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Strategies for the development of enantioselective catalysts*

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Abstract: Novel C_2-symmetric diiminosphosphoranes and diketimines are useful ligands for Pd-and Cu-catalyzed C–C bond forming reactions, Angermund's molecular modeling based on accessible molecular surface serving as a guide in predicting catalyst activity. The first highly enantioselective diphosphites as ligands in Rh-catalyzed hydrogenation are also described, the selectivity principle being based on *in situ* selection of conformational enantiomers. Finally, a systematic study of chiral diphosphonites reveals that ferrocene-based derivatives are ideal in hydrogenation and certain conjugate addition reactions. These methods are compared to biocatalytic strategies based on the creation of enantioselective biocatalysts by *in vitro* evolution, a rational process which is independent of the catalyst structure or mechanism.

INTRODUCTION

Research in the area of chiral metal catalysts for the stereoselective transformation of organic compounds continues to be a fascinating endeavor [1]. During the last three decades, thousands of chiral catalysts have been prepared, one by one, and subsequently tested in various reactions. For example, over 4000 chiral phosphorus-containing ligands are now available, and further examples appear almost monthly. This seems to be a sign that the simplicity of ligand preparation and degree of catalyst performance have not yet reached a satisfactory level in a general way. Indeed, of these chiral P-based catalysts, only a limited number show enantiomer excess-values of $>95\%$, and these are restricted to certain types of substrates. The 'success-rate' in the area of chiral catalysts lacking phosphorus is also not as high as one would like. What are the guidelines that need to be followed when attempting to develop efficient chiral catalysts? Most chemists in the field will agree that it is a combination of intuition, experience, knowledge of reaction mechanisms and a feel for theoretical aspects, coupled with a great deal of trial and error. A new aspect is currently emerging, namely the development of combinatorial methods in enantioselective catalysis [2–9]. Theoretically, it is a way to 'harness' serendipity by shortening the time scale of trial and error.

In 1996 we initiated several projects directed towards preparing new enantioselective catalysts, which are reviewed here. The focus is on new types of chiral ligands such as diiminophosphoranes (e.g. **1**) [10], diketimines (e.g. **2**) [11], diphosphites (e.g. **3**) [12] and diphosphonites (e.g. **4**) [13] (Schemes 1 and 2). Ligands **1**, **2** and **4** are available in both enantiomeric forms.

Parallel to these efforts we began to apply *in vitro* evolution as a means of creating enantioselective enzymes for use in organic synthesis [14,15]. Since the evolutive development of enantioselective enzymes requires the application of high-throughput-screening systems for *ee*, we have had to devise such assays. These are mentioned in this review because in principle they can also be used in combinatorial chemistry directed towards developing chiral metal catalysts.

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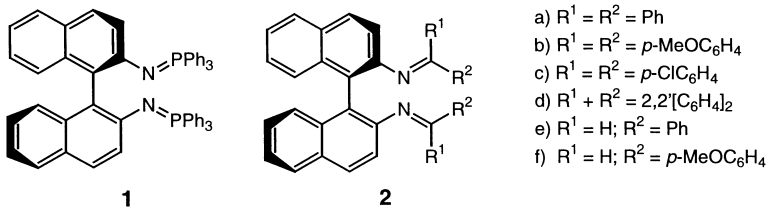
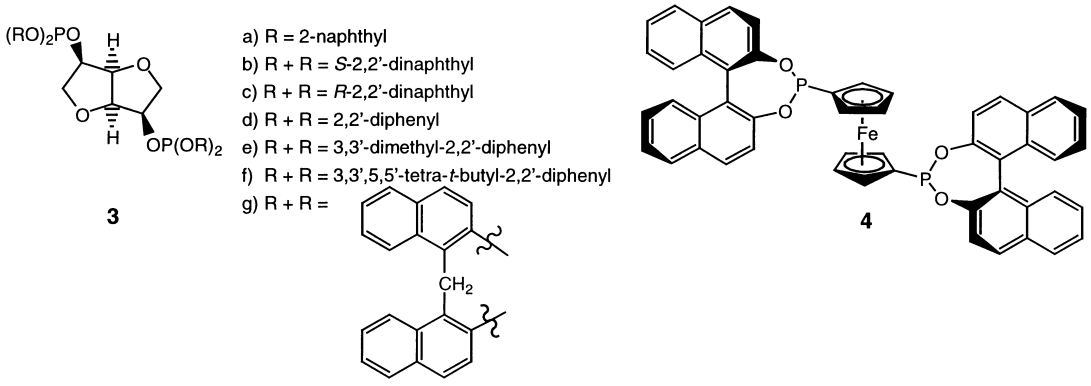


1 **2**

Scheme 1

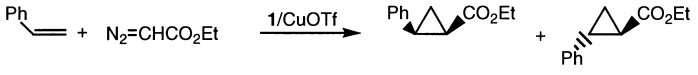


3 **4**

Scheme 2

C_2-SYMMETRIC DIIMINOPHOSPHORANES AND DIKETIMINES

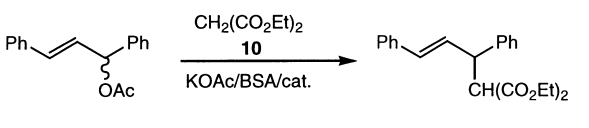
Ligands of the type **1** and their metal complexes are easily prepared [10]. A variety of metal salts form complexes of **1,** e.g. CuOTf or $Rh(COD)_2BF_4$. Whereas **1**/CuOTf turned out to be a fairly efficient catalyst for the enantioselective cyclopropanation of styrene (**5**) using ethyl diazoacetate (**6**), the *ee* of the major product **7** being 90% (Scheme 3), **1**/$Rh(COD)BF_4$ failed to show significant activity in hydrogenation reactions. Other reactions have not yet been studied. Since the iminophosphorane function has basic properties, compounds of type **1** constitute a new class of chiral bases.



5 **6** **7** **8**

Scheme 3

Parallel to these studies, the analogous chiral diketimines **2** were also prepared and tested in catalysis [11]. Previously, few cases of dialdimines derived from C_2-symmetric 1,2-diamines had been reported [17–20], including **2e** (in addition to the Jacobsen/Katsuki ligands). Interestingly, dialdimine **2e** was first reported in 1929 by Kuhn [21], although metal complexes were not described. In the early phase of our own efforts in this area unusual and unexpected observations were made in that the metal complexes of some of the ligands **2** were quite active, whereas others showed no activity whatsoever. For example, the Pd-complexes of **2d–f** were completely inactive in the allylic substitution reaction $\mathbf{9} + \mathbf{10} \rightarrow \mathbf{11}$, whereas the analogs **2a-b** showed appreciable activity. The catalyst derived from **2a** turned out to be the most active and selective (*ee* = 92%; Scheme 4) [11].

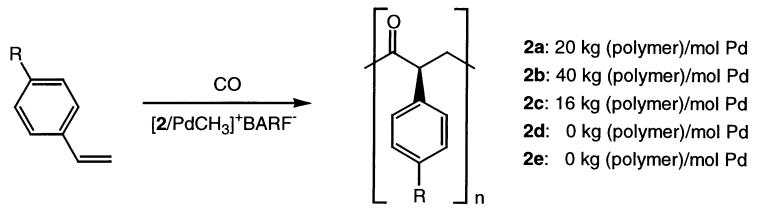


9 **11**

2a/Pd(Cl)C_3H_5:	78% (*ee* = 92%)	
2b/Pd(Cl)C_3H_5:	44% (*ee* = 92%)	
2c/Pd(Cl)C_3H_5:	3% (*ee* = 73%)	
2d/Pd(Cl)C_3H_5:	0%	(-)
2e/Pd(Cl)C_3H_5:	0%	(-)

Scheme 4

Why is the seemingly most sterically hindered catalyst the most reactive? In order to develop some guidelines on how to proceed in these and other catalytic reactions using ligands **2**, the concept of accessible molecular surface (AMS) as developed by Angermund *et al*. [22] was applied [11]. This type of molecular modeling combines the simplicity of a purely steric model with the capability of scrutinizing the conformationally dependent steric properties: (i) the conformational space of the active fragment is explored; (ii) selected relevant structures are superimposed, and (iii) the resulting pseudo-dynamic structure is analyzed. In the present case, a hypothetical Pd-fragment **2**/Pd was subjected to such an analysis. The results point to a remarkable phenomenon: the most active catalyst, derived from benzophenone (**2e**/Pd) has a much *larger* AMS than the least active catalyst derived from benzaldehyde (**2d**/Pd). This unexpected result can be explained by a locking-in effect originating from the phenyl groups *trans* to the metal. In the case of **2e**, the phenyl groups are free to rotate, a process which leads to greater shielding of the active Pd-center and therefore to lower reactivity. In the case of the fragment derived from fluorenone (**2d**/Pd), the overall AMS is similar to that of **2a**/Pd, but the two points of coordination in the square planar complex are on the very edges of the AMS, which is sterically unfavorable. It needs to be emphasized that this model is crude and cannot include possible electronic effects (cf. **2a** vs. **2c**). The AMS has previously been developed to explain the relative reactivity of homologous catalysts in reactions in which the coordination number *decreases* in the transition state, which means that catalysts with small AMSs show the highest activity [22]. In the present case the opposite pertains. We then decided to apply the AMS model in the search for active catalysts for the isotactic alternating copolymerization of *p-tert*-butylstyrene (**12**) with carbon monoxide. Several approaches using C_1- or C_2-symmetric Pd-catalysts had previously been reported [23–25]. Based on mechanistic studies it is known that in the rate determining step the number of ligands and reaction partners at palladium does *not* decrease. Therefore, the AMS analysis predicts an increase in catalyst activity as follows: **2e**/Pd < **2d**/Pd << **2a**/Pd (Scheme 5).



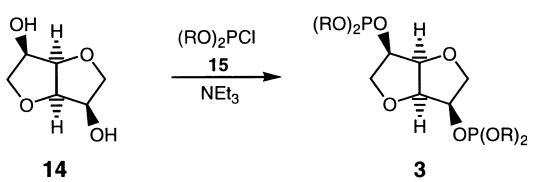
12 (R = *t*-Bu) **13** (> 97% isotactic)

Scheme 5

Remarkably, the theoretical prediction is in full accord with the experimental results. Catalysts derived from ligands **2d-e** show no activity whatsoever. Obviously, the difference in activity as a consequence of introducing electron donating or withdrawing substituents is outside of the AMS model. The polymerizations with the active catalysts based on **2a-c** are >97% isotactic [11]. Although the present version of the AMS model cannot yet be used to predict stereoselectivity reliably, it does constitute a useful guide in devising strategies for the development of active catalysts. This is not trivial since the problem of rate precedes that of stereoselectivity.

NEW CHIRAL DIPHOSPHITE LIGANDS

In contrast to chiral diphosphines, less is known concerning diphosphites [1,12,26–29]. We chose the easily accessible diol **14** as the chiral backbone and reacted it with various achiral and chiral chlorophosphoric acid diarylesters **15** to form ligands **3** (Scheme 6) [12].



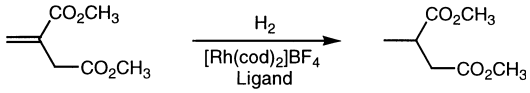
14 **3**

Scheme 6

In the case of diphosphites **3d-g,** each P/O heterocycle exists in two rapidly interconverting enantiomeric conformers, which means that upon metal catalyst formation three different diastereomeric complexes are possible (*R*/*R*, *S*/*S* and *R*/*S* combinations in the P/O heterocycle). In asymmetric catalysis one generally tries to avoid such situations. Nevertheless, we purposely set the above situation up, intending to explore the possibility that perhaps one of the three diastereomeric catalysts would be more reactive than the others and therefore determine the reaction course. If the local chirality induced by that particular P/O conformer were to dominate stereochemistry, one would in effect be gaining a stereochemical control element at a low cost (no need to separate antipodes as in the case of the stereochemically stable dinaphthol derivatives **3b-c**). In the Rh-catalyzed hydrogenation of itaconic acid ester (**16**) this was indeed observed (Table 1; Scheme 7) [12].

Table 1 Enantioselective hydrogenation of **16** [12]

Ligand	T (°C)	Conversion (%)	*ee* (%)	Configuration
3a	20	65	21.0	*S*-**17**
3b	20	>99	87.8	*S*-**17**
3c	20	>99	94.5	*R*-**17**
3c	−10	>99	96.2	*R*-**17**
3d	20	74	38.9	*S*-**17**
3e	20	>99	96.8	*R*-**17**
3e	−10	>99	98.2	*R*-**17**
3f	20	24	5.2	*R*-**17**
3g	20	>99	49.3	*R*-**17**



16 **17**

Scheme 7

It is clear that the chirality in the backbone of **3a**/Rh(COD)BF_4 is not efficiently transferred onto the product and that in the case of the dinaphthol pair it is **3c**/Rh(COD)BF_4 which represents the matched combination. More importantly, diastereomerically fluxional **3e**/Rh(COD)BF_4 is the most enantioselective catalyst of all. It is therefore likely that the most active form of this catalyst has the *R*,*R*-configuration in both P/O heterocycles. Indeed, qualitative observations regarding rate showed that hydrogenations with **3c**/Rh(COD)BF_4 are significantly faster than those with **3b**/Rh(COD)BF_4, and that **3e**/Rh(COD)BF_4 is the most active catalyst. The other diphenol-derived ligands are less stereoselective, and **3d**/Rh(COD)BF_4 even affords the *opposite* enantiomeric product (*S*-**17**). Thus, the P/O heterocycles play a crucial role in determining the direction *and* degree of enantioselectivity. Such an effect has not been previously observed in other systems involving diphenol ligands [26,27], It is known from a different study concerning hydroxylation [30] that diastereomeric catalysts can lead to opposite enantiomeric products, and that a type of nonlinear effect may pertain (although its origin remains unclear). In the present case a detailed kinetic study unveiled this type of nonlinear effect [31]. Its origin was traced not to the presence of dimeric species, but to differences in the kinetic profiles of the catalysts acting independently (Fig. 1).

NEW CHIRAL DIPHOSPHONITE LIGANDS

Other recent work in our laboratories has shown that diphosphonites **4** and **18–20** composed of an achiral backbone and a chiral P/O heterocycle derived from dinaphthol (or chiral 1,2-diols) constitute a remarkably efficient class of ligands [13,32]. The virtues include simplicity of preparation and high enantioselectivity in a variety of different reactions (Scheme 8).

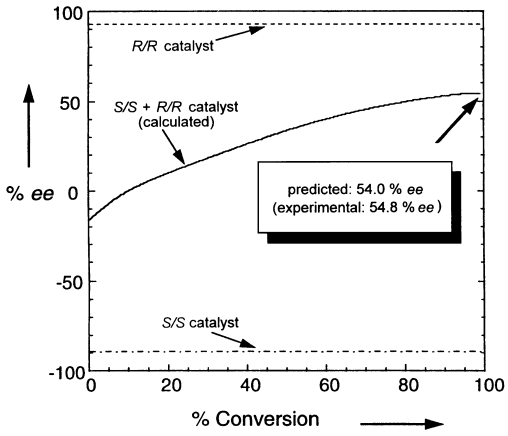
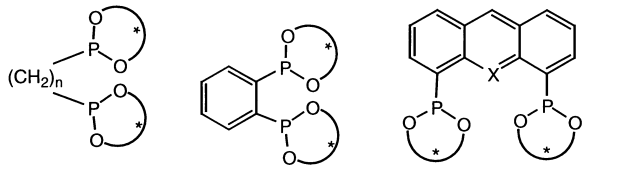
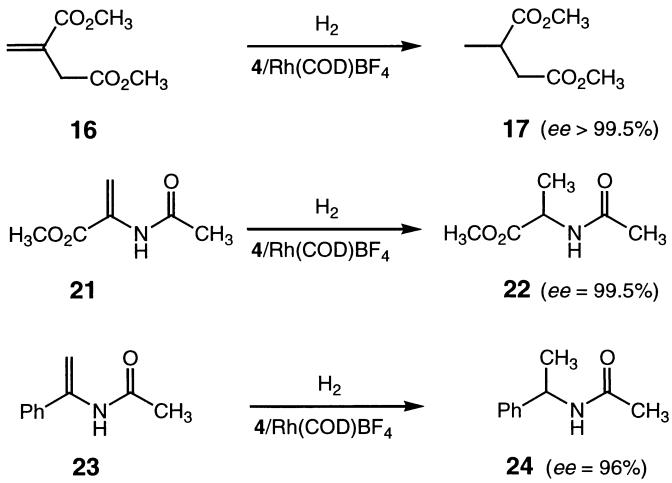


Fig. 1 Experimental and calculated percentage enantioselectivity of reaction **16** → **17** using the *S*/*S* catalyst (**3b**/Rh(COD)BF_4) and the *R*/*R* catalyst (**3c**/Rh(COD)BF_4) [31].



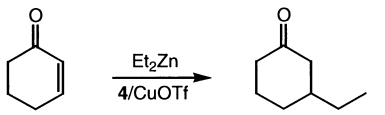
Scheme 8

Ligands derived from ferrocene (e.g. **4**) appear to be particularly effective, e.g. in the hydrogenation of olefins [13]. Since **4** is easily accessible, it competes well with other ligands known in the literature (Scheme 9) [1].



Scheme 9

Ligand **4** also proved to be highly enantioselective in the Cu-catalyzed conjugate addition of Et_2Zn to **25** [32], which again shows that it belongs to the best ligands known in this type of chemistry [33]. Other types of reactions such as Diels–Alder cycloadditions catalyzed by Mg, Zn or Cu complexes of **4** have yet to be studied (Scheme 10).

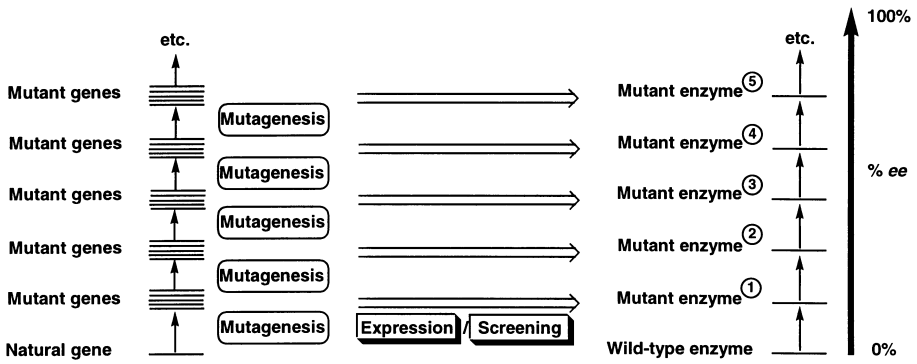


25 **26** (*ee* = 96%)

Scheme 10

CONCLUSIONS AND FUTURE DEVELOPMENTS

When attempting to prepare new and better enantioselective catalysts, such factors as steric and electronic effects, the influence of bite angle, the role of solvents, nonlinear effects and autocatalytic phenomena need to be considered. This review extends the list a little. For example, the concept of accessible molecular surface (AMS) may be useful as a guide in assessing catalyst activity in a homologous series of metal complexes. Another aspect relates to the use of fluxional conformational diastereomers as catalysts, provided that one form is most active, which again can in theory be predicted by the AMS model. In addition to chiral catalyst development based on design, intuition and trial and error [1], combinatorial enantioselective catalysis may turn out to be a complementary approach [2–9]. We are therefore developing high-throughput-screening methods for the assay of *ee*. One system is based on black body radiation using appropriate IR-thermographic cameras [34]. Whereas quantification still needs to be developed for this system, a second approach has reached maturity, namely the use of isotopically labeled substrates (*pseudo*-enantiomers or *pseudo*-prochiral compounds), the enantioselective reactions of which can be monitored by mass spectrometry [2]. About 1000 exact *ee* determinations are possible per day. These and other screening systems have already been applied to the *in vitro* evolution of enantioselective enzymes [14,15], a method which goes far beyond combinatorial catalysis due to its evolutive character. This approach to the creation of enantioselective catalysts is truly rational because it requires no knowledge of the structure or mechanism of the catalyst! Thus, the traditional way of thinking about 'designing' enantioselective catalysts, which includes the consideration of steric and electronic factors, is abandoned. Rather, known methods of random mutagenesis such as error-prone PCR [35] or DNA [36] shuffling are applied (Scheme 11) [14,15]. In each round of mutagenesis a library of mutant enzymes is created from which the best mutant is identified by an efficient screening systems (see above). The inferior variants are discarded and the process is then repeated as often as necessary, or a combination of mutagenesis methods (e.g. error-prone PCR and saturation mutagenesis) are applied. Indeed, on this 'Darwinian' basis the *ee* of a certain lipase-catalyzed reaction was increased from $ee = 2\%$ to $ee > 90\%$ [14,15]. Sequencing studies showed that the amino acid substitutions occur on the periphery of the enzyme, far removed from the active center. In fact, they appear to form 'hot spots', i.e. sensitive areas in which substitutions result in an increase in *ee*. No current theory or molecular modeling would have predicted these results. Rather, it is the randomness of mutagenesis coupled with the screening systems which ensures success.



Scheme 11 *In vitro* evolution of enantioselective enzymes for use in organic synthesis.

Thus, this approach may be an alternative to traditional ways of preparing enantioselective metal catalysts, especially in view of the fact that a wide variety of wild-type enzymes are available, which in principle can now be transformed into highly enantioselective variants to suit the particular needs of organic chemists. We conclude that new strategies in metal catalysis as well as *in vitro* evolution of enantioselective enzymes need to be pursued.

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