **21d** proved to be even more dramatic, with the mixture achieving 97.0% *ee* (*S*), whereas the individual ligands alone provided *ee* values of only 78.2% (*S*) and less than 3% (*S*), respectively. This result means that one of the homocombinations (**21d**) alone delivers essentially a racemate.[41a] The process of mixing also increases the reaction rate.

All of these experiments were performed using a Rh/L^a/L^b ratio of 1:1:1. To explore the possible effect of varying the ratio of the two phosphonites **21a**/**21d** while maintaining the original ratio of metal to total amount of ligand (Rh/L = 1:2), additional hydrogenations were carried out employing substrate **28a**. Upon raising the relative amount of the bulky *tert*-butyl phosphonite (**21a**/**21d** = 1:3), the increased to 97.4% (*S*). When doing the opposite (**21a**/**21d** = 3:1), the *ee* value decreased to 85.0% (*S*). Thus, this early study[41a] demonstrates two phenomena: 1) Variation of the ligand ratio in a heterocombination constitutes a further tool for catalyst optimization. 2) In this particular case the bulkier of the two ligands dominates when attempting to increase enantioselectivity beyond the *ee* value obtained when using the "usual" 1:1 ratio of ligands L^a/L^b. In later studies regarding other substrates the effects are even greater (see this section). When considering a given heterocombination, it must be remembered it is really a mixture of three catalysts, not just [ML^aL^b] alone. The two homocombinations [ML^aL^a] and [ML^bL^b] compete in the reaction vessel, thus lowering the true *ee* value of the pure heterocombination.

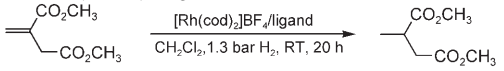
In a subsequent study in which the asymmetric Rh-catalyzed hydrogenation of the same substrates **28a–c** was considered once more, phosphites **20** and the known phosphines **42**,[93a] which had previously been used by Beller et al. as ligands in the Ru-catalyzed reduction of β-keto esters with *ee* values up to 95%,[93b,c] were included.[94] In all cases *S*-configurated ligands were used leading to (*R*)-**41**. Again certain mixtures proved to be the superior catalyst systems.[94] For example, in the hydrogenation of **28a**, mediocre results were obtained from using the homocombinations **20a** (76% *ee*), **21d** (13.2% *ee*), or **42a** (24% *ee*), whereas markedly better results were observed upon testing mixtures of these ligands such as **20a**/**21d** (95% *ee*), **20a**/**42a** (89% *ee*), or **21a**/**42a** (87% *ee*). Here once more the same trend regarding the combination of a strerically small ligand and a bulky ligand is apparent. However, an exception to this guideline was observed when testing the heterocombination **20j**/**21d** (97.4% *ee*) and comparing it to the previously studied ligand pair **20a**/**21d** (95% *ee*).[94]



42 a R = $C(CH_3)_3$
b R = C_6H_5

The third class of olefins studied in the initial publication pertains to dimethyl itaconate (**10**) with formation of the chiral diester **11**.[41a] Table 4 shows that the effect of mixing is again notable. Moreover, it was clearly demonstrated here and in the other cases that not only enantioselectivity increases markedly upon mixing the appropriate ligands, but concomitantly also the rate of hydrogenation.

Table 4: Rh-catalyzed hydrogenation of **10**.[a] [41a]

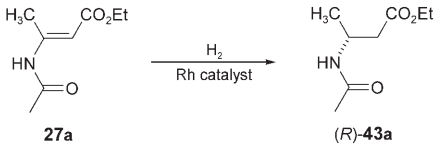


10 **11**

Entry	Ligands	*ee* [%] (config.)
Homocombinations		
1	(*R*)-**21a**/(*R*)-**21a**	90.2 (*R*)
2	(*R*)-**21b**/(*R*)-**21b**	71.4 (*R*)
3	(*R*)-**21c**/(*R*)-**21c**	21.9 (*R*)
4	(*R*)-**21d**/(*R*)-**21d**	57.3 (*R*)
5	(*R*)-**21e**/(*R*)-**21e**	28.8 (*R*)
Heterocombinations		
6	(*R*)-**21a**/(*R*)-**21b**	82.4 (*R*)
7	(*R*)-**21a**/(*R*)-**21c**	88.6 (*R*)
8	(*R*)-**21a**/(*R*)-**21d**	96.4 (*R*)
9	(*R*)-**21b**/(*R*)-**21d**	92.2 (*R*)
10	(*R*)-**21c**/(*R*)-**21d**	69.1 (*R*)
11	(*R*)-**21c**/(*R*)-**21e**	50.0 (*R*)
12	(*R*)-**21d**/(*R*)-**21e**	57.4 (*R*)

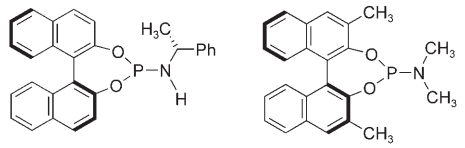
[a] In all cases the ratio Rh/P was kept constant at 1:2 and the Rh/substrate ratio at 1:1000. Solvent: CH_2Cl_2; $p(H_2) = 1.3$ bar; $T = 20$°C; reaction time: 20 h; conversion: 100%.

These and other results of this early study demonstrated that the enhancement of enantioselectivity and reaction rate as a result of mixing two chiral monodentate ligands was not just a fortuitous event observed in a single case, but that a new principle in combinatorial asymmetric catalysis had emerged. Following our initial reports, a note by de Vries, Feringa, et al appeared, describing the benefits of mixing certain binol-derived phosphoramidites in the Rh-catalyzed hydrogenation of the β-(acylamino)acrylate **27a** with formation of the β-amino acid derivative (*R*)-**43a** [Eq. (9)].[95]



27a (*R*)-**43a** (9)

The use of the parent binol-derived phosphoramidite ligands **22** with standard R groups at nitrogen (for example, R = CH_3) failed to induce notable effects. In contrast, the 1:1 mixture of the structurally modified binol derivatives (*S*,*R*)-**44**

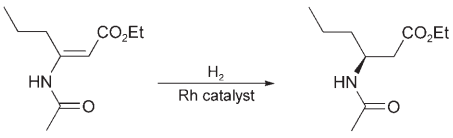


(*S*,*R*)-**44** (*S*)-**45**

and (*S*)-**45** responded positively when used as the ligand system in the hydrogenation of substrate **27a**. The heterocombination (*S*,*R*)-**44**/(*S*)-**45** led to 91% *ee* (*R*), whereas the two homocombinations by themselves proved to be mediocre ligands, providing *ee* values of only 80% (*R*) and 54% (*R*), respectively.[95] Thus, the increase in *ee* value upon mixing is small, yet noteworthy. The heterocombination comprises three elements of chirality, but the other diastereomeric combinations, which may give rise to match/mismatch effects,[53] were not considered.

In contrast to the best heterocombination (*S*,*R*)-**44**/(*S*)-**45**, we showed that appropriate mixtures of phosphites **20** and phosphonites **21** constitute a much better ligand system for the asymmetric Rh-catalyzed hydrogenation of the important class of β-acylamino acrylates **27**.[96] Five different substrates were successfully hydrogenated, including **27a**, the *ee* values in all cases being greater than 98%. The combination of a binol-derived phosphite with a relatively small substituent at phosphorus (**20a**) and one with a bulky phosphonite (**21d**) ensured optimal results. Only one example is shown here [Eq. (10)], and the reader is referred to the original literature for further substrates of this kind.[96] In all cases *R* ligands lead to *S* products.

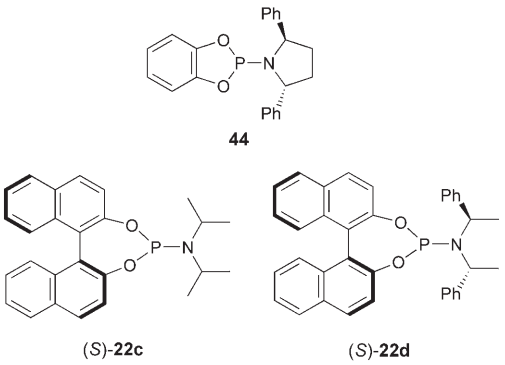
The principle of mixing monodentate ligands in transition-metal-catalyzed reactions is not restricted to asymmetric hydrogenation.[41] It was also applied to the asymmetric Rh-catalyzed conjugate addition of aryl boronic acids,[97] a synthetically useful reaction type originally developed by



27b (*S*)-**43b** (10)

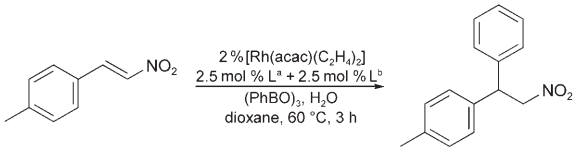
(*R*)-**20a**/(*R*)-**20a**: 85% *ee* [homocombination]
(*R*)-**21d**/(*R*) **21d**: 31% *ee* [homocombination]
(*R*)-**20a**/(*R*)-**21d**: 98% *ee* [heterocombination]

Miyaura, Hayashi, et al.[98] and applied by others.[99] Only three monodentate P ligands were tested in this study, namely the phosphoramidites **44**, (*S*)-**22c**, and (*S*)-**22d**. The nitro-



44 (*S*)-**22c** (*S*)-**22d**

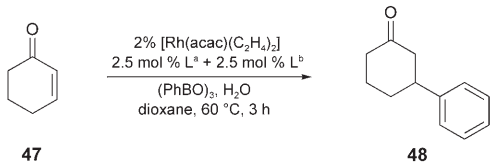
styrene **45** was initially employed as the Michael acceptor.[97] As can be seen, the effect of mixing is visible, although the results have little practical utility [Eq. (11)].



45 **46** (11)

44/**44** : –7% *ee* [homocombination]
(*S*)-**22c**/(*S*)-**22c** : 23% *ee* [homocombination]
(*S*)-**22d**/(*S*)-**22d** : 28% *ee* [homocombination]
44/(*S*)-**22c** : 31% *ee* [heterocombination]
44/(*S*)-**22d** : 37% *ee* [heterocombination]
(*S*)-**22c**/(*S*)-**22d** : 47% *ee* [heterocombination]

Upon subjecting enones such as **47** to similar conditions, the mixing effect turned out to be pronounced, although again not practical.[97] The homocombination of **44**/**44** constitutes a poor ligand system (33% *ee*), as do (*S*)-**22c**/(*S*)-**22c** (−27% *ee*) and (*S*)-**22d**/(*S*)-**22d** (−16% *ee*), which favor the opposite enantiomer. Interestingly, the heterocombination **44**/(*S*)-**22d** leads to 77% *ee*, while the combination (*S*)-**22c**/(*S*)-**22d** results in an *ee* value of −60% *ee* [Eq. (12)]. Thus, one homocombination favors a given enantiomer (+) and the other the mirror-image product (−), but the respective combination results in a synergistic effect.[97] Traditional transition-metal catalysts are clearly superior,[98,99] yet the results are of theoretical interest. Moreover, they suggest that the use of a larger library of monodentate ligands might well

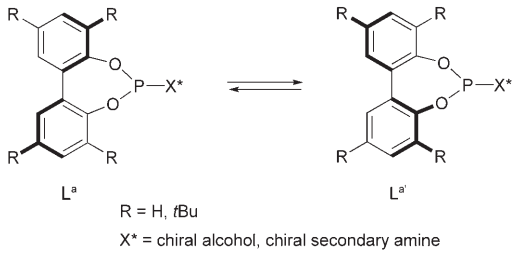


47 48 (12)

44/44	: 33% *ee*	[homocombination]
(*S*)-**22c**/(*S*)-**22c**	: –27% *ee*	[homocombination]
(*S*)-**22d**/(*S*)-**22d**	: –16% *ee*	[homocombination]
44/(*S*)-**22c**	: 75% *ee*	[heterocombination]
44/(*S*)-**22d**	: 77% *ee*	[heterocombination]
(*S*)-**22c**/(*S*)-**22d**	: –60% *ee*	[heterocombination]

afford synthetically useful levels of enantioselectivity in a practical manner.

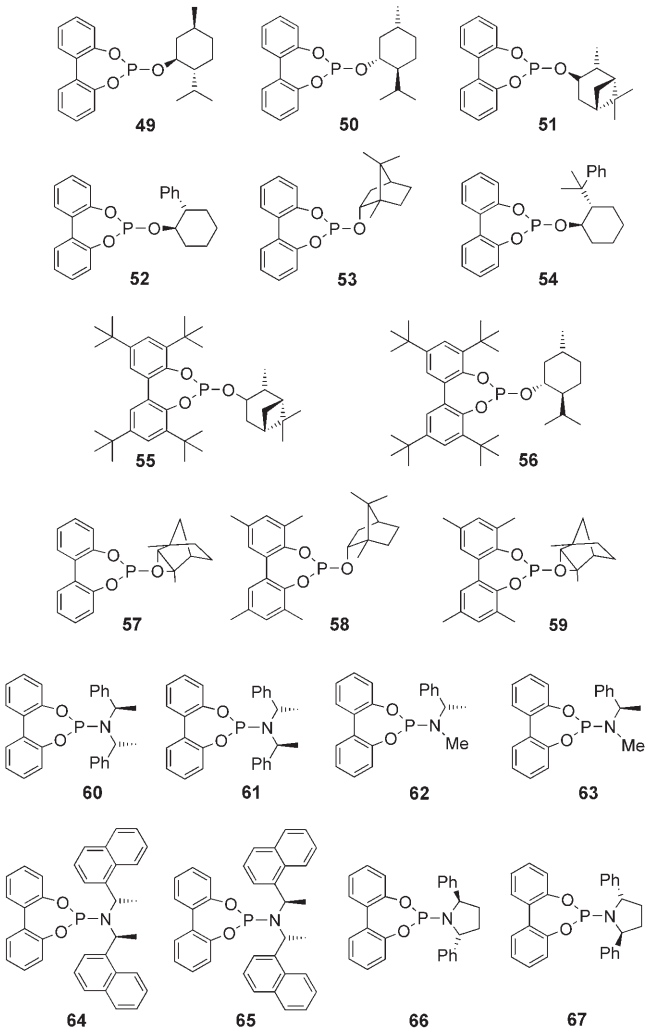
In an interesting extension of the concept of mixing monodentate compounds, Gennari et al. exploited the dynamic behavior of ligands composed of fluxional axially chiral (tropos) moieties and a covalently attached configurationally stable entity (Section 2) in Rh-catalyzed olefin hydrogenation (Scheme 7).[100] If two different ligands of



Scheme 7. Chiral phosphorus ligands based on a chiral P-bound alcohol or secondary amine and a flexible (tropos) P-bound biphenol unit.[100]

this kind are used in a mixture, an intriguing situation arises. When employing a "single" ligand, two diastereomeric homocombinations [ML^{a}L^a] and [ML$^{a'}$L$^{a'}$] as well as the heterocombination [ML^{a}L$^{a'}$] are possible. Consequently, three diastereomers are actually involved in the mixture, which are likely to have different catalytic profiles in terms of activity and enantioselectivity (which cannot be measured owing to rapid interconversion). Moreover, the ratio of the three species is not expected to be statistical (1:1:2) because the relative proportions are dictated by thermodynamics. In the case of two different ligands L^a and L^b of this kind, up to 10 different species may be formed: [ML^{a}L^a], [ML^{a}L$^{a'}$], [ML$^{a'}$L$^{a'}$], [ML^{b}L^b], [ML^{b}L$^{b'}$], [ML$^{b'}$L$^{b'}$], [ML^{a}L^b], [ML^{a}L$^{b'}$], [ML$^{a'}$L^b], and [ML$^{a'}$L$^{b'}$].[100]

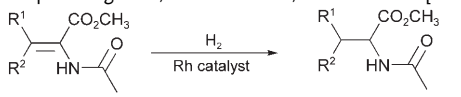
Intriguing observations were made in a study employing such compounds as **49**-**67** as ligands in the Rh-catalyzed hydrogenation of **26a**.[100] A total of 85 reactions were performed, which means that only a portion of the total chemical space was actually explored. As Table 5 shows, no homocombination of the ligands **49**–**67** performs well (some have been deleted from the list). Table 5 also contains part of the data from mixing, which indicates that certain phosphite/phosphoramidite combinations are optimal.[100] The best hit is **52**/**61**, which leads to an *ee* value of 87% (Table 5, entry 20) compared to 53% *ee* and 52% *ee* for the respective homocombinations (Table 5, entries 4 and 10). It is also clear that **52**/**61** constitutes the matched system, because **52**/**60** provides an *ee* value of only 35% (Table 5, entry 19). Similar results were observed when hydrogenating other substrates.[6e,100]



From a practical point of view the asymmetric hydrogenation of **26a** is best performed classically by using a single ligand; for example, the best phosphite **20** is picked as a result of testing a library of derivatives differing in the nature of the RO group at phosphorus (or by employing phosphonites **21** or phosphoramidites **22**). This is true in this particular example, but it may not be so in all cases. The importance of the present study lies in the proof of principle and in the mechanistic lessons learned therein. Extensive kinetic investigations were included, which led to a useful mathematical model.[100] The same system was utilized in Rh-catalyzed Miyaura–Hayashi reactions,[98] for example, **47**→**48**.[101] Enantioselectivities of up to 95% *ee* were observed when using the heterocombination **54**/**67**, compared to only 70% *ee* and 36% *ee* for the respective homocombinations.

In another study it was shown that structurally very different types of chiral monodentate P ligands can also be used successfully in mixtures.[102] These include ephedrine- and pseudo-ephedrine-derived oxazaphospholidines such as

Table 5: Selected examples of Rh-catalyzed hydrogenation of olefin **26a** using chiral tropos P ligands;[a] for full table, see reference [100].



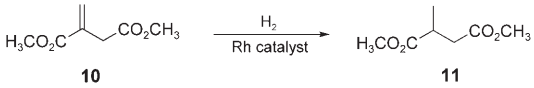
26 a $R^1 = R^2 = H$ **40 a** $R^1 = R^2 = H$

Entry	Ligands	Conversion [%]	*ee* [%] (config.)
Homocombinations			
1	**49**	100	11 (*S*)
2	**50**	100	11 (*R*)
3	**51**	100	25 (*R*)
4	**52**	80	53 (*S*)
5	**53**	100	55 (*R*)
6	**54**	100	48 (*R*)
7	**55**	100	0
8	**56**	100	36 (*S*)
9	**60**	7	52 (*R*)
10	**61**	7	52 (*S*)
11	**62**	100	44 (*S*)
12	**63**	100	44 (*R*)
13	**64**	15	0
14	**65**	15	0
15	**66**	30	13 (*S*)
16	**67**	30	13 (*R*)
Heterocombinations			
17	**49/60**	50	72 (*R*)
18	**51/61**	40	73 (*S*)
19	**52/60**	100	35 (*R*)
20	**52/61**	100	87 (*S*)

[a] Reaction conditions: $[Rh(cod)_2]BF_4$ (0.002 mmol); ligand (0.004 mmol); **26a** (0.2 mmol); $p(H_2) = 1$ bar; room temperature; 60 h; CH_2Cl_2 as solvent.

68 and **69**, known types of compounds that had previously been used by Alexakis et al. in pure form as ligands in Cu-mediated conjugate additions and other reactions.[103] In the study regarding mixtures, the small library of six ligands was extended to include the C_2-symmetric phosphites **70** and **71** (*R*,*R* and *S*,*S* configuration, respectively).[102]

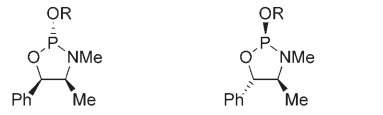
The performance of these ligands as homocombinations in the Rh-catalyzed hydrogenation of such substrates as **10** proved to be poor (0–56% *ee*).[102] Some improvements were observed through pairwise mixing. However, the best hit constitutes a mixture in which one of the components is a binol-derived monophosphonite, as in (*R*)-**21d**/**69b**, which gives rise to an *ee* value of 89% (*R*) for product **11** [Eq. (13)]. These results are all the more remarkable because one of the respective homocombinations induces the opposite sense of enantioselectivity. The diastereomeric heterocombination (*S*)-**21d**/**69b** results in considerably lower enantioseletivity (52% *ee* (*S*)), which means that this is the mismatched case.[102]



10 **11** (13)

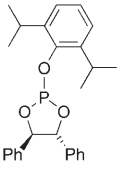
(*R*)-**21d**/(*R*)-**21d** : 56% *ee* (*R*) [homocombination]
69b/**69b** : 15% *ee* (*S*) [homocombination]
(*R*)-**21d**/**69b** : 89% *ee* (*R*) [matched heterocombination]
(*S*)-**21d**/**69b** : 52% *ee* (*S*) [mismatched heterocombination]

As already discussed in Section 2, chemical modification of binol leads to added structural diversity in the respective P ligands, although this is accomplished at the cost of additional synthetic effort. If only one naphthyl moiety in binol is modified, C_2 symmetry no longer holds, which means that the P atoms in the respective phosphites, phosphonites, or phosphoramidites turn into stereogenic centers (P_R or P_S). This gives rise to two diasteromers. We have prepared such compounds, for example, **72**–**74**, in the hope that chirality positioned closer to the Rh center would exert special effects.[104] The pure ligands as homocombinations proved to be quite effective in olefin hydrogenation reactions, as in **26a**→**40a**, with *ee* values in the range 97% to greater than 99%. In some cases an unusual effect was observed, namely that a mixture of two diastereomers differing only in the absolute configuration at phosphorus is more effective than either of the two respective homocombinations. The interesting area of ligands having stereogenic centers at phosphorus[105] has not been explored systematically in the present context.

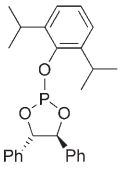


68a R = 2-naphthyl
b R = *t*-butyl
c R = 2,6-diiso-propylphenyl

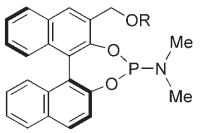
69a R = methyl
b R = *t*-butyl
c R = 2,6-diiso-propylphenyl



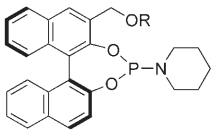
70



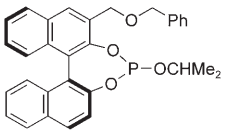
71



72a R = CPh
b R = CH_3
c R = CH_2Ph



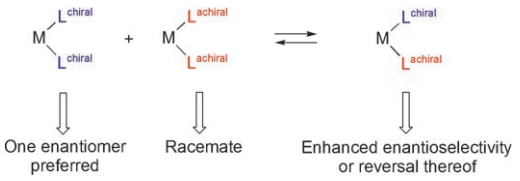
73a R = CPh
b R = CH_3
c R = CH_2Ph



74

3.2.2. *Mixtures Comprising a Chiral and an Achiral P Ligand*

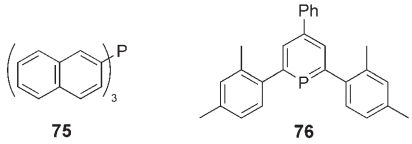
Early on, we also contemplated the use of mixtures of chiral and achiral ligands in Rh-catalyzed hydrogenation (Scheme 8).[41b,c,42,62c,d] This proposal seems counterintuitive,



Scheme 8. The concept of using mixtures of monodentate chiral and achiral ligands in transition-metal-catalyzed asymmetric reactions.[41b,c,42,62c,d]

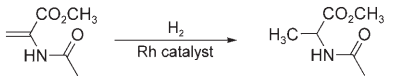
because one of the homocombinations in the mixture is achiral, necessarily leading to a racemic product. However, as before, the heterocombination may define the outcome of the reaction if it is more reactive and more enantioselective than the pure ligands themselves (or if it is the only species present). Since vast numbers of achiral P ligands are available at low cost, high structural diversity regarding the heterocombination is readily accessible.

Initially representatives of the three binol-derived types of P ligands **20**–**22** were each tested in mixtures with different achiral monodentate P ligands such as **75** or **76** and one



75 **76**

fluxional (tropos) phosphite, the hydrogenation **26a**→**40a** serving as the model reaction [Eq. (14)].[42] In most cases



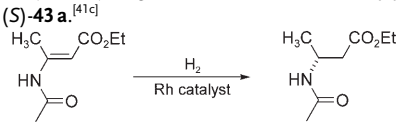
26a **40a** (14)

(*R*)-**20a**/(*R*)-**20a** : 92.0% *ee* (*S*) [homocombination]
(*R*)-**20d**/(*R*)-**20d** : 95.4% *ee* (*S*) [homocombination]
(*R*)-**21a**/(*R*)-**21a** : 92.0% *ee* (*S*) [homocombination]
(*R*)-**21d**/(*R*)-**21d** : 93.0% *ee* (*S*) [homocombination]
(*R*)-**20a/75** : 15.6% *ee* (*R*) [heterocombination]
(*R*)-**20d/75** : 34.8% *ee* (*R*) [heterocombination]
(*R*)-**21a/75** : 17.5% *ee* (*R*) [heterocombination]
(*R*)-**21a/76** : 58.6% *ee* (*R*) [heterocombination]
(*R*)-**21d/76** : 26.2% *ee* (*R*) [heterocombination]
(*R*)-**21d/76** : 52.6% *ee* (*R*) [heterocombination]

enantioselectivity decreased, which may not be surprising. However, in several instances the sense of enantioselectivity reversed upon using an achiral ligand as one of the components, especially when employing mixtures of **20** and tris(2-naphthyl)phosphine (**75**) or the phosphinine **76**, respectively. For example, the homocombination (*R*)-**21a**/(*R*)-**21a** is a respectable ligand system in the hydrogenation of **26a** (92.0% *ee* (*S*)), whereas the heterocombination **21a**/**76** induces reversal of the enantioselectivity (58.5% *ee* (*R*)).[42] Energetically, such a switch is dramatic ($\Delta\Delta G^{\neq} = 2.6$ kcal mol^{-1}), which means that the mixing effect is pronounced. Of course, to get a product with opposite absolute configuration, it is best to use the enantiomeric form of the binol-derived ligands (*S*)-**20** or (*S*)-**21**, which provide much higher *ee* values. Nevertheless, the results are of theoretical interest, and they also set the stage for further research using other mixtures of chiral and achiral monodentate ligands.[41b,c,62c,d]

Upon applying the mixture concept to chiral and achiral monodentate P ligands more systematically, remarkable observations were made.[41b,c] In this study β-*N*-acylamino acrylates **27** were used as model substrates, with phosphite **20a** and phosphonite **21d** serving as the chiral P ligands. In addition to the achiral P ligands **77**–**83**, fluxional diphenol-derived (tropos) phosphites **84a**–**d** (Section 2) were also employed [Eq. (15)]. Table 6 summarizes the results of a relatively short combinatorial search in the study of the Rh-catalyzed asymmetric hydrogenation of **27a**.[41c] It can be seen that pronounced effects result when using the *tert*-butylphosphonite **21d** as the chiral ligand in combination with achiral ligands. The homocombination **21d** leads to an *ee* value of

Table 6: Rh-catalyzed hydrogenation of olefin **27a**;[a] (*R*)-binol derivatives lead to (*S*)-**43a**.[41c]

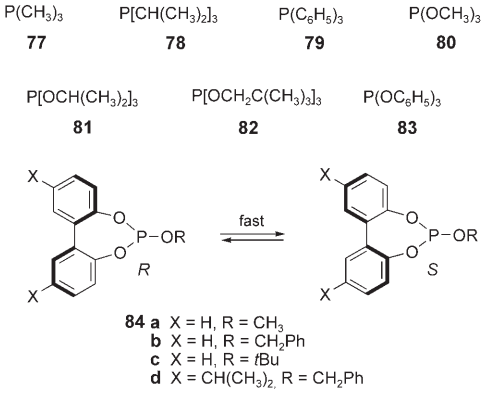


27a (*S*)-**43a**

Entry	Ligands	Conversion [%]	*ee* [%]
Homocombinations			
1	**20a**	95	75
2	**21d**	83	45
Heterocombinations			
3	**20a/78**	51	50
4	**20a/79**	92	14
5	**20a/80**	100	30
6	**20a/81**	96	30
7	**20a/82**	100	81
8	**20a/83**	84	79
9	**20a/84a**	83	73
10	**20a/84b**	92	67
11	**20a/84c**	57	83
12	**20a/84d**	97	65
13	**21d/77**	46	51
14	**21d/78**	67	17
15	**21d/79**	98	5
16	**21d/80**	99	84
17	**21d/81**	100	16
18	**21d/82**	89	45
19	**21d/83**	91	88
20	**21d/84a**	100	98
21	**21d/84b**	100	98
22	**21d/84c**	10	7
23	**21d/84d**	99	94

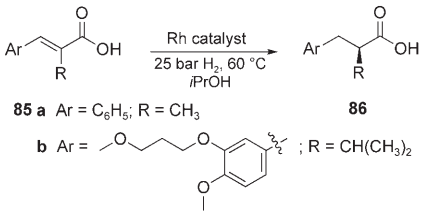
[a] Conditions: $p(H_2) = 60$ bar; CH_2Cl_2; room temperature; 20 h; Rh/**27a** = 1:50; $L^a/L^b = 1:1$; Rh/total ligands = 1:2.

only 45%. Upon employing a 1:1 mixture of **21d** and trimethylphosphite (**80**) or triphenylphosphite (**83**), the *ee* value climbs to 84 and 88%, respectively (Table 6, entries 16 and 19).[41c] When using the configurationally fluxional phosphites **84** in combination with **21d**, even higher enantioselectivities are observed. Accordingly, **21d**/**84a**, **21d**/**84b**, and **21d**/**84d** lead to *ee* values of 98, 98, and 94%, respectively (Table 6, entries 20, 21, and 23). In contrast, the sterically demanding fluxional phosphite **84c** in combination with the bulky phosphonite **21d** results in an almost racemic product (Table 6, entry 22). This result is reminiscent of the behavior of two bulky chiral P ligands (Section 3.2.1). Similar effects were observed when hydrogenating other β-acylamino acrylates **27** and itaconate **10**. For example, when hydrogenating **10**, ligand **21d** alone results in an *ee* value of 77%, whereas the use of **21d**/**83** or **21d**/**84a** boosts enantioselectivity to 94% *ee* in both cases.[41c]

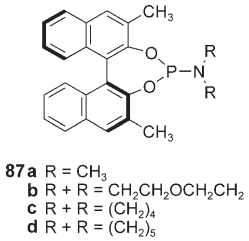


The use of stereochemically fluxional (tropos) phosphites **84** deserves a special comment. Although not rigorously proven, it is likely that the catalytically active heterocombination **21d**/**84** is the one in which both ligands have the same absolute configuration. For example, when employing (*R*)-**21d** as the chiral component, one can assume that it is the matched and more active combination (*R*)-**21d**/(*R*)-**84a** which dictates the course of the reaction, not the mismatched and presumably less active diastereomeric combination (*R*)-**21d**/(*S*)-**84a**. In a sense the additional chiral information originating from (*R*)-**84** is "free" since no optical resolution is necessary. This type of phenomenon, although for different situations, was discussed in Sections 2 and 3.1.[50,54–61]

Subsequent to these studies, Feringa, de Vries, et al. applied the idea of using a mixture of a chiral and an achiral monodentate P ligand in the hydrogenation of α,β-unsaturated acids of the type **85**, leading to chiral dihydrocinnamic acid derivatives **86** [Eq. (16)].[106] These are key intermediates in the synthesis of a number of bioactive compounds such as renin inhibitors, γ-secretase inhibitors, enkephalinase inhibitors, endothelin receptor antagonists, and opiod antagonists. A variety of different binol-derived phosphoramidites **22** with various achiral and chiral R groups in the amino group were first tested in respective mixtures with triphenylphosphine (**79**) using substrate **85a**. Unfortunately, improvements in enantioselectivity were meager. In contrast, *ortho*-dimethyl

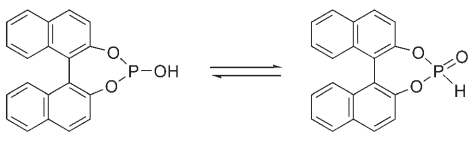


derivatives **87a–d** led to notable positive effects when used in mixtures with triphenylphosphine (**79**).[106] For example,



ligand **87d** failed completely when used alone, and this homocombination resulted in racemic product **86a** in a slow reaction. In contrast, upon using the heterocombination **79**/**87d**, a fast and quantitative reaction was found to occur with 85% *ee*. Upon tuning the achiral phosphine, further improvements proved to be possible, as in the heterocombination comprising tris(xylyl)phosphine and **87d**, leading to 92% *ee*. In other cases involving industrially relevant substrates such as **85b**, even higher *ee* values were achieved. DSM has utilized our technology[41b] in demonstrating that upscaling for industrial applications is readily achieved, as in the formation of **86b**, which is a key intermediate in the synthesis of the renin inhibitor aliskerin.[107] Similar developments were subsequently reported for other types of substrates such as *N*-formyl dehydroamino acid esters[108a] and 2-(acetylaminomethyl)-3-aryl acrylic acid esters.[108b]

In a more recent study we reported once more the remarkable effect that the process of mixing chiral and achiral monodentate P ligands can induce, specifically in the Ir-catalyzed asymmetric hydrogenation of prochiral ketimines.[109] Only a few chiral ligand systems are known to provide *ee* values of more than 90%, which indicates that enantioselective transformations of this kind are difficult.[110] In this endeavor we utilized the cheap phosphorous acid diester **88** as the chiral component together with various achiral monodentate P ligands. Phosphorous acid diesters are known to exist in an equilibrium $P^V \rightleftarrows P^{III}$, the five-valent form P^V being favored as in **88B** [Eq. (17)]. However, it is well known that transition metals bind to the P atom in the three-



valent form, as shown by crystal structures and spectroscopic data.[111] We had previously observed that this is also the case with (*S*)-**88 A** when complexed to $PtCl_2$, as proven by an X-ray structural analysis of the compound formed in the presence of NEt_3.[112] Two molecules of (*S*)-**88 A** bind to the metal, and the hydroxy moieties, which are acidified owing to the presence of Pt, are deprotonated by NEt_3 (Figure 9). In the case of the $PdCl_2$ complex in the absence of NEt_3, a dimeric structure results (Figure 10).

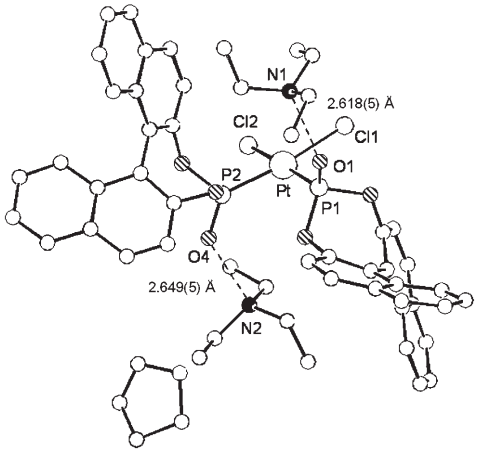


Figure 9. Crystal structure of the complex $[PtCl_2\{(S)\text{-}\mathbf{88\,A}\}_2(NEt_3)_2]$, showing the N–H···O$^-$ hydrogen-bonding interactions.[112]

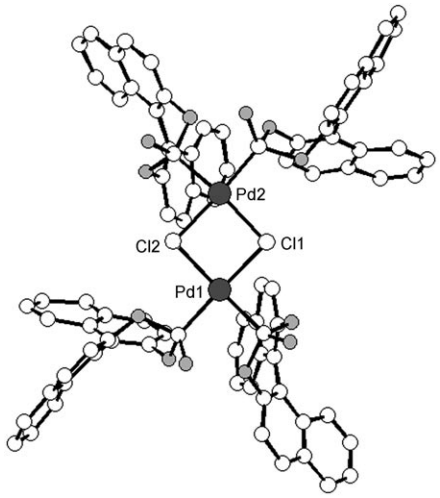
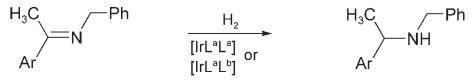


Figure 10. Crystal structure of dimeric $[PdCl_2\{(S)\text{-}\mathbf{88\,A}\}_2]$.[62c]

Subsequent to these observations we speculated that in the case of the analogous Ir complex in the absence of NEt_3, the acidified HO moiety might protonate and activate the nitrogen function of the ketimines.[109,112] Extensive diastereoselective hydrogenations of chiral ketimines were actually carried out first (Section 4); on the basis of the best results triphenylphosphine (**79**) was chosen as the achiral ligand in combination with **88**.[109] Ketimines **89 a–d** were subjected to Ir-catalyzed hydrogenation with formation of chiral amines **90 a–d** [Eq. (18)]. The results show that the chiral ligand **88** alone is a poor ligand (7–36 % *ee*), whereas the heterocombination **79**/**88** involving achiral triphenylphosphine leads to *ee* values of 88–92 %.[109] The use of (*R*)-**88** in the heterocombination results in *S*-configurated products **90**. This catalyst system thus competes well with other methods.[110] The taddol analogue of **88** has been used in asymmetric stoichiometric Michael additions,[113] as a ligand in Cu-catalyzed conjugate addition reactions,[114] and in Ir-catalyzed ketimine reduction (up to 83 % *ee*).[115]



(18)

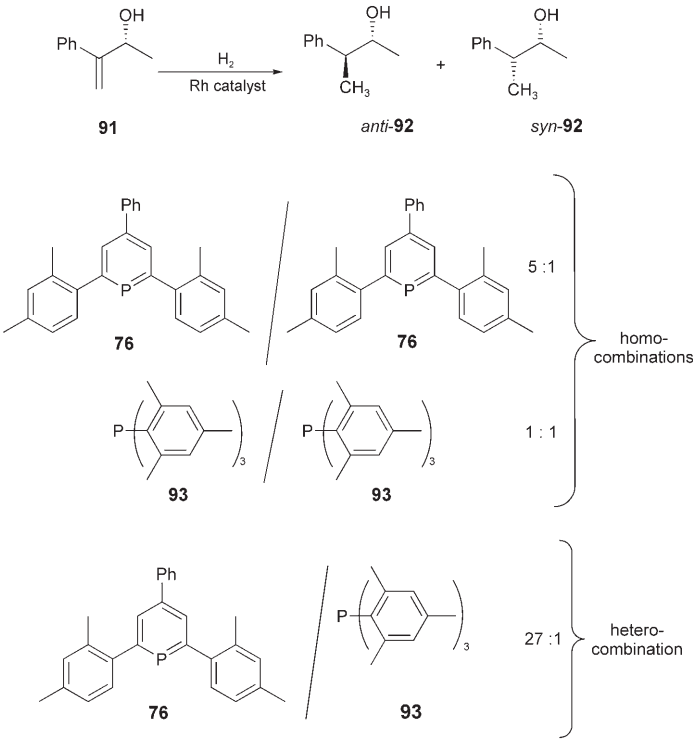
89 **a** Ar = phenyl
b Ar = 4-chlorophenyl
c Ar = 4-methoxyphenyl
d Ar = 2-naphthyl

90 **a** Ar = phenyl
88/**88** : 18% *ee*
79/**88** : 88% *ee*
b Ar = 4-chlorophenyl
88/**88** : 36% *ee*
79/**88** : 90% *ee*
c Ar = 4-methoxyphenyl
88/**88** : 35% *ee*
79/**88** : 92% *ee*
d Ar = 2-naphthyl
88/**88** : 7% *ee*
79/**88** : 92% *ee*

4. Controlling Diastereoselectivity by Using Mixtures of Monodentate P Ligands

We have extended the combinatorial concept of applying mixtures of monodentate P ligands in enantioselective processes to include the control of diastereoselectivity.[90,109] These are substrate-directable chemical reactions in which the existing stereochemical information influences the creation of a new stereogenic center (1,*n*-asymmetric induction).[116] The degree of diastereoselectivity has been shown to depend on the nature of the reagent or catalyst. In some studies chiral reagents or catalysts have been employed, although this entails a greater degree of effort. In such cases the matched/mismatched phenomenon operates.[53] In an initial investigation using mixtures of ligands, the Rh-catalyzed hydrogenation of the allylic alcohol **91** was considered which entails the traditional problem of 1,2-asymmetric induction.[90] One can expect 1,3-allylic strain to control this reaction with preferred formation of the *anti* diastereomer **92**.[117] This is indeed the case, but the degree of diastereoselectivity depends on the nature of the ligand. Using a library of 21 common monodentate P ligands that happened to be in our laboratory, most of them being achiral, a section of the chemical space was scanned, which becomes relevant when mixing the respective ligands pairwise.[90] Although a total of 210 different heterocombinations are possible, only 150 reactions were performed, which led to the identification of 15–20 positive hits. These are the heterocombinations which display a higher diastereoselectivity than either of the two respective homocombinations alone. Some of the hits resulted in extremely high diastereoselectivities.[90] An example is shown in Scheme 9, in which the optimized *anti*/*syn* ratio amounts to 27:1.

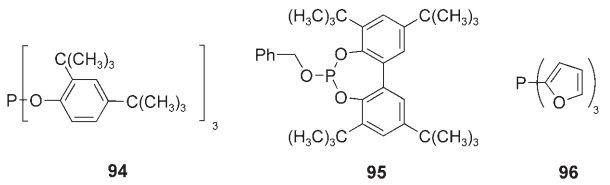
Chiral homoallylic alcohols were also studied; in this case the generally more difficult problem of 1,3-asymmetric induction was relevant. It was found that diastereoselectivi-



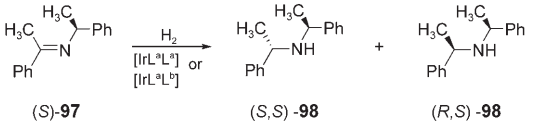
Scheme 9. Diastereoselective hydrogenation reactions.[90]

ties of up to 18:1 are possible by using mixtures of monodentate P ligands, and that reversal of diastereoselectivity (1:5) can also be achieved.[90] The reasons for this remarkable behavior have not been identified.

As already indicated in Section 3.2.2, we also studied the effect of using mixtures of monodentate P ligands in the quest to control the diastereoselectivity of the Ir-catalyzed hydrogenation of chiral ketimines. A fairly wide variety of chiral (for example, **88**) and achiral ligands such as **79**, **81**, **83**, **94**, **95**,



and **96** in the form of homo and heterocombinations were tested, and only a few results are reproduced here.[109] The Ir-catalyzed hydrogenation of the chiral ketimine (*S*)-**97** was chosen as a model reaction [Eq. (19)]. It can be seen that the two homocombinations (*R*)-**88**/(*R*)-**88** and **94**/**94** result in



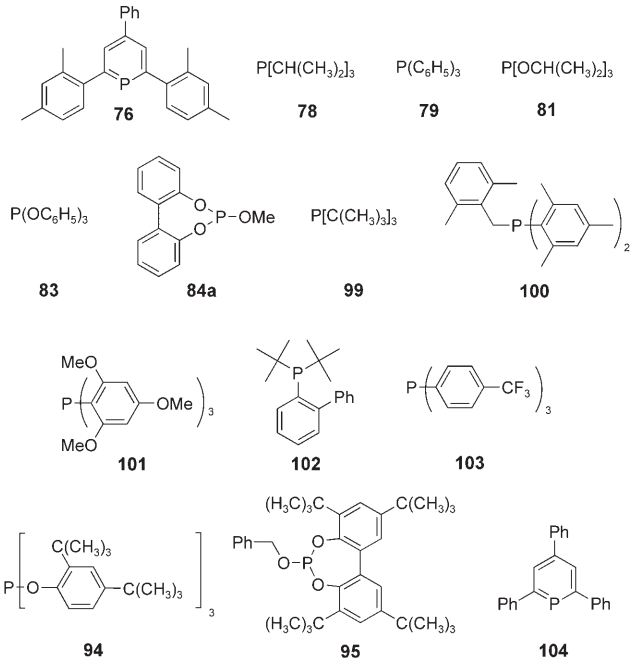
(19)

(*R*)-**88**/(*R*)-**88**	5.5 : 1	homocombinations
(*S*)-**88**/(*S*)-**88**	5.1 : 1	
94/**94**	5.3 : 1	
(*R*)-**88**/**94**	378 : 1	*matched* heterocombination
(*S*)-**88**/**94**	1 : 1	*mismatched* heterocombination

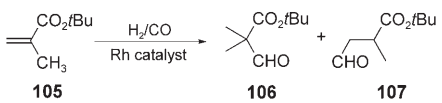
mediocre diastereoselectivities, whereas the respective matched heterocombination (*R*)-**88**/**94** leads to a spectacular diastereoselectivity of 378:1.[109] The matched versus mismatched effect[53] is dramatic in this case, because (*S*)-**88**/**94** results in unselective catalysis.[109]

5. Controlling Regioselectivity by Using Mixtures of Monodentate P Ligands

In principle, any parameter of a catalytic profile can be influenced by using mixtures of monodentate ligands. We therefore attempted to influence the regioselectivity of transition-metal-catalyzed reactions by applying this type of combinatorial catalysis. The initial target was the Rh-catalyzed hydroformylation.[91] Many different achiral monodentate P ligands are potential candidates for such an endeavor, but the combinatorial search was confined to a small library of 14 simple ligands **76**–**104**. Methacrylate **105** was chosen as the



model olefin with formation of the branched product **106** with a quaternary C atom and the linear regioisomer **107** [Eq. (20)]. As expected most common P ligands favor the linear product **107**. Thus, it was a challenge to find a catalyst system which leads to a strong preference for aldehyde **106**.



(20)

All precatalysts were prepared by treating [Rh(acac)(CO)$_2$] (acac = acetylacetonate) with the ligands, and the hydroformylation reactions were performed under standard conditions. After testing 83 of the 91 theoretically

possible heterocombinations, remarkable observations were made.[91] As expected, most of the homocombinations lead to the preferential formation of the linear regioisomer **107**, which means **106**/**107** < 1. The most notable exception was found to be phosphite **84a**, which provides a **106**/**107** ratio of 2.7:1. Attempts to increase regioselectivity by the conventional approach would require the preparation of further P ligands. In contrast, the ligand mixture approach does not require the synthesis of any new ligands. It was found that 12 heterocombinations induce the preferential formation of the branched product **106**, despite the fact that the respective homocombinations all display opposite regioselectivity favoring the linear isomer **107**. The best catalyst system results from a 1:1 mixture of phosphinine **76** and triphenylphosphine (**79**), leading to a regioselectivity of 8.4:1. The respective homocombinations induce ratios of 0.76:1 and 0.72:1, respectively. This system was then optimized by tuning the reaction conditions (80 bar $CO/H_2 = 1:1$; 40 °C, 30 h, substrate/Rh = 50:1, $L^a/L^b = 1:1$; Rh/total ligands = 1:2.4; toluene as solvent). As a result, the regioselectivity climbed to 20:1, which means 95 % regioselectivity in favor of the branched product **106**.[91]

One of the often encountered side reactions in hydroformylation is competing hydrogenation of the olefin. It was shown that the extent of this side reaction can be reduced by the proper choice of ligands in heterocombinations. One example concerns the best heterocombination **76**/**79**, which results in only 1 % side reaction. The respective homocombinations cause 6–8 % undesired hydrogenation.[91]

6. Mechanistic Challenges

In view of the considerable amount of information regarding positive hits when using mixtures of monodentate P ligands for influencing the enantio-, diastereo-, and regioselectivity of transition-metal-catalyzed transformations, the question of the origin of enhanced activity and selectivity becomes a pressing issue. Mechanistic clarity is important for several reasons. The long-term perspective of being able to design future catalysts based on mixtures is one of them. Unfortunately, to date not much useful mechanistic insight is available because, among other reasons, all past efforts have focused on synthetic aspects. It is also clear that each reaction type must be considered separately. Therefore, at present the only way to proceed when seeking an optimal ligand mixture for a given transformation is empirical, that is, by testing combinatorial libraries. Nevertheless, a few comments may be useful.

As discussed in Section 2, the mechanism of Rh-catalyzed olefin hydrogenation using monodentate P ligands in pure form (homocombination) has been clarified to a significant extent.[67] Two such ligands are attached to the metal in the transition state of the reaction, and an anti-Halpern pattern pertains (at least in the particular case studied). Of course, if a ligand is characterized by unusual steric bulk, double ligation may be prohibited,[118] and a Rh complex having only one monodentate ligand will certainly have a different catalytic profile. When considering the Rh-catalyzed olefin hydrogenation using a mixture of two different chiral P ligands, it is safe to assume that again both ligands are attached to the metal. NMR studies of the precatalysts have shown that the relative amounts of the two homocombinations $[ML^aL^a]$ and $[ML^bL^b]$ and the heterocombination $[ML^aL^b]$ are not of a statistical nature.[62c,d] Rather, the ratio is thermodynamically controlled and can therefore be influenced to a certain extent by adjusting the L^a/L^b ratio.

Generally, the heterocombination dominates. For example, when treating $[Rh(cod)_2]BF_4$ with the least bulky phophonite **21a** and the sterically most demanding analogue **21d** in a 1:1:1 ratio, the ^1H NMR spectrum of the mixture shows the presence of the two homocombinations $[Rh(\mathbf{21a})_2(cod)]BF_4$ and $[Rh(\mathbf{21d})_2(cod)]BF_4$ in addition to the heterocombination $[Rh(\mathbf{21a})(\mathbf{21d})(cod)]BF_4$ in a ratio of about 20:20:60. However, once the remaining cod in these precatalysts has been cleaved by hydrogenation, a new situation arises because solvent and/or substrate complexation sets in. So far this information is not available.

Detailed combined quantum mechanical and molcular mechanical (QM/MM) studies, as in the case of the homocombinations,[67] also need to be performed. Preliminary results show that one of the important conformers of the complex in which the heterocombination **21a**/**21d** and the substrate **26a** bind to Rh has the methyl and *tert*-butyl residues positioned in a "cisoid" geometry (Figure 11). One might speculate that lipophilic interaction between these alkyl groups supports a kind of chelation effect. However, the situation is more complex, because other conformers are likely, the relative reactivity of which is currently unknown.[62c,d,119] Moreover, it is not yet clear whether hydrogenation using this heterocombination constitutes a Halpern or an anti-Halpern case.

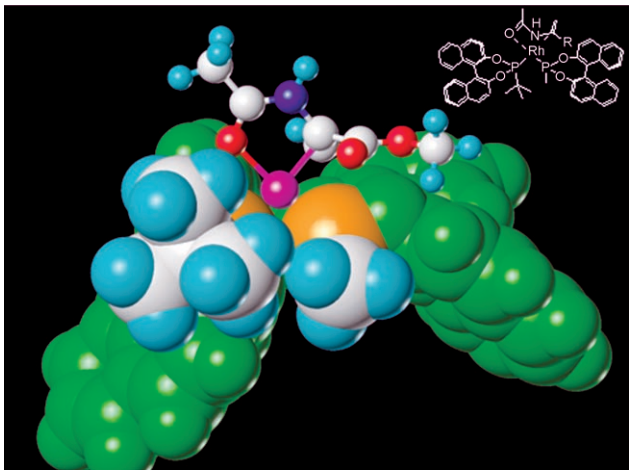


Figure 11. Molecular modeling of $[Rh(\mathbf{21a})(\mathbf{21d})(\mathbf{26a})]^+$ featuring one of the preferred conformers; binol groups green, C white, H cyan, N blue, O red, P orange, Rh magenta.[119]

Some mechanistic information emerged upon studying nonlinear effects in the Rh-catalyzed hydrogenation of itaconate **10** using a 1:1 mixture of phosphonites **21a** and **21d**.[120] It can be anticipated that nonlinear effects in a system comprising a mixture of two chiral ligands constitute a

considerably more complex situation than in traditional catalyst systems. Therefore, the usual mathematical treatment does not apply.[85] When varying the enantiomeric purity of one ligand, L^a_S from 100 and 0% *ee* (racemate) while keeping the partner ligand L^b pure, six different catalytic reactions are relevant [Eq. (21)].

$$\begin{aligned}
&[ML^a_SL^a_S] \xrightarrow{k_1}\\
&[ML^a_RL^a_R] \xrightarrow{k'_1}\\
&[ML^a_RL^a_S] \xrightarrow{k_2}\\
&[ML^b_SL^b_S] \xrightarrow{k_3}\\
&[ML^a_RL^b_S] \xrightarrow{k_4}\\
&[ML^a_SL^b_S] \xrightarrow{k_5}
\end{aligned} \qquad (21)$$

All rate constants can be expected to differ, except for $k_1 = k'_1$. Owing to rapid interconversion between the species, only k_1 (or k'_1) and k_3 can be measured. Thus, the observed rate when using a mixture of L^a/L^b results from the combined action of the relevant rate processes. When employing the enantiopure homocombinations (*S*)-**21a** and (*S*)-**21d** in separate experiments, product **11** has the *S* configuration with 90 and 57% *ee*, respectively. Earlier experiments had also shown that a 1:1 mixture of (*S*)-**21a** and (*S*)-**21d** increases the enantioselectivity to 96% *ee* (*S*). In the NLE study,[120] the enantiopurity of (*S*)-**21a** was first varied stepwise from 100 to 0% *ee* (racemate) while maintaining the enantiopurity of the partner ligand **21d** (100% *ee*). These experiments show that the *ee* value of product **11** decreases only slightly from 96 to 92% as the racemic state of **21a** is reached (Figure 12, blue line).[120] We also probed the other stereochemical region by once again maintaining 100% *S* enantiopurity of **21d**, but exploring the system in which the *R* configuration of ligand **21a** dominates, namely by employing (*R*)-**21a** at different levels of enantiopurity. Figure 12 (red line) shows that the enantioselectivity gradually decreases, but remains as the *S* configuration. This novel behavior indicates that the influence of the *tert*-butyl component **21d** dominates in the stereochemical outcome.

These observations lead to a practical conclusion, namely that 100% enantiopurity of a ligand is not necessary for reaching high *ee* values. A similar NLE curve was observed when keeping the enantiopurity of **21a** at 100% *ee* and varying that of **21d**, except that inversion of configuration of product **11** resulted when using *R*-configured **21d**. This again underlines the dominating role of the sterically bulky *tert*-butyl ligand in **21d**. Our study also includes rate data, which shows, among other things, that the [Rh]/[(*S*)-**21a**/(*S*)-**21d**] combination constitutes the most active catalyst, whereas the bulky homocombination [Rh]/[(*S*)-**21d**]$_2$ is the least active, and [Rh]/[(*S*)-**21a**/(*R*)-**21d**] is in between.[120]

We were also interested in studying this unusual NLE behavior when varying the enantiopurity of both ligands **21a** and **21d** simultaneously, which means that a total of 10 reactions are relevant [Eq. (22)].

$$\begin{aligned}
&[ML^a_SL^a_S] \xrightarrow{k_1}\\
&[ML^a_RL^a_R] \xrightarrow{k'_1}\\
&[ML^a_RL^a_S] \xrightarrow{k_2}\\
&[ML^a_RL^b_S] \xrightarrow{k_4}\\
&[ML^a_SL^b_R] \xrightarrow{k'_4}\\
&[ML^a_SL^b_S] \xrightarrow{k_5}\\
&[ML^a_RL^b_R] \xrightarrow{k'_5}\\
&[ML^b_SL^b_S] \xrightarrow{k_3}\\
&[ML^b_RL^b_R] \xrightarrow{k'_3}\\
&[ML^b_SL^b_R] \xrightarrow{k_6}
\end{aligned} \qquad (22)$$

To display the results of such a systematic search, a three-dimensional graphical representation is necessary (Figure 13).[120] The *ee* values vary from 96% (*S*) to 96% (*R*) in the extremes. Importantly, enantioselectivities of greater than 90% *ee* in favor of (*R*)- or (*S*)-**11** are possible even when both ligand partners have enantiopurities of only 80% (Figure 13, red areas). These experiments, taken

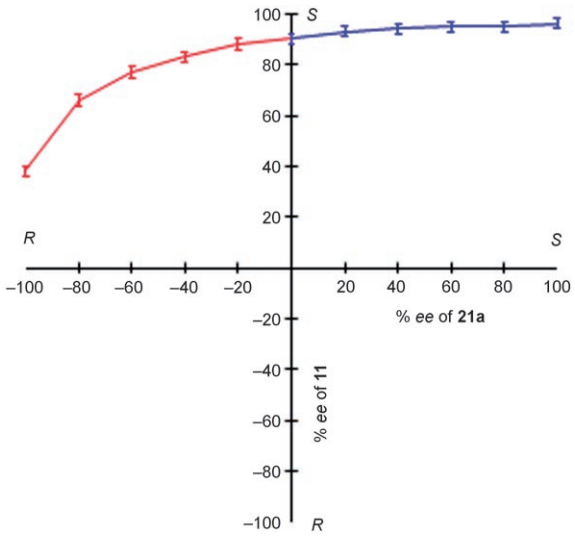


Figure 12. Nonlinear effects in the Rh-catalyzed hydrogenation of **10** using enantiopure (*S*)-**21d** and **21a** of varying enantiopurity.[120]

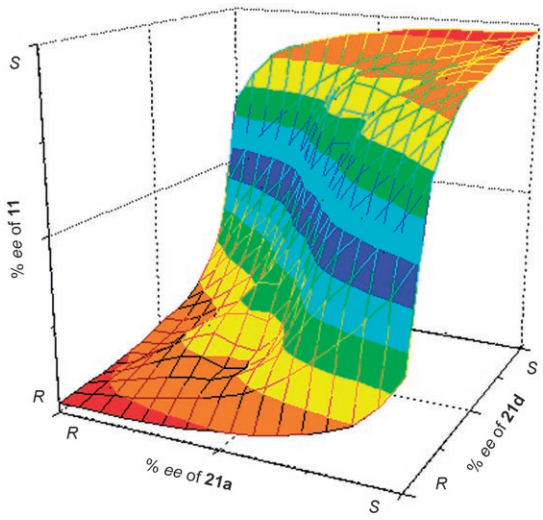


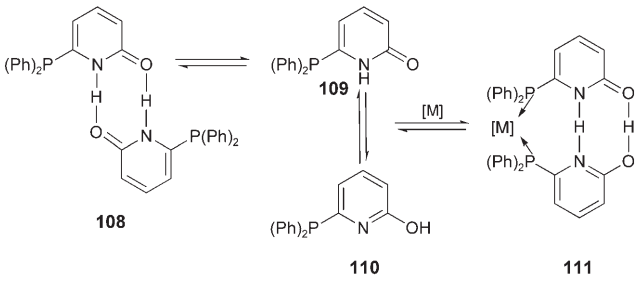
Figure 13. Nonlinear effects in the Rh-catalyzed hydrogenation of itaconate **10** using mixtures of ligands **21a** and **21d**, each with varying degrees of enantiopurity.[120]

together with the rate data, provide clear evidence for the existence and high catalytic activity of the heterocombination. However, more mechanistic work is necessary.

Mechanistic studies are also needed in the case of asymmetric Rh-catalyzed olefin hydrogenation using a heterocombination composed of a chiral and an achiral monodentate ligand. Here again, rate enhancements were observed.[41c] The study of nonlinear effects would be helpful, as would more detailed kinetic investigations. This also applies to other types of reactions, for example, hydroformylation or the Miyaura–Hayashi 1,4-addition of arylboronic acid derivatives to enones or nitroalkenes.

7. Supramolecular Assembly as an Alternative Approach

An alternative way to assemble (selectively) two monodentate ligands around a transition metal is possible if the system contains reversible supramolecular interactions in addition to the primary metal–ligand bonds, as first proposed by Breit and Seiche.[121] The advantage of this approach is the expectation that degrees of freedom in the respective metal coordination compound are reduced, resulting in the simulation of a bidentate system with predictable geometric properties, as in conventional bidentate ligands. Moreover, in ideal cases the heterocombination is formed selectively as the sole catalyst. The Breit system relies on hydrogen bonding in a predictable manner.[121] In a first example, the known property of the tautomeric pair 2-pyridone/2-hydroxypyridine to dimerize through hydrogen bonds mainly in the symmetrical pyridone dimer was exploited. Accordingly, an appropriately phosphine-modified pair **109**/**110** was prepared, which in the presence of a transition metal spontaneously self-assembles to form the geometrically well-defined coordination compound **111** with a "bidentate" structure (Scheme 10).

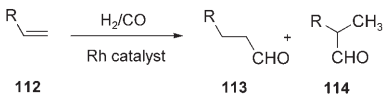


Scheme 10. The Breit system for the self-assembly of a monodentate P ligand.[121]

The X-ray structure of the supramolecular complex obtained in the case of $PtCl_2$ as the transition-metal salt validates the concept (Figure 14).[121] It features the predicted hydrogen bonding as well as the two P–Pt bonds, the overall interactions leading to a fairly well-defined cone angle. These are geometric parameters that are known to influence catalysis, as summarized earlier by Tolman, Casey, and van Leeuwen et al.[122]

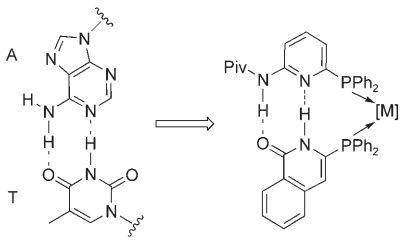
Figure 14. Crystal structure of *cis*-[$PtCl_2$(**111**)$_2$]; C gray, H white, Cl yellow, P orange, N blue, O red, Pt green.[121]

It was shown that the corresponding Rh complex catalyzes the hydroformylation of terminal alkenes **112** with greater than 95% regioselectivity in favor of the *n* isomers **113** [Eq. (23)], similar to the best (true) bidentate diphosphines such as *tert*-butyl-xantphos described in the literature. Conventional monodentate P ligands such as triphenylphosphine (**79**) are known to deliver approximately 3:2 ratios of **113**/**114**.[121]



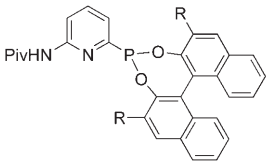
(23)

The concept of self-assembly of monodentate ligands through complementary hydrogen bonding was then generalized to include the selective positioning of two different monodentate P ligands around a given transition metal with exclusive formation of the respective heterocombination.[123] It was obvious that the pyridone/hydroxypyridine platform would result in a mixture of homo- and heterocombinations. Although such an approach could lead to successful catalysis (if the heterocombination imparts enhanced activity/selectivity), design based on appropriate hydrogen donors/acceptors can in principle ensure the selective self-assembly of the heterocombinations as the sole product. Inspired by DNA base pairing (for example, Watson–Crick adenine/thymine pairing), Breit and Seiche first focused on the aminopyridine/isoquinolone pair, which emulates the AT base pair.[123] Since 2-aminopyridines exist in the lactim form and isoquinolone strongly prefers the lactam tautomer, homodimerization should be suppressed, thereby ensuring exclusive heterodimer formation. Following the synthesis of a number of phosphines of the two respective heterocycles (Scheme 11), it was shown that this expectation was borne out experimentally. NMR spectroscopic data and X-ray structural analysis of the Pt complex confirmed the exclusive formation of Watson–Crick pairing.



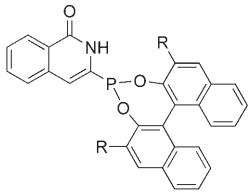
Scheme 11. Self-assembly through hydrogen bonding of the adenine/thymine (left) and aminopyridine/isoquinolone (right) systems; Piv = pivaloyl.[123]

The concept was then tested successfully in the regioselective Rh-catalyzed hydroformylation of terminal alkenes, which results in greater than 95% *n* selectivity.[123] Subsequently, it was applied in enantioselective Rh-catalyzed olefin hydrogenation.[124] In this case the two substituents at the P atom bound to the heterocycles are not two aryl groups, but the binol moiety leading to the respective phosphonites **115**



115

(*S*)-**115a** R = H
(*S*)-**115b** R = Me
(*S*)-**115b** R = *p*-Tol



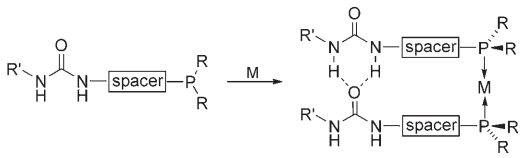
116

(*S*)-**116a** R = H
(*S*)-**116b** R = H
(*S*)-**116c** R = Me

and **116**, which dimerize spontaneously. The respective Rh complex, which constitutes the heterocombination, leads to high enantioselectivity (> 90% *ee*). It was also shown that one of the partners can harbor a diphenylphosphanyl moiety. This corresponds to the use of a mixture of an achiral and chiral monodentate P ligand (Section 3.2.2). This type of strategy was also applied in the Ru-catalyzed anti-Markovnikov hydration of terminal alkynes.[125]

Once a library of appropriate monodentate P ligands of this kind has been prepared, the simple process of mixing generates structural diversity without the need to synthesize new ligands.[126] This is analogous to the situation when mixing structurally simple achiral or chiral monodentate P ligands (see Sections 3–5), except with the added advantage that the heterocombination with a predictable geometry is formed exclusively. Of course, this advantage is achieved at the expense of added synthetic effort. Therefore, the two approaches are complementary.

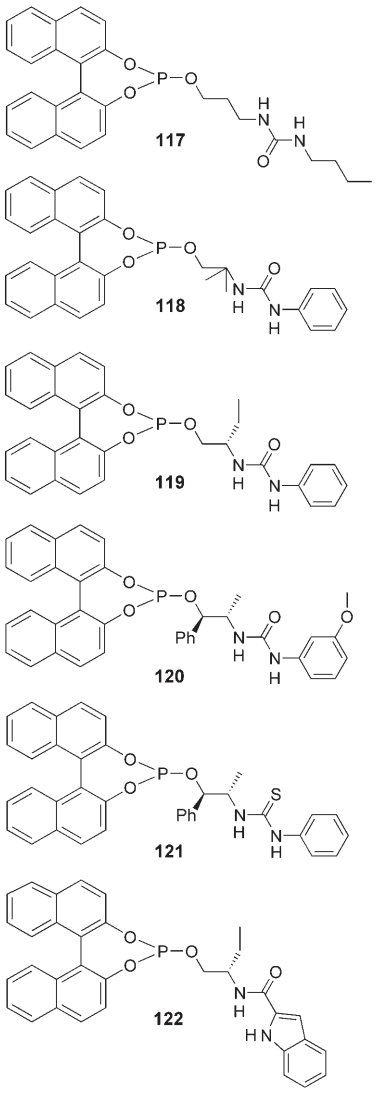
Following the initial report by Breit,[121] several other groups have utilized hydrogen bonding for the purpose of self-assembly of monodentate P ligands around a transition metal with spontaneous formation of "pseudo" chelates. For example, Love et al. described urea–phosphine complexes of palladium and rhodium in which the P atoms are positioned *trans* to each other, the two urea moieties forming hydrogen bonds with one another as shown by X-ray structural analysis.[127] In independent work, Reek, van Leeuwen, et al. have generalized this theme, one variation involving the known hydrogen bonding between two urea moieties (Scheme 12), and the other incorporating an anion complexed



Scheme 12. Urea-based self-assembly of phosphines; M = Pd, Rh.[128]

between the two urea units.[128] Numerous structural motifs of this sort were shown to be possible, and such metals as palladium and rhodium were used to form the corresponding metal complexes.

One of many potential applications of these interesting supramolecular catalysts is Rh-catalyzed asymmetric olefin hydrogenation. For example, binol-derived monophosphites **117**–**122** connected covalently to urea derivatives through



117

118

119

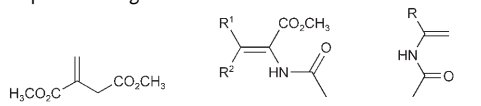
120

121

122

achiral or chiral spacers self-assemble around rhodium upon reacting with $[Rh(nbd)_2]BF_4$ (nbd = norbornadiene). NMR spectroscopic and ESI-MS studies showed that self-assembly proceeds according to Scheme 12. Since selective hydrogen bonding between different ligands cannot be expected in this system, only homocombinations were tested in the hydrogenation of substrates **10**, **26a**, and **28c** (Table 7).[128b] The

Table 7: Rh-catalyzed asymmetric hydrogenation of various substrates using urea–phoshine ligands.[128b]



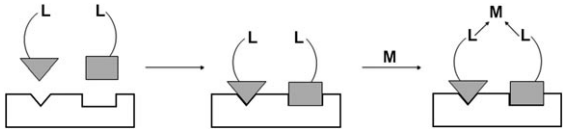
10 **26a** (R' = H; R^2 = H) **28c** (R = 2-naphthyl)

Entry	Ligand[a]	Substrate	Conversion [%]	*ee* [%] (config.)
1	**117**	**10**	0	0
2	**118**	**10**	100	16.6 (*S*)
3	**119**	**10**	100	46 (*S*)
4	**120**	**10**	100	92.7 (*S*)
5	**121**	**10**	100	13.8 (*R*)
6	**122**	**10**	100	95.8 (*S*)
7	**117**	**26a**	0	0
8	**118**	**26a**	100	93.6 (*R*)
9	**119**	**26a**	100	92.3 (*R*)
10	**120**	**26a**	100	82.1 (*R*)
11	**121**	**26a**	36.9	44.6 (*S*)
12	**117**	**28c**	4	4 (*R*)
13	**118**	**28c**	12.3	76.5 (*R*)
14	**119**	**28c**	4.1	60.7 (*R*)
15	**120**	**28c**	34.1	52.5 (*R*)
16	**121**	**28c**	0.4	37.9 (*S*)
17	**122**	**28c**	26.1	1.5 (*R*)

[a] All ligands based on the (*S*)-binol phosphite backbone, except in the case of entries 5, 11, and 17.

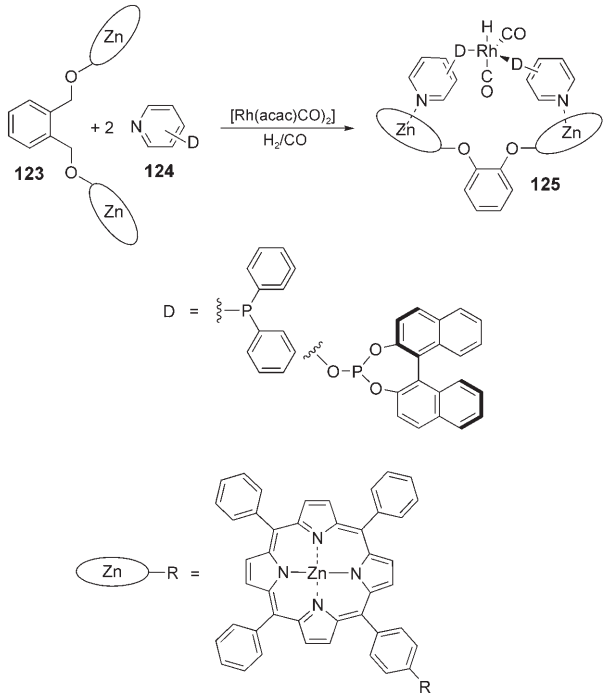
results are truly remarkable because conversion and enantioselectivity vary vastly. The highest *ee* value (95.8%) was observed when using phosphite **122** as the self-assembling ligand in the hydrogenation of itaconate **10** (Table 7, entry 6). Thus far, unambiguous explanations have not been offered.

Reek, van Leeuwen, and co-workers have also developed a second strategy for the formation of supramolecular catalysts based on the self-assembly of monodentate P ligands.[129] In general terms, it involves a metal-containing template which binds and thus positions two monodentate ligands L having an additional donor site. Subsequent chelation to a catalytically active transition metal M generates the catalyst or precatalyst (Scheme 13). The template is often a bis{Zn(porphyrin)} complex such as **123**, which binds the additional donor site (usually a pyridine moiety) bearing the P



Scheme 13. General strategy for the self-assembly of monodentate ligands.[129b]

ligand (Scheme 14). Achiral or chiral P ligands can be used, as in hydroformylation. The *n*/*iso* ratio was shown to depend on the structure of the supramolecular catalyst.[129a]

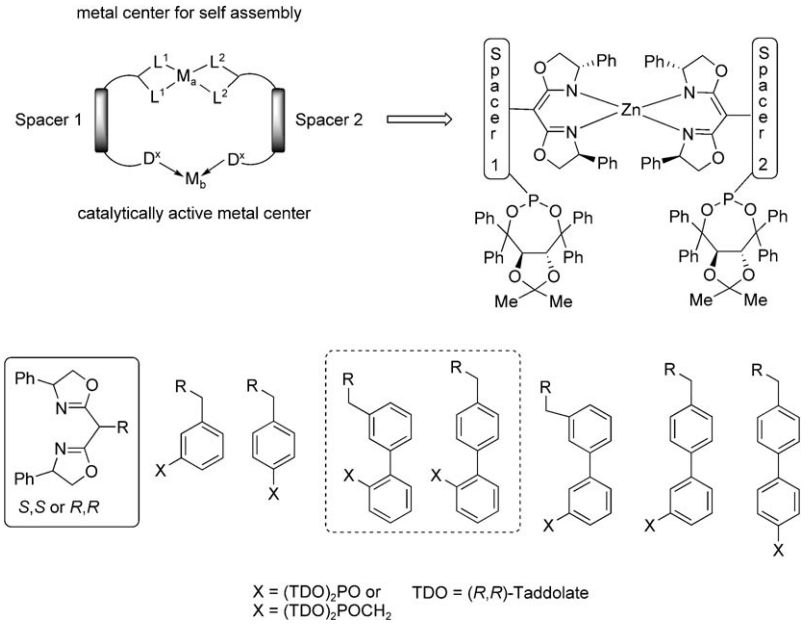


Scheme 14. Self-assembly of ligands through coordination of a zinc(II) porphyrin complex to pyridyl-functionalized P donors.[129a,b]

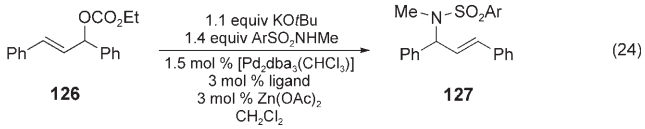
Since structural variations are easily envisioned, a combinatorial approach should be possible. Hydrogenation reactions have been performed using such supramolecular achiral and chiral catalysts. Template-induced formation of heterobidentate ligands (heterocombination) and their application in the Rh-catalyzed asymmetric hydroformylation of styrene has also been described.[129b] In the most recent application of the concept, palladium catalysts were used in the kinetic resolution of racemic cyclohexenyl acetate.[129c] All of these studies point to one and the same phenomenon: selectivity as a function of the supramolecular structure.[130] It may well be that future systems can be designed which show catalytic profiles not possible by simpler combinatorial systems (Sections 3–5).

A different and likewise intriguing approach to supramolecular combinatorial transition-metal catalysis was proposed by Takacs (Scheme 15).[131] It allows for the exclusive self-assembly of heterodimers (heterocombinations). Owing to steric reasons, the tetrahedral Zn compound can only be formed if the (*S*,*S*)- and (*R*,*R*)-taddol precursors come together. A variety of subunits (Scheme 15) were prepared, leading to 50 combinations of heterodimers which were tested in a Pd-catalyzed allylic amination [Eq. (24); dba = *trans*,*trans*-dibenzylideneacetone, Ar = *p*-tolyl]. This type of combinatorial search led to enantioselectivities of up to 97% *ee*.[131]

Since only *S*,*S*/*R*,*R* coordination at zinc occurs, it is possible to utilize structurally different chiral or achiral P

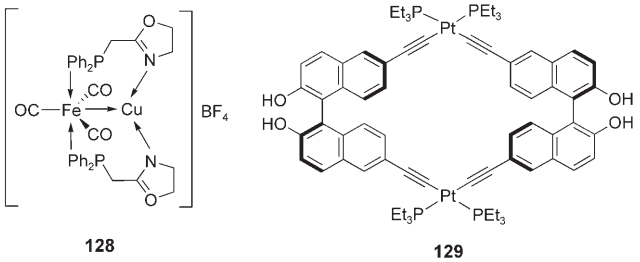


Scheme 15. Heterodimeric taddol–phosphite ligands resulting from a heterochiral metal complex template. M_a = Zn, M_b = Pd, D^x = chiral ligand.[131]



(24)

moieties with exclusive formation of the relevant heterocombination.[131] As in the second-generation Breit system,[126] this approach avoids the formation of a mixture in which the two homocombinations would also be present (Section 3–5), although it comes at the expense of added synthetic effort. More work is needed in this novel approach to combinatorial supramolecular catalysis. Several other ways to assemble ligands in homo- and heterometallic complexes have been described in the literature recently, including the systems devised by Braunstein et al.[132] (for example, **128**, which

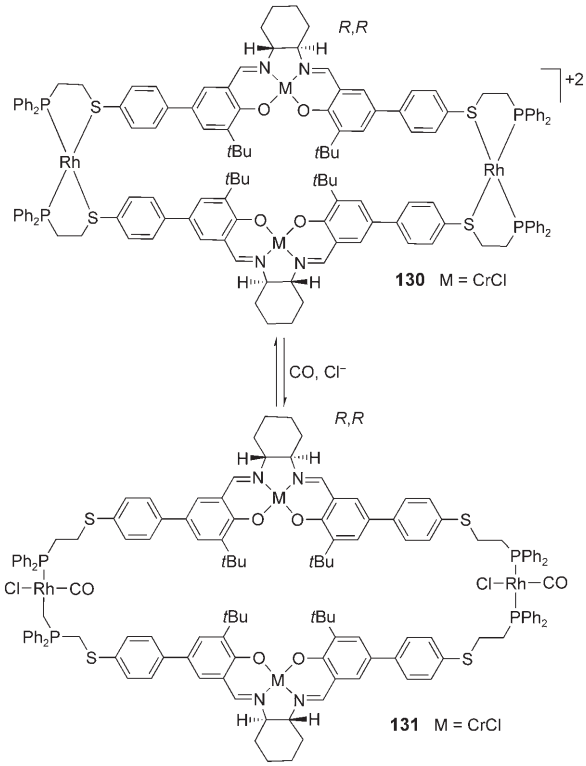


catalyzes cyclopropanation and Diels–Alder reactions) and by Lin et al.[133] (for example, **129**, which catalyzes asymmetric addition of Et_2Zn to aldehydes with *ee* values of up to 94%).

The supramolecular approach to an allosteric catalyst, conceived by Mirkin et al., is a rarity in the area of synthetic catalysis.[134] The Rh^I centers in complex **130** act as switches for Jacobsen-like catalysis upon ligation by CO and Cl^- to form **131**, which activates the system for catalysis because it brings the two Cr centers into the correct geometric positions (Scheme 16). As a model reaction, the amination of cyclohexene oxide by Me_3SiN_3 was successfully tested and gave rise to an enantioselectivity of 68% *ee* compared to only 12% *ee* for the respective monomeric ligand. This result is consistent with the supramolecular cooperativity observed earlier by Jacobsen and Ready.[135] The concept has been extended by designing catalytic molecular tweezers.[136] A combinatorial version may be possible by variation of the substituents, spacer, and metal.

8. Conclusions and Perspectives

The combinatorial ligand mixture concept,[41] although still in its infancy, has emerged as a surprisingly successful approach to enantio-, diastereo-, and regioselective transition-metal catalysis. Whereas mechanistic, structural, and theoretical studies still need to be performed, one general guideline has emerged (with exceptions), namely that a sterically large and a small ligand often constitute the best heterocombination. Obviously, it does not mean that positive hits in a combinatorial library can be expected in all cases, and indeed negative results can be found in the tables of all studies reported so far. Sometimes a given library of monodentate ligands does not give rise to any positive hits at all.[62c,d,137]



Scheme 16. Concept of an allosteric catalyst system.[134]

The attractive feature of this concept is the fact that structural diversity is generated by mixing ligands without the need to synthesize any new compounds (Table 2). More research is necessary, including the study of other transition-metal-catalyzed reactions, the inclusion of other types of monodentate P ligands, the testing of monodentate C, N, O, and S ligands, and mechanistic and structural investigations regarding the source of enhanced activity and selectivity as a result of ligand mixing. Moreover, larger libraries of ligands need to be tested in future studies. As a note of caution, it must be remembered that only those systems are viable in which ligand exchange is rapid. Since the discovery of new reaction types or the implementation of catalyst systems capable of catalyzing "difficult" reactions depends to a large degree on the appropriate choice of ligands, it may be useful to consider the ligand mixture concept in these important endeavors. Going through "evolutionary" cycles based on the use of defined sets of ligands is yet another unexplored possibility.

Once a highly efficient heterocombination [ML^aL^b] has been discovered as a consequence of a combinatorial search, it may be possible to design a corresponding bidentate ligand system in which L^a and L^b are connected covalently to one another by an appropriate spacer (backbone), leading to a catalyst system in which only one species is present ([M-{L^a-(spacer)-L^b}]). The length of this spacer can be expected to be decisive. Steps in this direction have already been undertaken, specifically in the preparation of appropriate diphosphoramidites as efficient bidentate P ligands for asymmetric olefin hydrogenation (> 95 % *ee*).[138] The "retro-process" is also conceivable, that is, to dissect a known bidentate ligand composed of two different donor sites D^1 and D^2, and to prepare and test the appropriate single monodentate ligands in mixtures such as, for example, the combination of an achiral phosphine and a chiral monodentate oxazoline. Systems with reversible noncovalent connections between two otherwise independent monodentate ligands as a result of hydrogen bonding or specific metal interactions also offer exciting opportunities for combinatorial and supramolecular transition-metal catalysis. Finally, mixtures of two different chiral bidentate ligands have hardly been investigated systematically, although the studies by Ding et al.[79c,139] and Shibasaki et al.[140] show that such investigations may be rewarding in appropriate systems.

Received: September 19, 2007

[1] Selected reviews of combinatorial chemistry: a) *Handbook of Combinatorial Chemistry*, *Vol. 1 and 2*, (Eds.: K. C. Nicolaou, R. Hanko, W. Hartwig), Wiley-VCH, Weinheim, **2002**; b) A. Furka, *Comb. Chem.* **2002**, *7*, 1–4; c) S. I. Woo, K. W. Kim, H. Y. Cho, K. S. Oh, M. K. Jeon, N. H. Tarte, T. S. Kim, A. Mahmood, *QSAR Comb. Sci.* **2005**, *24*, 138–154; d) A. Weber, E. von Roedern, H. U. Stilz, *J. Comb. Chem.* **2005**, *7*, 178–184; e) A. Kirschning, W. Solodenko, K. Mennecke, *Chem. Eur. J.* **2006**, *12*, 5972–5990; f) C. Schmuck, P. Wich, *New J. Chem.* **2006**, *30*, 1377–1385; g) J. M. Serra, A. Corma, S. Valero, E. Argente, V. Botti, *QSAR Comb. Sci.* **2007**, *26*, 11–26; h) A. Chighine, G. Sechi, M. Bradley, *Drug Discovery Today* **2007**, *12*, 459–464; i) S. H. Fitzgerald, M. Sabat, H. M. Geysen, *J. Comb. Chem.* **2007**, *9*, 724–734; j) W. F. Maier, K. Stöwe, S. Sieg, *Angew. Chem.* **2007**, *119*, 6122–6179; *Angew. Chem. Int. Ed.* **2007**, *46*, 6016–6067; k) *Combinatorial and High-Throughput Discovery and Optimization of Catalysts and Materials*, (Eds.: R. A. Potyrailo, W. F. Maier), CRC Press/Taylor & Francis, Boca Raton, **2007**.

[2] a) "Cornucopia of peptides by synthesis": A. Furka, F. Sebestyén, M. Asgedom, G. Dibó, *Highlights of Modern Biochemistry Proceedings of the 14th International Congress of Biochemistry VSP*, Utrecht, The Netherlands, **1988**, Vol. 5, p. 47; b) A. Furka, F. Sebestyen, M. Asgedom, G. Dibo, *Int. J. Pept. Protein Res.* **1991**, *37*, 487–493; c) K. S. Lam, S. E. Salmon, E. M. Hersh, V. J. Hruby, W. M. Kazmierski, R. J. Knapp, *Nature* **1991**, *354*, 82–84; d) R. A. Houghten, C. Pinilla, S. E. Blondelle, J. R. Appel, C. T. Dooley, J. H. Cuervo, *Nature* **1991**, *354*, 84–86.

[3] a) M. T. Reetz, *Angew. Chem.* **2001**, *113*, 292–320; *Angew. Chem. Int. Ed.* **2001**, *40*, 284–310; b) C. Jäkel, R. Paciello, *Chem. Rev.* **2006**, *106*, 2912–2942; c) M. T. Reetz in *Enzyme Assays—High-throughput Screening, Genetic Selection and Fingerprinting* (Ed.: J.-L. Reymond), Wiley-VCH, Weinheim, **2006**, pp. 41–76; d) M. Tsukamoto, H. B. Kagan, *Adv. Synth. Catal.* **2002**, *344*, 453–463; e) M. G. Finn, *Chirality* **2002**, *14*, 534–540; f) V. Charbonneau, W. W. Ogilvie, *Org. Chem.* **2005**, *2*, 313–332; g) M. L. Stanton, J. A. Holcombe, *J. Comb. Chem.* **2007**, *9*, 359–365; h) J. R. Kenseth, Y. He, D. Tallman, H. Pang, S. J. Coldiron, *Curr. Opin. Chem. Biol.* **2004**, *8*, 327–333; i) *Enzyme Assays—High-throughput Screening, Genetic Selection and Fingerprinting* (Ed.: J.-L. Reymond), Wiley-VCH, Weinheim, **2006**.

[4] a) W. Ehrfeld, V. Hessel, H. Löwe, *Microreactors*, Wiley-VCH, Weinheim, **2000**; b) J. Kobayashi, Y. Mori, S. Kobayashi, *Chem. Asian J.* **2006**, *1–2*, 22–35; c) K. Geyer, J. D. C. Codée, P. H. Seeberger, *Chem. Eur. J.* **2006**, *12*, 8434–8442; d) K. Jähnisch, V. Hessel, H. Löwe, M. Baerns, *Angew. Chem.* **2004**, *116*, 410–451; *Angew. Chem. Int. Ed.* **2004**, *43*, 406–446; e) P. Watts, J. S. Haswell, *Chem. Soc. Rev.* **2005**, *34*, 235–246; f) O. Brand, G. K. Fedder, C. Hierold, J. G. Korvink, T. Osamu, *Micro Process Engineering*, *Vol. 5* (Ed.: N. Kockmann), Wiley-VCH, Weinheim, **2006**; g) C. Cao, D. R. Palo, L. Y. Tonkovich, Y. Wang, *Catal. Today* **2007**, *125*, 29–33.

[5] a) A. Manz, J. C. T. Eijkel, *Pure Appl. Chem.* **2001**, *73*, 1555–1561; b) D. Belder, M. Ludwig, L.-W. Wang, M. T. Reetz, *Angew. Chem.* **2006**, *118*, 2523–2526; *Angew. Chem. Int. Ed.* **2006**, *45*, 2463–2466; c) C. I. Jönsson, S. Lundgren, S. J. Haswell, C. Moberg, *Tetrahedron* **2004**, *60*, 10515–10520; d) I. Atencia, D. J. Beebe, *Nature* **2005**, *437*, 648–655; e) J. Kobayashi, Y. Mori, K. Okamoto, R. Akiyama, M. Ueno, T. Kitamori, S. Kobayashi, *Science* **2004**, *304*, 1305–1308; f) M. Grumann, A. Geipel, L. Riegger, R. Zengerle, J. Ducrée, *Lab Chip* **2005**, *5*, 560–565; g) P. Watts, S. J. Haswell, *Curr. Opin. Chem. Biol.* **2003**, *7*, 380–387.

[6] Reviews of various aspects of combinatorial (asymmetric) homogeneous catalysis:[3a] a) M. B. Francis, T. F. Jamison, E. N. Jacobsen, *Curr. Opin. Chem. Biol.* **1998**, *2*, 422–428; b) K. W. Kuntz, M. L. Snapper, A. H. Hoveyda, *Curr. Opin. Chem. Biol.* **1999**, *3*, 313–319; c) B. Archibald, O. Brümmer, M. Devenney, S. Gorer, B. Jandeleit, T. Uno, W. H. Weinberg, T. Weskamp in *Handbook of Combinatorial Chemistry*, *Vol. 2* (Eds.: K. C. Nicolaou, R. Hanko, W. Hartwig), Wiley-VCH, Weinheim, **2002**, pp. 885–990; d) A. H. Hoveyda in *Handbook of Combinatorial Chemistry*, *Vol. 2* (Eds.: K. C. Nicolaou, R. Hanko, W. Hartwig), Wiley-VCH, Weinheim, **2002**, pp. 991–1016; e) C. Gennari, U. Piarulli, *Chem. Rev.* **2003**, *103*, 3071–3100; f) K. Ding, H. Du, Y. Yuan, J. Long, *Chem. Eur. J.* **2004**, *10*, 2872–2884; g) L. Lefort, J. A. F. Boogers, A. H. M. de Vries, J. G.

de Vries, *Top. Catal.* **2006**, *40*, 185 – 191; h) J. G. de Vries, A. H. M. de Vries, *Eur. J. Org. Chem.* **2003**, 799 – 811; i) P. Chen, *Angew. Chem.* **2003**, *115*, 2938 – 2954; *Angew. Chem. Int. Ed.* **2003**, *42*, 2832 – 2847; S. Dahmen, S. Bräse, *Synthesis* **2001**, 1431 – 1449; j) J. P. Stambuli, J. F. Hartwig, *Curr. Opin. Chem. Biol.* **2003**, *7*, 420 – 426; k) O. Lavastre, F. Bonnette, L. Gallard, *Curr. Opin. Chem. Biol.* **2004**, *8*, 311 – 318; l) S. J. Reyes, K. Burgess, *Chem. Soc. Rev.* **2006**, *35*, 416 – 423.

[7] T. Satyanarayana, H. B. Kagan, *Adv. Synth. Catal.* **2005**, *347*, 737 – 748.

[8] For an application of a medium-throughput GC assay for determination of enantiopurity, see: M. T. Reetz, K. M. Kühling, S. Wilensek, H. Husmann, U. W. Häusig, M. Hermes, *Catal. Today* **2001**, *67*, 389 – 396.

[9] For an application of an HPLC-based *ee*-screening system in directed evolution of enantioselective monooxidases, see: M. T. Reetz, F. Daligault, B. Brunner, H. Hinrichs, A. Deege, *Angew. Chem.* **2004**, *116*, 4170 – 4173; *Angew. Chem. Int. Ed.* **2004**, *43*, 4078 – 4081.

[10] M. T. Reetz, M. H. Becker, H.-W. Klein, D. Stöckigt, *Angew. Chem.* **1999**, *111*, 1872 – 1875; *Angew. Chem. Int. Ed.* **1999**, *38*, 1758 – 1761.

[11] Reviews of directed evolution of enantioselective enzymes: a) M. T. Reetz, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5716 – 5722; b) M. T. Reetz in *Advances in Catalysis, Vol. 49* (Eds.: B. C. Gates, H. Knözinger), Elsevier, San Diego, **2006**, pp. 1 – 69.

[12] W. Schrader, A. Eipper, D. J. Pugh, M. T. Reetz, *Can. J. Chem.* **2002**, *80*, 626 – 632.

[13] M. T. Reetz, L.-W. Wang, M. Bocola, *Angew. Chem.* **2006**, *118*, 1258 – 1263; *Angew. Chem. Int. Ed.* **2006**, *45*, 1236 – 1241; erratum: M. T. Reetz, L.-W. Wang, M. Bocola, *Angew. Chem.* **2006**, *118*, 2556; *Angew. Chem. Int. Ed.* **2006**, *45*, 2494.

[14] G. DeSantis, K. Wong, B. Farwell, K. Chatman, Z. Zhu, G. Tomlinson, H. Huang, X. Tan, L. Bibbs, P. Chen, K. Kretz, M. J. Burk, *J. Am. Chem. Soc.* **2003**, *125*, 11476 – 11477.

[15] O. Trapp, *Angew. Chem.* **2007**, *119*, 5706 – 5710; *Angew. Chem. Int. Ed.* **2007**, *46*, 5609 – 5613.

[16] G. Liu, J. A. Ellman, *J. Org. Chem.* **1995**, *60*, 7712 – 7713.

[17] B. M. Cole, K. D. Shimizu, C. A. Krueger, J. P. A. Harrity, M. L. Snapper, A. H. Hoveyda, *Angew. Chem.* **1996**, *108*, 1776 – 1779; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1668 – 1671.

[18] a) K. D. Shimizu, B. M. Cole, C. A. Krueger, K. W. Kuntz, M. L. Snapper, A. H. Hoveyda, *Angew. Chem.* **1997**, *109*, 1782 – 1785; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1704 – 1707; b) K. D. Shimizu, M. L. Snapper, A. H. Hoveyda, *Chem. Eur. J.* **1998**, *4*, 1885 – 1889; c) A. H. Hoveyda, *Chem. Biol.* **1998**, *5*, R187 – R191; d) C. A. Krueger, K. W. Kuntz, C. D. Dzierba, W. G. Wirschun, J. D. Gleason, M. L. Snapper, A. H. Hoveyda, *J. Am. Chem. Soc.* **1999**, *121*, 4284 – 4285; e) L. C. Akullian, M. L. Snapper, A. H. Hoveyda, *J. Am. Chem. Soc.* **2006**, *128*, 6532 – 6533; f) Y. Zhao, J. Rodrigo, A. H. Hoveyda, M. L. Snapper, *Nature* **2006**, *443*, 67 – 70.

[19] a) C. Gennari, S. Ceccarelli, U. Piarulli, C. A. G. N. Montalbetti, R. F. W. Jackson, *J. Org. Chem.* **1998**, *63*, 5312 – 5313; b) C. Gennari, H. P. Nestler, U. Piarulli, B. Salom, *Liebigs Ann.* **1997**, 637 – 647.

[20] J. Brouwer, H. J. van der Linden, R. M. J. Liskamp, *J. Org. Chem.* **2000**, *65*, 1750 – 1757.

[21] a) M. S. Sigman, E. N. Jacobsen, *J. Am. Chem. Soc.* **1998**, *120*, 4901 – 4902; See also: b) P. Vachal, E. N. Jacobsen, *J. Am. Chem. Soc.* **2002**, *124*, 10012 – 10014.

[22] a) M. B. Francis, E. N. Jacobsen, *Angew. Chem.* **1999**, *111*, 987 – 991; *Angew. Chem. Int. Ed.* **1999**, *38*, 937 – 941; See also: b) K. L. Tan, E. N. Jacobsen, *Angew. Chem.* **2007**, *119*, 1337 – 1339; *Angew. Chem. Int. Ed.* **2007**, *46*, 1315 – 1317.

[23] a) K. Burgess, H.-J. Lim, A. M. Porte, G. A. Sulikowski, *Angew. Chem.* **1996**, *108*, 192 – 194; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 220 – 222; b) K. Burgess, A. M. Porte, *Tetrahedron: Asymmetry* **1998**, *9*, 2465 – 2469.

[24] a) S. R. Gilbertson, X. Wang, *Tetrahedron* **1999**, *55*, 11609 – 11618; b) S. R. Gilbertson, S. E. Collibee, A. Agarkov, *J. Am. Chem. Soc.* **2000**, *122*, 6522 – 6523; c) A. Agarkov, S. Greenfield, D. J. Xie, R. Pawlick, G. Starkey, S. R. Gilbertson, *Biopolymers* **2006**, *84*, 48 – 73.

[25] S. Kobayashi, R. Akiyama, *Pure Appl. Chem.* **2001**, *73*, 1103 – 1111.

[26] a) O. Huttenloch, E. Laxman, H. Waldmann, *Chem. Eur. J.* **2002**, *8*, 4767 – 4780; b) O. Huttenloch, E. Laxman, H. Waldmann, *Chem. Commun.* **2002**, 673 – 675.

[27] A. Berkessel, *Curr. Opin. Chem. Biol.* **2003**, *7*, 409 – 419.

[28] R. Kranich, K. Eis, O. Geis, S. Mühle, J. W. Bats, H.-G. Schmalz, *Chem. Eur. J.* **2000**, *6*, 2874 – 2894.

[29] See for example: a) P. Västilä, J. Wettergren, H. Adolfsson, *Chem. Commun.* **2005**, 4039 – 4041; b) C. A. Christensen, M. Meldal, *J. Comb. Chem.* **2007**, *9*, 79 – 85; c) P. Västilä, J. Wettergren, H. Adolfsson, *Chem. Commun.* **2005**, 4039 – 4041; d) W. Braun, A. Salzer, F. Spindler, E. Alberico, *Appl. Catal. A* **2004**, *274*, 191 – 203; e) Y. Kobayashi, D. Tanaka, H. Danjo, Y. Uozumi, *Adv. Synth. Catal.* **2006**, *348*, 1561 – 1566; f) H.-C. Guo, X.-Y. Shi, X. Wang, S.-Z. Liu, M. Wang, *J. Org. Chem.* **2004**, *69*, 2042 – 2047; g) J. Aires-de-Sousa, J. Gasteiger, *J. Comb. Chem.* **2005**, *7*, 298 – 301; h) J. L. Melville, B. I. Andrews, B. Lygo, J. D. Hirst, *Chem. Commun.* **2004**, 1410 – 1411; i) J. Rudolph, M. Lormann, C. Bolm, S. Dahmen, *Adv. Synth. Catal.* **2005**, *347*, 1361 – 1368.

[30] M. Hechavarría Fonseca, B. List, *Curr. Opin. Chem. Biol.* **2004**, *8*, 319 – 326.

[31] a) C. A. Lewis, S. J. Miller, *Angew. Chem.* **2006**, *118*, 5744 – 5747; *Angew. Chem. Int. Ed.* **2006**, *45*, 5616 – 5619; b) S. J. Miller, *Acc. Chem. Res.* **2004**, *37*, 601 – 610; c) A. Clouet, T. Darbre, J.-L. Reymond, *Angew. Chem.* **2004**, *116*, 4712 – 4715; *Angew. Chem. Int. Ed.* **2004**, *43*, 4612 – 4615, and references therein.

[32] P. Krattiger, C. McCharthy, A. Pfaltz, H. Wennemers, *Angew. Chem.* **2003**, *115*, 1763 – 1766; *Angew. Chem. Int. Ed.* **2003**, *42*, 1722 – 1724.

[33] E. Burello, G. Rothenberg, *Int. J. Mol. Sci.* **2006**, *7*, 375 – 404.

[34] a) K. Mikami, M. Terada, T. Korenaga, Y. Matsumoto, S. Matsukawa, *Acc. Chem. Res.* **2000**, *33*, 391 – 401; b) K. Mikami, M. Yamanaka, *Chem. Rev.* **2003**, *103*, 3369 – 3400.

[35] J. W. Faller, A. R. Lavoie, J. Parr, *Chem. Rev.* **2003**, *103*, 3345 – 3367.

[36] a) D. J. Berrisford, C. Bolm, K. B. Sharpless, *Angew. Chem.* **1995**, *107*, 1159 – 1171; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1059 – 1070; b) K. B. Sharpless, *Angew. Chem.* **2002**, *114*, 2126 – 2135; *Angew. Chem. Int. Ed.* **2002**, *41*, 2024 – 2032.

[37] a) M. T. Reetz, M. Rentzsch, A. Pletsch, M. Maywald, *Chimia* **2002**, *56*, 721 – 723; b) M. T. Reetz, *Tetrahedron* **2002**, *58*, 6595 – 6602; c) M. T. Reetz, DE-A 10129187.6, **2001**.

[38] M. T. Reetz, J. J.-P. Peyralans, A. Maichele, Y. Fu, M. Maywald, *Chem. Commun.* **2006**, 4318 – 4320.

[39] Review of directed evolution of enantioselective hybrid catalysts: M. T. Reetz, M. Rentzsch, A. Pletsch, M. Maywald, P. Maiwald, J. J.-P. Peyralans, A. Maichele, Y. Fu, N. Jiao, F. Hollmann, R. Mondière, A. Taglieber, *Tetrahedron* **2007**, *63*, 6404 – 6414.

[40] a) M. W. Kanan, M. M. Rozenman, K. Sakurai, T. M. Snyder, D. R. Liu, *Nature* **2004**, *431*, 545 – 549; b) M. M. Rozenman, B. R. McNaughton, D. R. Liu, *Curr. Opin. Chem. Biol.* **2007**, *11*, 259 – 268.

[41] a) M. T. Reetz, T. Sell, A. Meiswinkel, G. Mehler, *Angew. Chem.* **2003**, *115*, 814 – 817; *Angew. Chem. Int. Ed.* **2003**, *42*,

790 – 793; b) M. T. Reetz, T. Sell, A. Meiswinkel, G. Mehler, DE-A 10247633.0, **2002**; c) M. T. Reetz, X. Li, *Angew. Chem.* **2005**, *117*, 3019 – 3021; *Angew. Chem. Int. Ed.* **2005**, *44*, 2959 – 2962.

[42] M. T. Reetz, G. Mehler, *Tetrahedron Lett.* **2003**, *44*, 4593 – 4596.

[43] a) L. Horner, H. Siegel, H. Büthe, *Angew. Chem.* **1968**, *80*, 1034 – 1035; *Angew. Chem. Int. Ed. Engl.* **1968**, *7*, 942; b) W. S. Knowles, M. J. Sabacky, *J. Chem. Soc. Chem. Commun.* **1968**, 1445 – 1446.

[44] W. S. Knowles, M. J. Sabacky, B. D. Vineyard, *J. Chem. Soc. Chem. Commun.* **1972**, 10 – 11.

[45] T. P. Dang, H. B. Kagan, *J. Chem. Soc. D* **1971**, 481.

[46] W. S. Knowles, M. J. Sabacky, B. D. Vineyard, D. J. Weinkauff, *J. Am. Chem. Soc.* **1975**, *97*, 2567 – 2568.

[47] Early reviews of asymmetric Rh-catalyzed hydrogenation: a) H. B. Kagan in *Asymmetric Synthesis*, *Vol. 5* (Ed.: J. D. Morrison), Academic Press, Orlando, **1985**, pp. 1 – 39; b) J. Halpern in *Asymmetric Synthesis*, *Vol. 5* (Ed.: J. D. Morrison), Academic Press, Orlando, **1985**, pp. 40 – 69; c) J. M. Brown, P. L. Evans, *Tetrahedron* **1988**, *44*, 4905 – 4916.

[48] a) A. Miyashita, A. Yasuda, H. Takaya, K. Toriumi, T. Ito, T. Souchi, R. Noyori, *J. Am. Chem. Soc.* **1980**, *102*, 7932 – 7934; b) R. Noyori, *Angew. Chem.* **2002**, *114*, 2108 – 2123; *Angew. Chem. Int. Ed.* **2002**, *41*, 2008 – 2022; c) R. Noyori, M. Kitamura, T. Ohkuma, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5356 – 5362; d) C. A. Sandoval, T. Ohkuma, N. Utsumi, K. Tsutsumi, K. Murata, R. Noyori, *Chem. Asian J.* **2006**, *1–2*, 102 – 110.

[49] Reviews of asymmetric hydrogenation including new ligand systems:[48b] a) J. M. Brown in *Comprehensive Asymmetric Catalysis*, *Vol. 5* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Spinger, Berlin, **1999**, chap. 5.1; b) W. S. Knowles, *Angew. Chem.* **2002**, *114*, 2096 – 2107; *Angew. Chem. Int. Ed.* **2002**, *41*, 1998 – 2007; c) I. D. Gridnev, T. Imamoto, *Acc. Chem. Res.* **2004**, *37*, 633 – 644; d) H.-U. Blaser, C. Malan, B. Pugin, F. Spindler, H. Steiner, M. Studer, *Adv. Synth. Catal.* **2003**, *345*, 103 – 151; e) T. Dwars, G. Oehme, *Adv. Synth. Catal.* **2002**, *344*, 239 – 260; f) S. Jeulin, S. Duprat de Paule, V. Ratovelomanana-Vidal, J. P. Genêt, N. Champion, P. Dellis, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5799 – 5804; g) *Handbook of Chiral Fine Chemicals* (Ed.: D. J. Ager), Marcel Dekker, New York, **2005**; h) *Comprehensive Asymmetric Catalysis*, *Vol. I–III* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **1999**; i) *Asymmetric Catalysis on Industrial Scales*, (Eds.: H.-U. Blaser, E. Schmidt), Wiley-VCH, Weinheim, **2004**; j) C. Saluzzo, M. Lemaire, *Adv. Synth. Catal.* **2002**, *344*, 915 – 928; k) I. C. Lennon, P. H. Moran, *Chim. Oggi* **2004**, *22*, 34 – 37; l) J. Wu, A. S. C. Chan, *Acc. Chem. Res.* **2006**, *39*, 711 – 720; m) T. P. Clark, C. R. Landis, *Tetrahedron: Asymmetry* **2004**, *15*, 2123 – 2137; n) W. Tang, X. Zhang, *Chem. Rev.* **2003**, *103*, 3029 – 3069; o) C. Nájera, J. M. Sansano, *Chem. Rev.* **2007**, *107*, 4584 – 4671; p) W. S. Knowles, R. Noyori, *Acc. Chem. Res.* **2007**, *40*, 1238 – 1239; see also the other articles in this special issue regarding asymmetric catalysis.

[50] a) M. T. Reetz, T. Neugebauer, *Angew. Chem.* **1999**, *111*, 134 – 137; *Angew. Chem. Int. Ed.* **1999**, *38*, 179 – 181; b) D. G. Blackmond, T. Rosner, T. Neugebauer, M. T. Reetz, *Angew. Chem.* **1999**, *111*, 2333 – 2335; *Angew. Chem. Int. Ed.* **1999**, *38*, 2196 – 2199.

[51] J. E. Babin, G. T. Whiteker, WO93/03839; US 911,518, **1992**.

[52] Brunner and Wink used chiral diphosphite ligands based on carbohydrates and tartaric acid derivatives in Rh-catalyzed hydrogenation and obtained *ee* values of 1–34%: a) H. Brunner, W. Pieronczyk, *J. Chem. Res. Synop.* **1980**, 76; b) D. J. Wink, T. J. Kwok, A. Yee, *Inorg. Chem.* **1990**, *29*, 5006 – 5008.

[53] a) A. Horeau, H. B. Kagan, J. P. Vigneron, *Bull. Soc. Chim. Fr.* **1968**, *9*, 3795 – 3797; b) S. Masamune, W. Choy, J. S. Petersen, L. R. Sita, *Angew. Chem.* **1985**, *97*, 1 – 31; *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 1 – 30.

[54] a) K. Mikami, T. Korenaga, M. Terada, T. Ohkuma, T. Pham, R. Noyori, *Angew. Chem.* **1999**, *111*, 517 – 519; *Angew. Chem. Int. Ed.* **1999**, *38*, 495 – 497; see also: b) M. Yamanaka, K. Mikami, *Organometallics* **2005**, *24*, 4579 – 4587; c) K. Mikami, K. Wakabayashi, Y. Yusa, K. Aikawa, *Chem. Commun.* **2006**, 2365 – 2367; see also: d) K. Mikami, S. Matsukawa, *Nature* **1997**, *385*, 613 – 615; e) K. Mikami, M. Terada, T. Korenaga, Y. Matsumoto, M. Ueki, R. Angelaud, *Angew. Chem.* **2000**, *112*, 3676 – 3701; *Angew. Chem. Int. Ed.* **2000**, *39*, 3532 – 3556; f) a forerunner of this concept is the use by Katsuki et al. of achiral oxo Mn–salen complexes, which occur as interconverting chiral conformers, in combination with sparteine as catalysts in epoxidation: T. Hashihayata, Y. Ito, T. Katsuki, *Synlett* **1996**, 1079 – 1081; g) K. Miura, T. Katsuki, *Synlett* **1999**, 783 – 785.

[55] a) O. Pàmies, G. Net, A. Ruiz, C. Claver, *Tetrahedron: Asymmetry* **1999**, *10*, 2007 – 2014; see also later papers: b) M. Diéguez, S. Deerenberg, O. Pàmies, C. Claver, P. W. N. M. van Leeuwen, P. Kamer, *Tetrahedron: Asymmetry* **2000**, *11*, 3161 – 3166; c) M. Diéguez, A. Ruiz, C. Claver, *Chem. Commun.* **2001**, 2702 – 2703; d) M. Diéguez, A. Ruiz, C. Claver, *J. Org. Chem.* **2002**, *67*, 3796 – 3801; e) M. Diéguez, O. Pàmies, A. Ruiz, Y. Díaz, S. Castillón, C. Claver, *Coord. Chem. Rev.* **2004**, *248*, 2165 – 2192; f) for example, diphenol-derived diphosphites with carbohydrate backbones had been described earlier by Selke et al. as ligands in asymmetric hydroformylation (ca. 14% *ee*), but the fluxional (tropos) property was not specifically addressed: R. Kadyrov, D. Heller, R. Selke, *Tetrahedron: Asymmetry* **1998**, *9*, 329 – 340.

[56] C. Bolm, O. Beckmann, *Chirality* **2000**, *12*, 523 – 525.

[57] a) A. Alexakis, S. Rosset, J. Allamand, S. March, F. Guillen, C. Benhaim, *Synlett* **2001**, 1375 – 1379; b) K. Tissot-Croset, D. Polet, A. Alexakis, *Angew. Chem.* **2004**, *116*, 2480 – 2482; *Angew. Chem. Int. Ed.* **2004**, *43*, 2426 – 2428; c) L. Palais, I. S. Mikhel, C. Bournaud, L. Micouin, C. A. Falciola, Vuagnoux-d'Augustin, S. Rosset, G. Bernardinelli, A. Alexakis, *Angew. Chem.* **2007**, *119*, 7606 – 7609; *Angew. Chem. Int. Ed.* **2007**, *46*, 7462 – 7465.

[58] See, for example: a) N. Sakai, K. Nozaki, K. Mashima, H. Takaya, *Tetrahedron: Asymmetry* **1992**, *3*, 583 – 586; b) G. J. H. Buisman, L. A. van der Veen, A. Klootwijk, W. G. J. de Lange, P. C. J. Kamer, P. W. N. M. van Leeuwen, D. Vogt, *Organometallics* **1997**, *16*, 2929 – 2939.

[59] a) J. J. Becker, P. S. White, M. R. Gagné, *J. Am. Chem. Soc.* **2001**, *123*, 9478 – 9479; b) J. B. Becker, M. R. Gagné, *Acc. Chem. Res.* **2004**, *37*, 798 – 804; c) S. Wünnemann, R. Fröhlich, D. Hoppe, *Org. Lett.* **2006**, *8*, 2455 – 2458; d) R. Zalubovskis, A. Bouet, E. Fjellander, S. Constant, D. Linder, A. Fischer, J. Lacour, T. Privalov, C. Moberg, *J. Am. Chem. Soc.* **2008**, *130*, 1845 – 1855.

[60] a) J. Balsells, P. J. Walsh, *J. Am. Chem. Soc.* **2000**, *122*, 1802 – 1803; b) review of the use of achiral and *meso* ligands in asymmetric catalysis: P. J. Walsh, A. E. Lurain, J. Balsells, *Chem. Rev.* **2003**, *103*, 3297 – 3344; c) see also enantioselective molecular recognition of a diammonium salt of *meso*-1,2-diaminocyclohexane by chiral crown ethers in which one fluxional enantiomer is selectively complexed: M. T. Reetz, J. Rudolph, R. Mynott, *J. Am. Chem. Soc.* **1996**, *118*, 4494 – 4495.

[61] a) M. P. Sibi, S. Manyem, H. Palencia, *J. Am. Chem. Soc.* **2006**, *128*, 13660 – 13661; b) O. Corminboeuf, L. Quaranta, P. Renaud, M. Liu, C. P. Jasperse, M. P. Sibi, *Chem. Eur. J.* **2003**, *9*, 29 – 35.

[62] a) M. T. Reetz, G. Mehler, *Angew. Chem.* **2000**, *112*, 4047 – 4049; *Angew. Chem. Int. Ed.* **2000**, *39*, 3889 – 3890; b) M. T.

Reetz, G. Mehler, A. Meiswinkel, DE-A 10027505.2; WO 01/94278 A1, **2000**; c) T. Sell, Dissertation, Ruhr-Universität Bochum (G), **2002**; d) A. Meiswinkel, Dissertation, Ruhr-Universität Bochum (G), **2003**.

[63] The synthesis of binol-derived phosphites was first described in 1982: V. V. Ovchinnikov, O. A. Cherkasova, L. V. Verizhnikov, *Zh. Obshch. Khim.* **1982**, *52*, 707 – 708.

[64] a) T. Bartik, I. Gerdes, P. Heimbach, H.-G. Schulte, *J. Organomet. Chem.* **1989**, *367*, 359 – 370; b) P. Heimbach, T. Bartik, U. Drescher, I. Gerdes, W. Knott, R. Rienäcker, H.-G. Schulte, K. Tani, *Kontakte (Darmstadt)* **1988**, *3*, 19 – 31; c) K. Fuji, N. Kinoshita, K. Tanaka, T. Kawabata, *Chem. Commun.* **1999**, 2289 – 2290.

[65] a) (*R*)- and (*S*)-binol cost about $400 per kg, and bulk quantities (500–1000 kg) about $150–180 per kg at Reuter Chemische Apparatebau KG, Freiburg, Germany; b) other commercial sources of binol are also available; c) (*R*)- and (*S*)-binol have been prepared by a variety of routes, and have been used in a multitude of enantioselective reactions: J. M. Brunel, *Chem. Rev.* **2007**, *107*, 1 – -45.

[66] a) M. T. Reetz in *Perspectives in Organometallic Chemistry* (Eds.: C. G. Screttas, B. R. Steele), Royal Society of Chemistry, Cambridge, UK, **2003**, pp. 265 – 274; b) M. T. Reetz, *Russ. J. Org. Chem.* **2003**, *39*, 392 – 396; c) M. T. Reetz, *Chim. Oggi* **2003**, *21*, 5 – 8; d) M. T. Reetz in *Comprehensive Coordination Chemistry II*, *Vol. 9* (Ed.: M. D. Ward), Elsevier, Amsterdam, **2004**, pp. 509 – 548; e) K. N. Gavrilov, S. E. Lyubimov, O. G. Bondarev, M. G. Maksimova, S. V. Zheglov, P. V. Petrovskii, V. A. Davankov, M. T. Reetz, *Adv. Synth. Catal.* **2007**, *349*, 609 – 616.

[67] M. T. Reetz, A. Meiswinkel, G. Mehler, K. Angermund, M. Graf, W. Thiel, R. Mynott, D. G. Blackmond, *J. Am. Chem. Soc.* **2005**, *127*, 10305 – 10313.

[68] C. Claver, E. Fernandez, A. Gillon, K. Heslop, D. J. Hyett, A. Martorell, A. G. Orpen, P. G. Pringle, *Chem. Commun.* **2000**, 961 – 962.

[69] M. T. Reetz, T. Sell, *Tetrahedron Lett.* **2000**, *41*, 6333 – 6336.

[70] a) M. van den Berg, A. J. Minnaard, E. P. Schudde, J. van Esch, A. H. M. de Vries, J. G. de Vries, B. L. Feringa, *J. Am. Chem. Soc.* **2000**, *122*, 11539 – 11540; b) M. van den Berg, A. J. Minnaard, A. Jacobus, B. Feringa, J. G. de Vries (DSM NV), NL 1015655C, **2000**; c) D. Peña, A. J. Minnaard, J. G. de Vries, B. L. Feringa, *J. Am. Chem. Soc.* **2002**, *124*, 14552 – 14553; d) M. van den Berg, R. M. Haak, A. J. Minnaard, A. H. M. de Vries, J. G. de Vries, B. L. Feringa, *Adv. Synth. Catal.* **2002**, *344*, 10031007; e) R. Hoen, M. van den Berg, H. Bernsmann, A. J. Minnaard, J. G. de Vries, B. L. Feringa, *Org. Lett.* **2004**, *6*, 1433 – 1436; f) L. Panella, B. L. Feringa, J. G. de Vries, A. J. Minnaard, *Org. Lett.* **2005**, *7*, 4177 – 4180; binol-derived phosphoramidites have also been used as ligands in many other reaction types by the Feringa group and by others: g) B. L. Feringa, *Chimia* **2006**, *60*, 90 – 94 (Prelog Lecture).

[71] Reviews and selected key papers of various types of monodentate P ligands:[66] a) F. Lagasse, H. B. Kagan, *Chem. Pharm. Bull.* **2000**, *48*, 315 – 324; b) I. V. Komarov, A. Börner, *Angew. Chem.* **2001**, *113*, 1237 – 1240; *Angew. Chem. Int. Ed.* **2001**, *40*, 1197 – 1200; c) T. Jerphagnon, J.-L. Renaud, C. Bruneau, *Tetrahedron: Asymmetry* **2004**, *15*, 2101 – 2111; d) J. Ansell, M. Wills, *Chem. Soc. Rev.* **2002**, *31*, 259 – 268; e) B. D. Chapsal, Z. Hua, I. Ojima, *Tetrahedron: Asymmetry* **2006**, *17*, 642 – 657; f) K. N. Gavrilov, O. G. Bondarev, A. I. Polosukhin, *Russ. Chem. Rev.* **2004**, *73*, 671 – 699; g) A. Marinetti, F. Mathey, L. Ricard, *Organometallics* **1993**, *12*, 1207 – 1212; h) A. Marinetti, L. Ricard, *Organometallics* **1994**, *13*, 3956 – 3962; i) S. Saito, Y. Nakamura, Y. Morita, *Chem. Pharm. Bull.* **1985**, *33*, 5284 – 5293; j) M. Ostermeier, J. Prieß, G. Helmchen, *Angew. Chem.* **2002**, *114*, 625 – 628; *Angew. Chem. Int. Ed.* **2002**, *41*, 612 – 614; k) A. Marinetti, J.-P. Genêt, *C. R. Chim.* **2003**, *6*, 507 – 514; l) A. Marinetti, S. Jus, F. Labrue, A. Lemarchand, J.-P. Genêt, L. Ricard, *Synthesis* **2001**, 2095 – 2104; m) M. J. Burk, J. E. Feaster, R. L. Harlow, *Tetrahedron: Asymmetry* **1991**, *2*, 569 – 592; n) F. Guillen, M. Rivard, M. Toffano, J.-Y. Legros, J.-C. Daran, J.-C. Fiaud, *Tetrahedron* **2002**, *58*, 5895 – 5904; o) Z. Pakulski, O. M. Demchuk, J. Frelek, R. Luboradzki, K. M. Pietrusiewicz, *Eur. J. Org. Chem.* **2004**, 3913 – 3918; p) M. Ostermeier, B. Brunner, C. Korff, G. Helmchen, *Eur. J. Org. Chem.* **2003**, 3453 – 3459; q) review of the MOP ligand: T. Hayashi, *Acc. Chem. Res.* **2000**, *33*, 354 – 362.

[72] a) M. T. Reetz, G. Mehler, P. Scholz, unpublished results; b) M. T. Reetz, L. J. Goossen, A. Meiswinkel, J. Paetzold, J. Feldthusen Jensen, *Org. Lett.* **2003**, *5*, 3099 – 3101; c) M. T. Reetz, G. Mehler, unpublished results.

[73] H. Huang, X. Liu, H. Chen, Z. Zheng, *Tetrahedron: Asymmetry* **2005**, *16*, 693 – 697.

[74] Q.-H. Zeng, X.-P. Hu, Z.-C. Duan, X.-M. Liang, Z. Zheng, *J. Org. Chem.* **2006**, *71*, 393 – 396.

[75] a) M. T. Reetz, G. Mehler, results cited in footnote (9) of reference [66c]; see also: b) L. Lefort, J. A. F. Boogers, A. H. M. de Vries, J. G. de Vries, *Org. Lett.* **2004**, *6*, 1733 – 1735; phosphoramidite **22 f** is now considered to be a privileged ligand: c) H. Bernsmann, M. van den Berg, R. Hoen, A. J. Minnaard, G. Mehler, M. T. Reetz, J. G. de Vries, B. L. Feringa, *J. Org. Chem.* **2005**, *70*, 943 – 951.

[76] H. Huang, Z. Zheng, H. Luo, C. Bai, X. Hu, H. Chen, *J. Org. Chem.* **2004**, *69*, 2355 – 2361.

[77] a) C. Dreisbach, B. Meseguer, T. Prinz, U. Scholz, H.-C. Militzer, F. Agel, B. Driessen-Hoelscher (Bayer AG), EP 1298136, **2003**; b) Z. Hua, V. C. Vassar, I. Ojima, *Org. Lett.* **2003**, *5*, 3831 – 3834; c) D. Nakano, M. Yamaguchi, *Tetrahedron Lett.* **2003**, *44*, 4969 – 4971.

[78] a) A.-G. Hu, Y. Fu, J.-H. Xie, H. Zhou, L.-X. Wang, Q.-L. Zhou, *Angew. Chem.* **2002**, *114*, 2454 – 2456; *Angew. Chem. Int. Ed.* **2002**, *41*, 2348 – 2350; b) Y. Fu, J.-H. Xie, A.-G. Hu, H. Zhou, L.-X. Wang, Q.-L. Zhou, *Chem. Commun.* **2002**, 480 – 481; c) Y. Fu, X.-X. Guo, S.-F. Zhu, A.-G. Hu, J.-H. Xie, Q.-L. Zhou, *J. Org. Chem.* **2004**, *69*, 4648 – 4655; chiral monodentate phosphoramidite having a different spiro skeleton: d) S. Wu, W. Zhang, Z. Zhang, X. Zhang, *Org. Lett.* **2004**, *6*, 3565 – 3567.

[79] a) Y. Liu, C. A. Sandoval, Y. Yamaguchi, X. Zhang, Z. Wang, K. Kato, K. Ding, *J. Am. Chem. Soc.* **2006**, *128*, 14212 – 14213; b) B. Zhao, Z. Wang, K. Ding, *Adv. Synth. Catal.* **2006**, *348*, 1049 – 1057; c) K. Ding, *Pure Appl. Chem.* **2006**, *78*, 293 – 301.

[80] a) D. Seebach, M. Hayakawa, J.-I. Sakaki, W. B. Schweizer, *Tetrahedron* **1993**, *49*, 1711 – 1724; b) D. Seebach, A. K. Beck, A. Heckel, *Angew. Chem.* **2001**, *113*, 96 – 142; *Angew. Chem. Int. Ed.* **2001**, *40*, 92 – 138; c) S. A. Moteki, D. Wu, K. L. Chandra, D. S. Reddy, J. M. Takacs, *Org. Lett.* **2006**, *8*, 3097 – 3100.

[81] D. Gridnev, C. Fan, P. G. Pringle, *Chem. Commun.* **2007**, 1319 – 1321.

[82] a) H. J. Drexler, W. Baumann, A. Spannenberg, C. Fischer, D. Heller, *J. Organomet. Chem.* **2001**, *621*, 89 – 102; b) Y. K. Sun, R. N. Landau, J. Wang, C. LeBlond, D. G. Blackmond, *J. Am. Chem. Soc.* **1996**, *118*, 1348 – 1353; c) Y. Sun, J. Wang, C. LeBlond, R. A. Reamer, J. Laquidara, J. R. Sowa Jr, D. G. Blackmond, *J. Organomet. Chem.* **1997**, *548*, 65 – 72.

[83] a) A. S. C. Chan, J. J. Pluth, J. Halpern, *J. Am. Chem. Soc.* **1980**, *102*, 5952 – 5954; b) J. Halpern, *Science* **1982**, *217*, 401 – 407; c) C. R. Landis, J. Halpern, *J. Am. Chem. Soc.* **1987**, *109*, 1746 – 1754; d) B. McCulloch, J. Halpern, M. R. Thompson, C. R. Landis, *Organometallics* **1990**, *9*, 1392 – 1395; e) J. Halpern in *Chiral Catalysis*, *Vol. 5* (Ed.: J. D. Morrison), Academic Press, Orlando, **1985**, pp. 41 – 69; f) J. Halpern, D. P. Riley, A. S. C. Chan, J. J. Pluth, *J. Am. Chem. Soc.* **1977**, *99*, 8055 – 8057.

[84] a) C. R. Landis, P. Hilfenhaus, S. Feldgus, *J. Am. Chem. Soc.* **1999**, *121*, 8741 – 8754; b) S. Feldgus, C. R. Landis, *J. Am. Chem. Soc.* **2000**, *122*, 12714 – 12727; c) C. R. Landis, S. Feldgus, *Angew. Chem.* **2000**, *112*, 2985 – 2988; *Angew. Chem. Int. Ed.* **2000**, *39*, 2863 – 2866; d) S. Feldgus, C. R. Landis, *Organometallics* **2001**, *20*, 2374 – 2386.

[85] a) C. Puchot, O. Samuel, E. Dunach, S. Zhao, C. Agami, H. B. Kagan, *J. Am. Chem. Soc.* **1986**, *108*, 2353 – 2357; b) C. Girard, H. B. Kagan, *Angew. Chem.* **1998**, *110*, 3088 – 3127; *Angew. Chem. Int. Ed.* **1998**, *37*, 2922 – 2959; c) D. G. Blackmond, *Acc. Chem. Res.* **2000**, *33*, 402 – 411; d) D. G. Blackmond, C. R. McMillan, S. Ramdeehul, A. Schorm, J. M. Brown, *J. Am. Chem. Soc.* **2001**, *123*, 10103 – 10104.

[86] H.-J. Drexler, W. Baumann, T. Schmidt, S. Zhang, A. Sun, A. Spannenberg, C. Fischer, H. Buschmann, D. Heller, *Angew. Chem.* **2005**, *117*, 1208 – 1212; *Angew. Chem. Int. Ed.* **2005**, *44*, 1184 – 1188.

[87] a) D. A. Evans, F. E. Michael, J. S. Tedrow, K. R. Campos, *J. Am. Chem. Soc.* **2003**, *125*, 3534 – 3543; b) A. Marinetti, S. Jus, J.-P. Genêt, *Tetrahedron Lett.* **1999**, *40*, 8365 – 8368; see also: c) J. P. Genet, A. Marinetti, V. Ratovelomanana-Vidal, *Pure Appl. Chem.* **2001**, *73*, 299 – 303.

[88] a) Y. Xu, N. W. Alcock, G. J. Clarkson, G. Docherty, G. Woodward, M. Wills, *Org. Lett.* **2004**, *6*, 4105 – 4107; b) M. T. Reetz, X. Li, *J. Am. Chem. Soc.* **2006**, *128*, 1044 – 1045.

[89] a) P. T. Corbett, J. Leclaire, L. Vial, K. R. West, J.-L. Wietor, J. K. M. Sanders, S. Otto, *Chem. Rev.* **2006**, *106*, 3652 – 3711; b) J.-M. Lehn, *Chem. Eur. J.* **1999**, *5*, 2455 – 2463.

[90] M. T. Reetz, H. Guo, *Beilstein J. Org. Chem.* **2005**, *1*, 3.

[91] M. T. Reetz, X. Li, *Angew. Chem.* **2005**, *117*, 3022 – 3024; *Angew. Chem. Int. Ed.* **2005**, *44*, 2962 – 2964.

[92] M. T. Reetz, X. Li, *Chem. Commun.* **2006**, 2159 – 2160.

[93] a) S. Gladiali, A. Dore, D. Fabbri, O. De Lucchi, M. Manassero, *Tetrahedron: Asymmetry* **1994**, *5*, 511 – 514; b) K. Junge, B. Hagemann, S. Enthaler, G. Oehme, M. Michalik, A. Monsees, T. Riermeier, U. Dingerdissen, M. Beller, *Angew. Chem.* **2004**, *116*, 5176 – 5179; *Angew. Chem. Int. Ed.* **2004**, *43*, 5066 – 5069; c) K. Junge, G. Oehme, A. Monsees, T. Riermeier, U. Dingerdissen, M. Beller, *J. Organomet. Chem.* **2003**, *675*, 91 – 96.

[94] M. T. Reetz, G. Mehler, A. Meiswinkel, T. Sell, *Tetrahedron: Asymmetry* **2004**, *15*, 2165 – 2167.

[95] D. Peña, A. J. Minnaard, J. A. F. Boogers, A. H. M. de Vries, J. G. de Vries, B. L. Feringa, *Org. Biomol. Chem.* **2003**, *1*, 1087 – 1089.

[96] M. T. Reetz, X. Li, *Tetrahedron* **2004**, *60*, 9709 – 9714.

[97] a) A. Duursma, R. Hoen, J. Schuppan, R. Hulst, A. J. Minnaard, B. L. Feringa, *Org. Lett.* **2003**, *5*, 3111 – 3113; b) A. Duursma, D. Peña, A. J. Minnaard, B. L. Feringa, *Tetrahedron: Asymmetry* **2005**, *16*, 1901 – 1904.

[98] a) Y. Takaya, M. Ogasawara, T. Hayashi, M. Sakai, N. Miyaura, *J. Am. Chem. Soc.* **1998**, *120*, 5579 – 5580; b) T. Hayashi, M. Senda, Y. Takaya, M. Ogasawara, *J. Am. Chem. Soc.* **1999**, *121*, 11591 – 11592; c) T. Hayashi, M. Senda, M. Ogasawara, *J. Am. Chem. Soc.* **2000**, *122*, 10716 – 10717; d) S. Sakuma, M. Sakai, R. Itooka, N. Miyaura, *J. Org. Chem.* **2000**, *65*, 5951 – 5955; e) Y. Takaya, T. Senda, H. Kurushima, M. Ogasawara, T. Hayashi, *Tetrahedron: Asymmetry* **1999**, *10*, 4047 – 4056; f) M. Kuriyama, K. Tomioka, *Tetrahedron Lett.* **2001**, *42*, 921 – 923; g) T. Hayashi, *Synlett* **2001**, 879 – 887; h) R. Itooka, Y. Iguchi, N. Miyaura, *Chem. Lett.* **2001**, 722 – 723; i) T. Hayashi, K. Yamasaki, *Chem. Rev.* **2003**, *103*, 2829 – 2844.

[99] See, for example: a) M. T. Reetz, D. Moulin, A. Gosberg, *Org. Lett.* **2001**, *3*, 4083 – 4085; b) M. Pucheault, S. Darses, J.-P. Genêt, *Eur. J. Org. Chem.* **2002**, 3552 – 3557; c) Y. Ma, C. Song, C. Ma, Z. Sun, Q. Chai, M. B. Andrus, *Angew. Chem.* **2003**, *115*, 6051 – 6054; *Angew. Chem. Int. Ed.* **2003**, *42*, 5871 – 5874; d) M. Kuriyama, K. Nagai, K. Yamada, Y. Miwa, T. Taga, K. Tomioka, *J. Am. Chem. Soc.* **2002**, *124*, 8932 – 8939; e) R. B. C. Jagt, J. G. de Vries, B. L. Feringa, A. J. Minnaard, *Org. Lett.* **2005**, *7*, 2433 – 2435; f) Y. Suzuma, T. Yamamoto, T. Ohta, Y. Ito, *Chem. Lett.* **2007**, *36*, 470 – 471.

[100] a) C. Monti, C. Gennari, U. Piarulli, *Tetrahedron Lett.* **2004**, *45*, 6859 – 6862; b) C. Monti, C. Gennari, U. Piarulli, J. G. de Vries, A. H. M. de Vries, L. Lefort, *Chem. Eur. J.* **2005**, *11*, 6701 – 6717.

[101] a) C. Monti, C. Gennari, U. Piarulli, *Chem. Commun.* **2005**, 5281 – 5283; b) C. Monti, C. Gennari, U. Piarulli, *Chem. Eur. J.* **2007**, *13*, 1547 – 1558.

[102] M. T. Reetz, M. Surowiec, *Heterocycles* **2006**, *67*, 567 – 574.

[103] a) A. Alexakis, J. Vastra, J. Burton, P. Mangeney, *Tetrahedron: Asymmetry* **1997**, *8*, 3193 – 3196; b) A. Alexakis, C. Benhaim, *Tetrahedron: Asymmetry* **2001**, *12*, 1151 – 1157; c) M. D. K. Boele, P. C. J. Kamer, M. Lutz, A. L. Spek, J. G. de Vries, P. W. N. M. van Leeuwen, G. P. F. van Strijdonck, *Chem. Eur. J.* **2004**, *10*, 6232 – 6246.

[104] M. T. Reetz, J.-A. Ma, R. Goddard, *Angew. Chem.* **2005**, *117*, 416 – 419; *Angew. Chem. Int. Ed.* **2005**, *44*, 412 – 415.

[105] a) R. Engel, J. I. Rizzo, *Curr. Org. Chem.* **2006**, *10*, 2393 – 2405; b) K. V. L. Crépy, T. Imamoto, *Adv. Synth. Catal.* **2003**, *345*, 79 – 101; c) P.-H. Leung, *Acc. Chem. Res.* **2004**, *37*, 169 – 177; d) W. Tang, W. Wang, Y. Chi, X. Zhang, *Angew. Chem.* **2003**, *115*, 3633 – 3635; *Angew. Chem. Int. Ed.* **2003**, *42*, 3509 – 3511; e) G. Hoge, *J. Am. Chem. Soc.* **2003**, *125*, 10219 – 10227; f) T. Imamoto, V. L. Crépy, K. Katagiri, *Tetrahedron: Asymmetry* **2004**, *15*, 2213 – 2218; g) W.-M. Dai, K. K. Y. Yeung, W. H. Leung, R. K. Haynes, *Tetrahedron: Asymmetry* **2003**, *14*, 2821 – 2826.

[106] R. Hoen, J. A. F. Boogers, H. Bernsmann, A. J. Minnaard, A. Meetsma, T. D. Tiemersma-Wegman, A. H. M. de Vries, J. G. de Vries, B. L. Feringa, *Angew. Chem.* **2005**, *117*, 4281 – 4284; *Angew. Chem. Int. Ed.* **2005**, *44*, 4209 – 4212.

[107] H. M. de Vries, L. Lefort, J. A. F. Boogers, J. G. de Vries, D. J. Ager, *Chim. Oggi* **2005**, *23*, 18 – 22.

[108] a) L. Panella, A. M. Aleixandre, G. J. Kruidhof, J. Robertus, B. L. Feringa, J. G. de Vries, A. J. Minnaard, *J. Org. Chem.* **2006**, *71*, 2026 – 2036; b) R. Hoen, T. Tiemersma-Wegman, B. Procuranti, L. Lefort, J. G. de Vries, A. J. Minnaard, B. L. Feringa, *Org. Biomol. Chem.* **2007**, *5*, 267 – 275.

[109] M. T. Reetz, O. Bondarev, *Angew. Chem.* **2007**, *119*, 4607 – 4610; *Angew. Chem. Int. Ed.* **2007**, *46*, 4523 – 4526.

[110] See, for example: a) C. Moessner, C. Bolm, *Angew. Chem.* **2005**, *117*, 7736 – 7739; *Angew. Chem. Int. Ed.* **2005**, *44*, 7564 – 7567; b) E. Guiu, M. Aghmiz, Y. Díaz, C. Claver, B. Meseguer, C. Militzer, S. Castillón, *Eur. J. Org. Chem.* **2006**, 627 – 633; c) T. Imamoto, N. Iwadate, K. Yoshida, *Org. Lett.* **2006**, *8*, 2289 – 2292; d) A. Dervisi, C. Carcedo, L. Ooi, *Adv. Synth. Catal.* **2006**, *348*, 175 – 183; e) G. Shang, Q. Yang, X. Zhang, *Angew. Chem.* **2006**, *118*, 6508 – 6510; *Angew. Chem. Int. Ed.* **2006**, *45*, 6360 – 6362; f) A. Trifonova, J. S. Diesen, C. J. Chapman, P. G. Andersson, *Org. Lett.* **2004**, *6*, 3825 – 3827; g) M. Solinas, A. Pfaltz, P. G. Cozzi, W. Leitner, *J. Am. Chem. Soc.* **2004**, *126*, 16142 – 16147.

[111] a) L. D. Quin, *A Guide to Organophosphorus Chemistry*, Wiley-Interscience, New York, **2000**; b) B. Walther, *Coord. Chem. Rev.* **1984**, *60*, 67 – 105; c) N. V. Dubrovina, A. Börner, *Angew. Chem.* **2004**, *116*, 6007 – 6010; *Angew. Chem. Int. Ed.* **2004**, *43*, 5883 – 5886; d) L. Ackermann, *Synlett* **2007**, 507 – 526.

[112] M. T. Reetz, T. Sell, R. Goddard, *Chimia* **2003**, *57*, 290 – 292.

[113] D. Enders, L. Tedeschi, J. W. Bats, *Angew. Chem.* **2000**, *112*, 4774 – 4776; *Angew. Chem. Int. Ed.* **2000**, *39*, 4605 – 4607.

[114] A. Alexakis, J. Burton, J. Vastra, C. Benhaim, X. Fournioux, A. van den Heuvel, J.-M. Levêque, F. Mazé, S. Rosset, *Eur. J. Org. Chem.* **2000**, 4011 – 4027.

[115] X. Jiang, A. J. Minnaard, B. Hessen, B. L. Feringa, A. L. L. Duchateau, J. G. O. Andrien, J. A. F. Boogers, J. G. de Vries, *Org. Lett.* **2003**, *5*, 1503 – 1506.
[116] a) M. T. Reetz, *Angew. Chem.* **1984**, *96*, 542 – 555; *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 556 – 569; b) A. H. Hoveyda, D. A. Evans, G. C. Fu, *Chem. Rev.* **1993**, *93*, 1307 – 1370.
[117] Review of 1,3-allylic strain: R. W. Hoffmann, *Chem. Rev.* **1989**, *89*, 1841 – 1860.
[118] a) F. Giacomina, A. Meetsma, L. Panella, L. Fefort, A. H. M. de Vries, J. G. de Vries, *Angew. Chem.* **2007**, *119*, 1519 – 1522; *Angew. Chem. Int. Ed.* **2007**, *46*, 1497 – 1500; b) we have prepared a chiral propellerlike monophosphite which binds only once to Rh: M. T. Reetz, H. Guo, J.-A. Ma, R. Goddard, R. Mynott, unpublished results.
[119] K. Angermund, M. T. Reetz, unpublished results.
[120] M. T. Reetz, Y. Fu, A. Meiswinkel, *Angew. Chem.* **2006**, *118*, 1440 – 1443; *Angew. Chem. Int. Ed.* **2006**, *45*, 1412 – 1415.
[121] B. Breit, W. Seiche, *J. Am. Chem. Soc.* **2003**, *125*, 6608 – 6609.
[122] a) Z. Freixa, P. W. N. M. van Leeuwen, *Dalton Trans.* **2003**, 1890 – 1901; b) P. W. N. M. van Leeuwen, P. C. J. Kamer, J. N. H. Reek, P. Dierkes, *Chem. Rev.* **2000**, *100*, 2741 – 2769; c) C. A. Tolman, *Chem. Rev.* **1977**, *77*, 313 – 348; d) C. P. Casey, G. T. Whiteker, *Isr. J. Chem.* **1990**, *30*, 299 – 304.
[123] B. Breit, W. Seiche, *Angew. Chem.* **2005**, *117*, 1666 – 1669; *Angew. Chem. Int. Ed.* **2005**, *44*, 1640 – 1643.
[124] M. Weis, C. Waloch, W. Seiche, B. Breit, *J. Am. Chem. Soc.* **2006**, *128*, 4188 – 4189.
[125] a) F. Chevallier, B. Breit, *Angew. Chem.* **2006**, *118*, 1629 – 1632; *Angew. Chem. Int. Ed.* **2006**, *45*, 1599 – 1602.
[126] a) B. Breit, *Angew. Chem.* **2005**, *117*, 6976 – 6986; *Angew. Chem. Int. Ed.* **2005**, *44*, 6816 – 6825; b) B. Breit, W. Seiche, *Pure Appl. Chem.* **2006**, *78*, 249 – 256.
[127] P. A. Duckmanton, A. J. Blake, J. B. Love, *Inorg. Chem.* **2005**, *44*, 7708 – 7710.
[128] a) L. K. Knight, Z. Freixa, P. W. N. M. van Leeuwen, J. N. H. Reek, *Organometallics* **2006**, *25*, 954 – 960; b) A. J. Sandee, A. M. van der Burg, J. N. H. Reek, *Chem. Commun.* **2007**, 864 – 866.
[129] a) V. F. Slagt, P. W. N. M. van Leeuwen, J. N. H. Reek, *Chem. Commun.* **2003**, 2474 – 2475; b) M. Kuil, P. E. Goudriaan, P. W. N. M. van Leeuwen, J. N. H. Reek, *Chem. Commun.* **2006**, 4679 – 4681; c) X.-B. Jiang, P. W. N. M. van Leeuwen, J. N. H. Reek, *Chem. Commun.* **2007**, 2287 – 2289.
[130] Review of "bidentate" ligands from the supramolecular concepts of Love[127] and Reek/van Leeuwen:[128,129] A. J. Sandee, J. N. H. Reek, *Dalton Trans.* **2006**, 3385 – 3391.
[131] a) J. M. Takacs, D. S. Reddy, S. A. Moteki, D. Wu, H. Palencia, *J. Am. Chem. Soc.* **2004**, *126*, 4494 – 4495; b) J. M. Takacs, K. Chaiseeda, S. A. Moteki, D. S. Reddy, D. Wu, K. Chandra, *Pure Appl. Chem.* **2006**, *78*, 501 – 509.
[132] a) P. Braunstein, G. Clerc, X. Morise, R. Welter, G. Mantovani, *Dalton Trans.* **2003**, 1601 – 1605; b) P. Braunstein, G. Clerc, X. Morise, *New J. Chem.* **2003**, *27*, 68 – 72.
[133] H. Jiang, A. Hu, W. Lin, *Chem. Commun.* **2003**, 96 – 97.
[134] N. C. Gianneschi, P. A. Bertin, S. T. Nguyen, C. A. Mirkin, L. N. Zakharov, A. L. Rheingold, *J. Am. Chem. Soc.* **2003**, *125*, 10508 – 10509.
[135] J. M. Ready, E. N. Jacobsen, *Angew. Chem.* **2002**, *114*, 1432 – 1435; *Angew. Chem. Int. Ed.* **2002**, *41*, 1374 – 1377.
[136] N. C. Gianneschi, S.-H. Cho, S. T. Nguyen, C. A. Mirkin, *Angew. Chem.* **2004**, *116*, 5619 – 5623; *Angew. Chem. Int. Ed.* **2004**, *43*, 5503 – 5507.
[137] a) E. Alberico, I. Nieddu, R. Taras, S. Gladiali, *Helv. Chim. Acta* **2006**, *89*, 1716 – 1729; b) W. Chen, J. Xiao, *Tetrahedron Lett.* **2001**, *42*, 8737 – 8740.
[138] a) M. T. Reetz, G. Mehler, O. G. Bondarev, *Chem. Commun.* **2006**, 2292 – 2294; b) M. T. Reetz, G. Mehler, DE-A 102005044355.9, **2005**.
[139] J. Long, J. Hu, X. Shen, B. Ji, K. Ding, *J. Am. Chem. Soc.* **2002**, *124*, 10 – 11.
[140] S. Tosaki, K. Hara, V. Gnanadesikan, H. Morimoto, S. Harada, M. Sugita, N. Yamagiwa, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.* **2006**, *128*, 11776 – 11777.

